



CCTB 2021

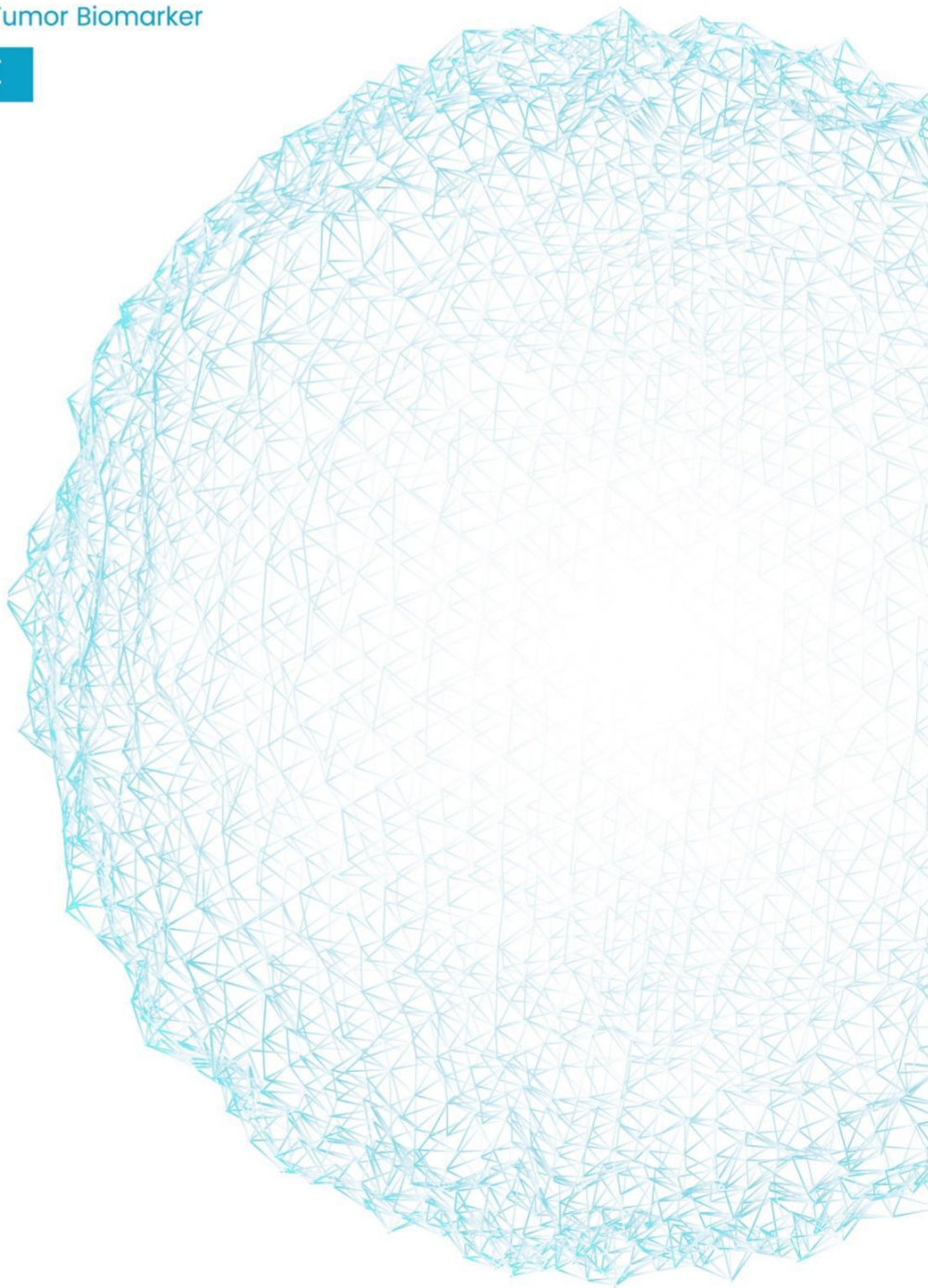
中国肿瘤标志物学术大会

暨第十五届肿瘤标志物青年科学家论坛

Chinese Academic Conference on Tumor Biomarker

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论文集
Proceedings



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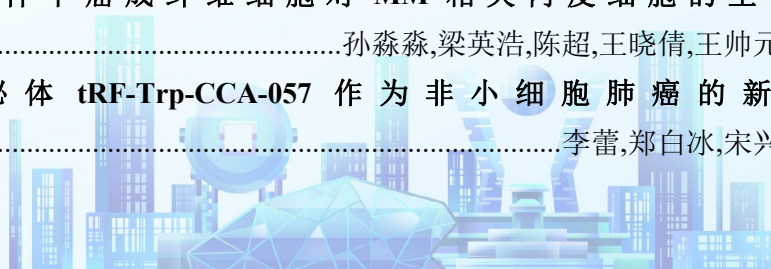
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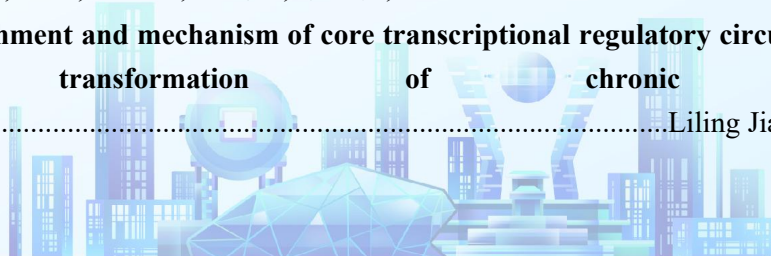
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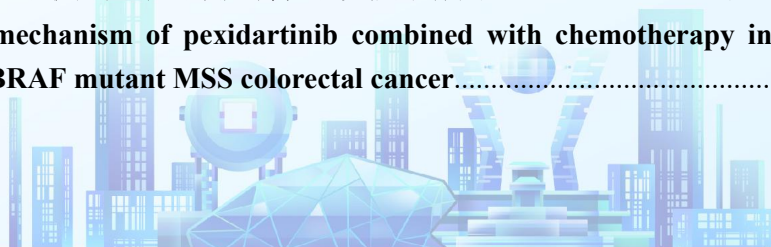
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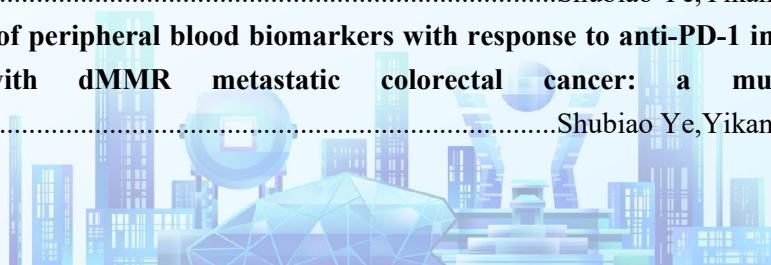
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TBM 优秀论文

1. Long non-coding RNA ZFAS1 promotes the invasion and proliferation of gastric cancer cells by regulating LIN28 and CAPRIN1 and has the potential value of tumor marker

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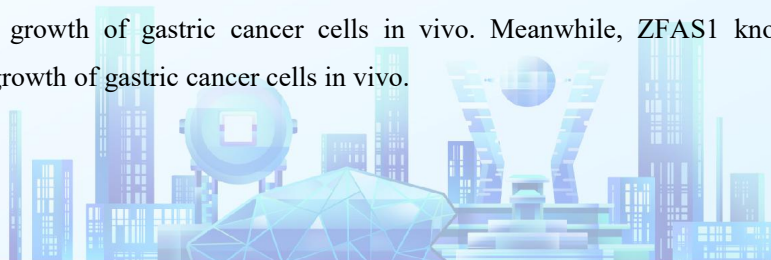
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Background: LncRNA ZNF1-AS1 (ZFAS1) is a newly discovered long non-coding RNA (LncRNA), but its value in the diagnosis of gastric cancer is unclear. The aim of this study was to investigate the potential role of ZFAS1 in gastric cancer and to evaluate the clinical significance of ZFAS1 as a biomarker for gastric cancer screening.

Methods: Quantitative real-time polymerase chain reaction (qRT-PCR) was used to screen for gastric cancer-associated LncRNAs in gastric cancer patients, gastric stromal tumor patients, gastritis or gastric ulcer patients, and healthy controls. The correlation between ZFAS1 expression and clinicopathological features was analyzed. The biological effects of ZFAS1 on proliferation, migration and invasion of gastric cancer cells were studied by MTT assay, colony formation assay and transwell migration assay. The potential mechanism of ZFAS1 was demonstrated using ELISA and qRT-PCR. The relationship between ZFAS1 and tumorigenesis was demonstrated using in vivo tumor formation assays.

Results: The expression of LncRNA ZFAS1 in plasma of preoperative patients with gastric cancer was significantly higher than that of the other 4 groups. Increased expression of ZFAS1 was significantly associated with lymph node metastasis, TNM staging, and poor prognosis. ZFAS1 knockdown inhibited the proliferation, migration and invasion of gastric cancer cells. In contrast, ZFAS1 overexpression promoted proliferation, migration and invasion of gastric cancer cells. LIN28 and CAPRIN1 are key downstream mediators of ZFAS1 in gastric cancer cells. ZFAS1 overexpression promoted the growth of gastric cancer cells in vivo. Meanwhile, ZFAS1 knockdown expression inhibited the growth of gastric cancer cells in vivo.



Conclusion: LncRNA ZFAS1 promoted invasion and proliferation of gastric cancer cells by modulating LIN28 and CAPRN1, suggesting that ZFAS1 can be used as a potential biomarker for the diagnosis and prognosis of gastric cancer.

Key words: LncRNA; ZFAS1; Gastric cancer; Biomarker

2. Neoadjuvant chemotherapy modulates the tumor microenvironment in high-grade serous ovarian cancer

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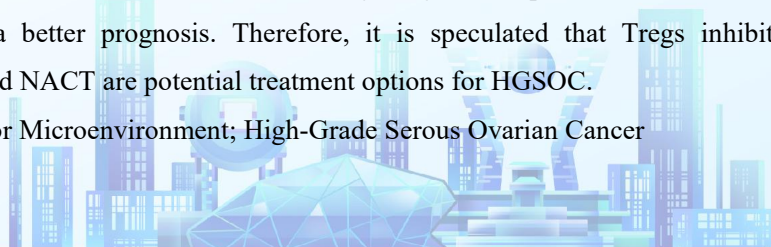
Background: While surgical reduction with adjuvant chemotherapy is the traditional treatment for high-grade serous ovarian cancer (HGSOC), neoadjuvant chemotherapy (NACT) has increasingly been applied. This work aims to investigate the expression profiles before and after NACT, explore changes in the tumor microenvironment, expand current treatments, and design a combination of treatment options for patients.

Methods: We downloaded 326 pre-NACT RNA sequencing data and 37 matched pre- and post-NACT samples from The Cancer Genome Atlas (TCGA) and Gene Expression Omnibus (GEO) databases. Differentially expressed genes (DEGs) were determined with EdgeR, and Gene Ontology analysis was performed to identify the clusters responsible for the biological processes and pathways of HGSOC. Immune infiltration was analyzed using Single-sample Gene Set Enrichment Analysis (ssGSEA) and CIBERSORT. Kaplan-Meier (KM) survival analysis was performed to assess prognosis, and the potential correlations between modules and phenotypes were explored using weighted gene co-expression network analysis (WGCNA).

Results: After NACT, a total of 352 genes showed significant changes in RNA expression, among which 180 genes were up-regulated and 172 down-regulated. The most influential pathway was the positive regulation of mitogen-activated protein kinase (MAPK) cascade. Correlation analysis and KM survival analysis showed that overexpression of MAPK cascade genes correlated with shorter survival time in HGSOC patients. ssGSEA results showed that the expressions of anti-tumor cells (central memory CD4⁺ T cell and central memory CD8⁺ T cell) and pro-tumor cells (neutrophil and dendritic cells) were significantly increased after NACT. CIBERSORT showed that the abundances of memory B cells, NK cells, and monocytes were increased and the abundance of plasma cells was decreased after NACT. WGCNA and KM survival analysis showed that a lower abundance of Regulatory T cells (Tregs) was correlated with a better prognosis.

Conclusions: Gene expression of the MAPK pathway is up-regulated and the abundance of CD4⁺ T regulation cell decreases after NACT. Thus, the MAPK pathway may promote the differentiation of CD4⁺ T cells into Th17 cells while inhibiting Tregs development. The inhibited Tregs development can lead to a better prognosis. Therefore, it is speculated that Tregs inhibitors combined with platinum-based NACT are potential treatment options for HGSOC.

Key words: Tumor Microenvironment; High-Grade Serous Ovarian Cancer



3. Long-read sequencing enables the detecting of complex HBV integrated genome structures in hepatocellular carcinoma patients

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Objective: The integration of HBV into the human genome is a crucial mechanism of Hepatocellular carcinoma (HCC), but the intricate HBV integration pattern is still unclear. In this study, we evaluated the feasibility of identifying complex HBV integrated genome structures by Nanopore and PacBio platforms.

Methods: The DNA library was sequenced using the long-read sequencing on GridION and PacBio Sequel II, respectively. Simultaneously the DNA and mRNA were sequenced using next-generation sequencing on Illumina NextSeq. We established a workflow, analyzed HBV integration patterns using BLAST and local scripts, and verified the accuracy of this workflow.

Results: In this study, we evaluated the feasibility of identifying complex HBV integrated genome structures through Nanopore and PacBio platforms and established an analytical strategy. Based on the long-read sequences of the Nanopore and PacBio platforms, we can not only identify the breakpoints of HBV integration but also obtain complex HBV integrated genome structures. We obtained the entire HBV integration patterns in sequences, not based on algorithm predicting for the first time. The HBV integration pattern was extremely complicated, HBV was not integrated with a complete genome, but the genome was fragmented and integrated into the human genome in different orientations.

Conclusion: Our results proved that long-read sequencing enables detecting complex HBV integrated genome structures in HCC patients. It provides evidence to support the potential application of long-read sequencing in virus integration identification and helps people fully elucidated the role of HBV integration in carcinogenesis.

Key words: HBV integration; hepatocellular carcinoma; Nanopore; PacBio

4. 血清中的 miR-454-3p 可作为胶质瘤的生物标记物

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目的: 胶质瘤是成人最常见的原发性恶性脑瘤。虽然在胶质瘤的诊断和治疗方面已取得了重大的进展, 但是胶质瘤患者的预后仍然不太乐观, 因此迫切需要早期诊断和新的治疗策略来提高胶质瘤患者的生存率。我们前期的研究工作发现血浆 miR-454-3p 可能在胶质瘤预后方面有一定优



势，但对于 miR-454-3p 在胶质瘤中的临床意义和调控机制，尤其是在循环和组织 miR-454-3p 的关系方面尚未进行系统的研究。

方法：通过实时荧光定量 PCR（qRT-PCR）技术分析了 miR-454-3p 在胶质瘤患者血清和组织中的表达水平。采用 CCK-8,划痕,侵袭,凋亡和免疫荧光检测等方法，评价 miR-454-3p 在胶质瘤肿瘤细胞中的功能。通过生物信息学分析筛选 miR-454-3p 的靶基因。通过荧光素酶报告试验和免疫印迹分析进一步验证 ATG12 与 miR-454-3p 的关系。在本研究中，我们旨在鉴定 miR-454-3p 在外泌体和组织中的表达模式，并评估其作为一种新型生物标志物的可能作用，以便更好地监测患者。

结果：miR-454-3p 在肿瘤组织中显著下调，而在同一胶质瘤患者的外泌体中显著上调。外泌体 miR-454-3p 在胶质瘤诊断中的曲线下面积（AUC）为 0.8663。外泌体 miR-454-3p 在术后血清中明显低于术前血清。外泌体中 miR-454-3p 高表达或组织中 miR-454-3p 低表达与预后不良相关。miR-454-3p 的恢复表达抑制了胶质瘤细胞的增殖,迁移,侵袭和自噬。ATG12 被确认为 miR-454-3p 的直接靶点。过表达 ATG12 可以部分逆转 miR-454-3p 抑制的作用。

结论：miR-454-3p 在胶质瘤细胞生长过程中发挥抑癌功能。miR-454-3p 可能作为一种外泌体生物标志物，并可能发展成为一种新的胶质瘤治疗方法。

关键词：胶质瘤；外泌体；miR-454-3p

5. 观察血清异常糖链糖蛋白表达和细胞免疫功能对肺癌预后的影响

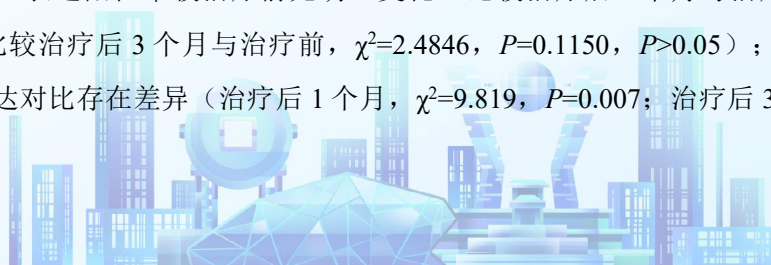
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陕西中医药大学附属医院

目的：观察血清异常糖链糖蛋白（TAP）表达和细胞免疫功能对肺癌患者预后的影响。

方法：选取 2016 年 1 月—2017 年 5 月陕西中医药大学附属医院收治的 49 例肺癌患者的临床资料，依据治疗方式不同分为观察组（肺癌根治术加术后辅助化疗，n=28）和对照组（化疗，n=21）。分别于治疗前及治疗后 1,3 个月检测两组患者血清 TAP 表达和细胞免疫功能指标，卡氏（Karnofsky, KPS）功能状态评分。

结果：两组患者治疗前 TAP 表达阳性率比较，差异无统计学意义（ $\chi^2=1.647$, $P>0.05$ ）；观察组治疗后 TAP 表达阳性率较治疗前显著下降，差异有统计学意义（比较治疗后 1 个月与治疗前， $\chi^2=4.2486$, $P=0.0393$ ；比较治疗后 3 个月与治疗前， $\chi^2=31.2391$, $P=0.0000$, $P<0.05$ ）；对照组治疗后 TAP 表达阳性率较治疗前无明显变化（比较治疗后 1 个月与治疗前， $\chi^2=0.8281$, $P=0.3628$ ；比较治疗后 3 个月与治疗前， $\chi^2=2.4846$, $P=0.1150$, $P>0.05$ ）；两组间治疗后 1,3 个月 TAP 表达对比存在差异（治疗后 1 个月， $\chi^2=9.819$, $P=0.007$ ；治疗后 3 个月， $\chi^2=6.716$,



$P=0.035$, $P<0.05$)。观察组治疗后 $CD4^+/CD8^+$ 比值较治疗前升高 (比较治疗后 1 个月与治疗前, $t=-9.6353$, $P=0.0000$; 比较治疗后 3 个月与治疗前, $t=-6.7035$, $P=0.0000$, $P<0.05$)。对照组治疗后 $CD4^+/CD8^+$ 比值较治疗前下降 (比较治疗后 1 个月与治疗前, $t=-1.6487$, $P=0.1050$; 比较治疗后 3 个月与治疗前, $t=2.1757$, $P=0.0340$, $P>0.05$)。治疗后 1,3 个月, 观察组 $CD4^+/CD8^+$ 比值均显著高于对照组, 差异有统计学意义 ($P<0.01$)。治疗后 3 个月生活质量评分 (KPS 评分), 观察组有效率 57.14%, 对照组有效率 38.09%, 治疗后观察组生活质量评分较对照组明显升高, 有统计学意义 ($\chi^2=7.2746$, $P=0.0070$, $P<0.05$)。

结论: 血清 TAP 和细胞免疫功能可作为评估肺癌预后疗效,复发的指标, 有临床应用价值。

关键词: 肺癌; 异常糖链糖蛋白; 细胞免疫功能; 预后

6. Identification of a specific peptide binding to cancer-testis antigen KK-LC-1 from a phage-displayed peptide library

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Every year there are nearly 1 million new cases of gastric cancer reported worldwide, making it the third leading cause of cancer-related deaths. Diagnosis of gastric cancer mainly depends on the diagnostic radiology examination, which is one of the effective means to predict the metastasis of retroperitoneal lymph nodes in gastric cancer. However, it is not ideal for the diagnosis of metastases less than 0.5 cm. Kita-kyushu lung cancer antigen 1 (KK-LC-1) is a novel tumor target with great therapeutic potential. The KK-LC-1 antigen was originally found in human lung cancer cells but was soon found to be expressed at high levels in breast cancer and gastric cancer. KK-LC-1 is a type of cancer-testis antigen, which will not be expressed in normal tissues other than testis, placenta, and fetal ovary. Targeting of cancer-testis antigen could improve the specificity of anti-tumor drug molecule, which is a unique advantage for targeted therapy.

Antibodies with strong specificity have many applications in clinical. However, small-molecule peptides have better tumor permeability, better immunogenicity, and pharmacokinetic parameters. A phage-display peptide library is comprised of a heterogeneous mixture of billions of phage clones. Through multiple rounds of biological panning for specific antigens, the targeting peptides can be quickly and efficiently separated.

In this study, we screened several candidate peptides from a phage library. Its affinity was confirmed by ELISA and SPR. In cellular immunofluorescence, the targeting peptide showed good tumor cell affinity and could form effective competitive binding with antibodies. Validation in patient tumors and tissue sections also showed excellent specificity. In vivo, the peptides could be effectively enriched in the tumor with little systemic non-specific binding. The enrichment process of target peptides in vivo was reproduced by micro-PET/CT imaging. The radioactivity signal of the nuclide-labeled target

peptides at the tumor site was obvious and higher than the background, which suggested the high specific uptake of peptides by tumor.

This is the first KK-LC-1 targeting peptide reported. The results showed that this targeting peptide had excellent affinity, specificity, and excellent drug-forming potential, and could be useful for labeling and clinical imaging of specific tumor cells in the future.

Targeting peptides have a variety of unique active advantages, such as good tumor penetration, high affinity, and stable structure. The KK-LC-1 antigen-specific peptide obtained in this study is the first publicly reported KK-LC-1 small-molecule conjugate. We have repeatedly verified its affinity and specificity through a series of experiments. However, the effective binding sites of targeting peptides and KK-LC-1 remain to be revealed. The analysis and modification of molecular structure may help to further improve its affinity and activity. Also, the pharmacokinetic parameters can be further improved by adding modified groups, thus prolonging plasma half-life and improving clinical application value.

In conclusion, we screened KK-LC-1 specific targeting binding peptides based on the phage display library, and a series of in vivo and in vitro experiments verified its excellent affinity and specificity. Targeting peptides showed excellent imaging, therapeutic potential, and smaller organ side effects. The PET/CT imaging reagents or coupling drugs based on the targeting peptide may have extremely high clinical application value. Gastric cancer diagnostic reagents, imaging reagents, or therapeutic drugs based on targeting peptides may bring practical clinical benefits to more patients with gastric cancer in the near future.

Key words: KK-LC-1; Gastric cancer; Targeted therapy; Phage display; Molecular probe

7. 人重组细胞因子 rhIL-6 上调 p-FLNC 促进骨肉瘤细胞化疗耐药

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目的: 细胞因子 IL-6 可在多种肿瘤中诱导肿瘤细胞对化疗药物产生耐受, 本研究旨在探讨人重组细胞因子 rhIL-6 促进骨肉瘤细胞 SOSP-9607 化疗耐药后, 骨肉瘤细胞在翻译后修饰水平的改变。

方法: 将骨肉瘤细胞 SOSP-9607 分为三组: 对照组, 肿瘤细胞经顺铂处理组, 及肿瘤细胞在顺铂处理 8 小时前给予 60 ng/mL rhIL-6 处理组。每组做三个平行生物学重复。利用基于 TMT 标记的定量磷酸化蛋白组学筛选 rhIL-6 预先干预后的顺铂处理组肿瘤细胞与单独顺铂处理的肿瘤细胞间差异表达的磷酸化蛋白及其特异性磷酸化位点, 通过 GO 和 KEGG 富集分析, 差异磷酸化蛋白的激酶预测及蛋白间相互关系的分析确定潜在的耐药靶标, 进而选取临床标本对其进行免疫组织化学验证。

结果: 我们鉴定到 3562 个蛋白和 13524 个肽段, 其中有 3125 个磷酸化蛋白和 10263 个磷酸化肽段。

对比 rhIL-6 预先干预组与单独顺铂处理组的骨肉瘤细胞, 我们鉴定到 25 个有统计学差异的磷

酸化肽段。结合 GO 与 KEGG 富集,差异磷酸化蛋白的激酶预测及相互间网络关系我们选取差异显著的 p-FLNC 进行后续验证。临床标本的免疫组化结果显示, p-FLNC 及其预测的激酶 AKT1 在化疗敏感和耐受的骨肉瘤患者石蜡标本中的表达与磷酸化蛋白组学结果相一致, 且 p-FLNC 参与的 MAPK 信号通路的关键分子 ERK1/2 在化疗耐受患者中亦为高表达。

结论: p-FLNC 过表达及其参与的 MAPK 信号通路的激活可能在 IL-6 促使骨肉瘤细胞对顺铂产生耐药的过程中发挥了重要的作用。

关键词: 人重组细胞因子 rhIL-6; 骨肉瘤; 化疗耐受; 磷酸化蛋白组学

8. 膜联蛋白 A2 突变与乳腺癌患者临床病理特点之间的联系

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背景: 某些基因的突变能够诱导肿瘤的发生, 前期研究发现膜联蛋白 A2 (ANXA2) 在乳腺癌组织中存在差异表达。此研究旨在检测乳腺癌组织中 ANXA2 突变情况, 并进一步分析该突变基因与乳腺癌患者临床病理特征之间的关系。

方法: 选取 112 位乳腺癌患者肿瘤组织与癌旁正常组织作为研究样本, 提取样本总 RNA, 通过 PCR-SSCP 与双向一代基因测序进行检测, 通过 NCBI 的 BLAST 分析工具 (blastn 和 blastx) 检测 ANXA2 的突变情况, 并分析其与患者临床病理指标及预后的关系。

结果: 检测出 ANXA2 突变率在肿瘤组织中 (错义突变率 38.39%) 显著高于癌旁正常组织 (错义突变率 8.04%), 肿瘤组织中的 ANXA2 突变与患者临床分期,分子亚型,ER,PR,淋巴转移率有相关性。c.(350TC>CT), c.(375G>A), c.(487T>A) 和 c.(693C>T) 这些突变位点可能与乳腺癌的发生有关。无错义突变的患者 5 年生存率高于有错义突变的患者, Kaplan-Meier 和 Cox 回归模型分析显示: c.(350AG>GA) 和 c.(693G>A) 突变与乳腺癌患者的 5 年生存率相关 ($P<0.05$)。

结论: ANXA2 基因突变可能与乳腺癌的发生和临床病理特点及预后相关。突变位点 c.(350TC>CT) 和 c.(693C>T) 可以作为乳腺癌的预后指标, 可能是乳腺癌筛查,诊断,治疗的潜在靶点。

关键词: ANXA2; 乳腺癌; 双向一代测序; DNA 突变分析; 预后

9. N6-甲基腺苷在肿瘤中的研究进展

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转录后修饰是多种生理过程和疾病进展的重要调节因子, 在众多的 RNA 修饰中, N6-甲基腺苷 (m6A) 是真核细胞 mRNA 上最丰富的内部修饰。m6A 是发生在腺苷 N6 位置的甲基化, 通过

改变靶基因的表达,从而影响相应的细胞过程和生理功能。在综述这一领域的最新进展时,我们发现近年来其引起了生物科学研究的广泛关注,特别是在肿瘤的发生和进展方面。m6A 在肿瘤发生中的作用体现在一些肿瘤相关基因的改变上。m6A 可促进肿瘤的发生发展,主要在两方面发挥作用。其一, m6A 促进癌基因的表达,例如,已有研究发现, WTAP 以 m6A 依赖的方式稳定 DUSP6 mRNA,从而促进鼻型 NK/T 淋巴瘤的进展和化疗敏感性;在急性髓系白血病中, METTL3 表达上调,通过促进 m6A 来增强癌基因如 c-MYC, BCL2 和 PTEN 的翻译;在卵巢癌中, SRF 促进肿瘤细胞的增殖和转移, IGF2BP1 通过 m6A 依赖的方式抑制 miRNA 介导的 SRF 的表达,导致 SRF, FOXK1 和 PDLIM7 的表达增加;在鼻咽癌中,癌基因 lncRNAFAM225A 的 m6A 水平升高,导致 FAM225A 的稳定性增强和高表达, FAM225A 通过作为 ceRNA 和海绵状 miR-590-3p, miR-1275 发挥促癌作用,引起 ITGB3 的高表达以及 FAK/PI3K/Akt 通路的激活。其二, m6A 抑制肿瘤抑制基因的表达。Xiaoyu Cheng 等人曾报道过, VIRMA 在肝细胞癌中的高表达,并通过增强 m6A 的修饰和抑制 ID2 mRNA 的表达,导致细胞增殖和侵袭增加。YuanHe 等人研究发现,在胰腺癌中, ALKBH5 的表达减少,导致 m6A 水平升高,肿瘤抑制基因 KCNK15-AS1 的表达减少,从而引起胰腺癌细胞迁移和侵袭增强。m6A 也可抑制肿瘤的发生发展。一方面, m6A 抑制癌基因的表达,已有研究发现,在子宫内膜癌中,由于 METTL3 表达减少或 METTL14 突变, m6A 水平较低,从而导致细胞增殖,集落形成,迁移和侵袭增强;在肺鳞状细胞癌中, FTO 表达升高, FTO 通过抑制 m6A 甲基化和增加 mRNA 的稳定性促进癌基因 MZF1 的表达。另一方面, m6A 促进肿瘤抑制基因的表达。Jinzhao Ma 等人发现在肝癌中 METTL14 通过 m6A 依赖的方式正调控 microRNA126 的表达,从而降低了肝癌的转移潜能。综上, m6A 通过调控肿瘤相关基因的表达参与肿瘤恶性表型的调控。因此,与 m6A 相关的更多有效药物和新的治疗策略有待应用于肿瘤疾病。

关键词: N6-甲基腺苷; 肿瘤; 发生和进展; 治疗策略

10. mTOR 调控硒蛋白家族抑制细胞铁死亡介导黑素瘤 PD-1 单抗治疗抵抗

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目的: 基于 PD-1/PD-L1 单抗的免疫检查点阻断疗法是目前治疗黑素瘤的有效方法,但存在治疗反应率和治疗抵抗等缺陷严重限制其疗效。近期研究表明,在 PD-1 单抗治疗后,肿瘤浸润的 CD8⁺T 细胞被显著激活,通过分泌 IFN- γ 抑制黑素瘤细胞膜表面的 Xc⁻系统的表达,进一步促进肿瘤细胞的铁死亡。然而,铁死亡是否参与 PD-1 单抗治疗抵抗及其上游调控机制尚不清楚。



材料与方法：通过 RNA-seq 方法检测 PD-1 单抗诱导黑素瘤细胞铁死亡发生时分子通路的变化；通过免疫印迹,qRT-PCR,免疫荧光染色和流式细胞术等方法明确 mTOR 信号在 PD-1 单抗诱导黑素瘤细胞铁死亡中的变化和具体作用；通过 RNA-seq,免疫印迹,代谢物检测和萤光素酶报告实验明确 mTOR 调控硒蛋白家族抑制细胞铁死亡的作用和具体机制；通过基于完全免疫系统小鼠的荷瘤实验和免疫组织化学染色方法阐明 mTOR 抑制铁死亡介导 PD-1 治疗抵抗的重要作用和硒蛋白家族的表达变化情况。

结果：PD-1 单抗诱导黑素瘤细胞发生铁死亡后，mTOR 信号及其下游分子显著活化，且与其复合物多个组成分子表达的异常密切相关；通过基因干预或者药物阻断方法抑制 mTOR 信号可以显著增强 PD-1 单抗治疗后 IFN- γ 诱导肿瘤细胞铁死亡的效果；在此基础上发现，mTOR 信号激活可通过促进硒蛋白家族多个抗氧化分子的表达，抑制脂质过氧化物合成，从而阻断 PD-1 单抗治疗后 IFN- γ 诱导的黑素瘤细胞铁死亡；通过临床前小鼠荷瘤模型证实，联合阻断 mTOR 信号可以通过促进黑素瘤细胞铁死亡增加 PD-1 单抗治疗敏感性，且该协同治疗作用和调控硒蛋白家族表达有关。

结论：mTOR 信号在 PD-1 单抗诱导黑素瘤细胞铁死亡时显著激活，可通过促进硒蛋白家族表达削弱脂质过氧化物生成抑制肿瘤细胞铁死亡的发生。联合阻断 mTOR 可通过加剧铁死亡增加 PD-1 治疗敏感性，是 PD-1 单抗联合治疗的新策略。

关键词：PD-1；mTOR；硒蛋白家族

11. 纳米颗粒递送 miR-21-3p 促进铁死亡增加黑素瘤 PD-1 治疗敏感性

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目的：PD-1/PD-L1 免疫检查点阻断疗法已经被证明对进展期黑素瘤具有很好的治疗效果。然而，治疗反应率低和较高的耐药发生率严重限制了疗效，影响了患者总生存期的进一步改善。近期研究表明，在 PD-1 单抗治疗后，肿瘤浸润的 CD8⁺T 细胞被显著激活，通过分泌 IFN- γ 抑制黑素瘤细胞膜表面的 Xc-系统的表达，进一步促进肿瘤细胞的铁死亡。然而，铁死亡逃逸是否参与 PD-1 单抗的治疗抵抗及其上游调控机制仍不清楚。

材料和方法：通过 RNA-seq 方法获得 IFN- γ 诱导黑素瘤细胞铁死亡后的 miRNA 表达谱；通过基因干预，CCK8 和荧光原位杂交等方法揭示 miR-21-3p 在黑素瘤细胞铁死亡中的作用。通过生物信息学分析，萤光素酶报告实验,RT-PCR,western blot，基因干预，CCK8 和克隆形成实验等方法阐明 miR-21-3p 的直接作用靶分子及参与调控铁死亡的具体机制。通过小鼠皮下荷瘤，免疫荧光染色和流式细胞分析等方法明确 miR-21-3p 协同 PD-1 单抗治疗黑素瘤的作用的具体机制。



通过体外实验分析搭载 miR-21-3p 的纳米金颗粒的物理化学特性，并在体内水平通过 ELISA, 血常规检测和免疫组织化学染色方法揭示其协同 PD-1 单抗治疗黑素瘤的安全性和有效性。通过生物信息学分析, 染色质免疫共沉淀和免疫组织化学染色等方法揭示 miR-21-3p 的上游调控机制。

结果: 通过 RNA-seq 方法, 我们首先获得在 IFN- γ 诱导黑素瘤细胞铁死亡后的异常 miRNA 表达谱。进一步通过功能学研究发现, miR-21-3p 表达水平的升高可通过增强脂质过氧化而非通过影响铁离子负载促进 IFN- γ 介导的黑素瘤细胞铁死亡。生物信息学分析和生物化学方法实验证实, miR-21-3p 可直接靶向抑制 TXNRD1 表达水平, 促进脂质氧自由基的产生, 增强黑素瘤细胞对铁死亡的敏感性。进一步我们通过小鼠皮下荷瘤实验证明, miR-21-3p 过表达可通过与 PD-1 抗体协同作用促进细胞铁死亡, 抑制黑素瘤的生长。在此基础上, 我们构建了搭载 miR-21-3p 的纳米金活性颗粒, 其具有良好的物理化学稳定性且可以被肿瘤细胞有效摄取, 更为重要的是, 可以在体内水平有效增强 PD-1 抗体治疗黑素瘤的效果, 且没有明显的毒副作用。最后我们通过筛选发现, 转录因子 ATF3 可以通过直接与 miR-21-3p 启动子结合, 转录激活促进铁死亡诱导过程中 miR-21-3p 的表达水平。

结论: miR-21-3p 表达水平升高通过直接靶向抑制 TXNRD1 表达促进 IFN- γ 诱导的黑素瘤细胞铁死亡, 并可与 PD-1 抗体产生协同抑癌作用。搭载 miR-21-3p 的纳米金颗粒作为免疫检查点阻断剂的协同治疗手段具有广阔的应用前景, 且具有良好的系统使用安全性。

关键词: 纳米递送; miR-21-3p; PD-1; 铁死亡; 黑素瘤

12. circBCBM1 as a novel diagnostic and therapeutic target for breast cancer brain metastasis

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Accumulating evidence indicates that circular RNAs (circRNAs) play critical roles in tumorigenesis and progression of various cancers. We previously identified a novel upregulated circRNA, circBCBM1, in the context of breast cancer brain metastasis. However, the potential biological function and molecular mechanism of circBCBM1 in breast cancer brain metastasis remain largely unknown. In this study, we confirmed that circBCBM1 was a stable and cytoplasmic circRNA. Functionally, circBCBM1 promoted 231-BR cell proliferation and migration in vitro and growth and brain metastasis in vivo. Mechanistically, circBCBM1 acted as an endogenous miR-125a sponge to inhibit miR-125a activity, resulting in the upregulation of BRD4 expression and subsequent upregulation of MMP9 (matrix metalloproteinase 9) through Sonic hedgehog (SHH) signaling pathway. Importantly, circBCBM1 was markedly upregulated in the breast cancer brain metastasis cells and clinical tissue and plasma samples; besides, the overexpression of circBCBM1 in primary cancerous tissues was associated with shorter brain metastasis-free survival (BMFS) of breast cancer patients. These findings



indicate that circBCBM1 is involved in breast cancer brain metastasis via circBCBM1/miR-125a/BRD4 axis. CircBCBM1 may serve as a novel diagnostic or prognostic biomarker and potential therapeutic target for breast cancer brain metastasis.

Key words: breast cancer brain metastasis; circBCBM1; miR-125a; BRD4; biomarker; therapeutic target

13. 趋化因子 CCL21 介导 IRBIT 在肝癌恶性生物学行为的机制研究

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目的: 肝癌的发病率越来越高, 目前认为肝癌的迁移侵袭是导致肝癌患者预后不良的主要因素, 但具体机制尚不清楚。研究表明, 趋化因子 CCL21 对肿瘤的恶性生物学行为具有重要作用, 但在肝癌中的研究甚少, 我们的研究表明 CCL21 引起细胞内钙 $[Ca^{2+}]_i$ 升高, 并促进肝癌的迁移, 侵袭, 提示相关离子通道参与调节 $[Ca^{2+}]_i$ 的激活。IRBIT 是一个 IP3 受体的结合蛋白, 游离的 IRBIT 可以激活多种离子通道。此外, 我们的研究表明 CCL21 可以诱导 IRBIT 的表达上调。因此, 本研究旨在探索趋化因子 CCL21 介导 IRBIT 在肝癌迁移侵袭的潜在机制, 以寻求治疗肝癌的新的药物作用靶点。

方法: 免疫印迹和免疫组织化学检测 IRBIT 在肝癌中的表达。通过增殖实验, 穿膜实验, 划痕实验检测在沉默 IRBIT 的肝癌细胞以及 CCL21 刺激肝癌细胞后的增殖, 迁移能力; 构建 shRNA 慢病毒载体转染细胞沉默 IRBIT 表达, 通过 Western-Bolt 检测沉默 IRBIT 后肝癌细胞以及 CCL21 刺激肝癌细胞后 E-cadheren, N-cadherin, ZO-1, Vimentin 的表达, 以及 CCL21 刺激肝癌细胞后 IRBIT 的表达。使用细胞钙离子成像技术检测 CCL21 在肝癌中 $[Ca^{2+}]_i$ 的变化以及筛选受钙通道阻滞剂影响开放的钙通道, 并用钙通道阻滞剂反向验证 CCL21 在肝癌发展中的作用。

结果: 与正常肝组织及肝细胞系比较, IRBIT 在肝癌组织和细胞系中的表达明显增加; 慢病毒感染沉默 IRBIT 表达后, Huh7 细胞的增殖, 迁移以及侵袭能力均明显下降, 并且 EMT 标志物 E-cadheren, ZO-1 表达上升, N-cadherin, Vimentin 表达下降, 提示 IRBIT 在肝癌中扮演着促癌角色; 趋化因子 CCL21 刺激 Huh7 细胞 24h 后, 细胞的迁移, 侵袭能力均明显上升, 并且 E-cadheren, ZO-1 表达下降, N-cadherin, Vimentin 以及 IRBIT 表达增加, 提示 CCL21 可能通过调控 IRBIT 影响肝癌的恶性生物学行为; 动态钙测定发现 CCL21 刺激可诱导 Huh7 细胞内钙增高, 并且可以被 NCX1 的抑制剂 KB-R7943 明显抑制, 加入 KB-R7943 与 CCL21 共培养后, CCL21 诱导的 E-cadheren, ZO-1 表达上升和 N-cadherin, Vimentin 表达下降均被有效逆转, 提示 CCL21 可能通过调控 IRBIT, 影响细胞膜上的 NCX1 通道介导外钙内流, 进而促进肝癌恶性生物学行为。



结论：本研究首次揭示了趋化因子 CCL21 通过 IRBIT/NCX1/Ca²⁺通路轴促进肝癌恶性生物学行为的新机制，为治疗或预防肝癌复发转移提供新的理论依据。

关键词：趋化因子；IRBIT；肝癌；迁移；侵袭；钙通道

14. NKG7 mRNA therapy increases the anti-tumor cytotoxicity of CD8⁺ T cells and improves response to immune checkpoint inhibitors

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Translating information gained from single cell RNA-sequencing (scRNA-seq) analyses into clinical therapeutics remains a challenge. However, with the advent of technology that makes mRNA-based modulation of primary cells possible, targets identified in scRNA-seq datasets can now be manipulated directly. Here we model this approach in the context of cancer immunotherapy. We performed scRNA-seq analysis of peripheral CD8⁺ T cells from patients who received anti-PD-1 checkpoint blockade and found that natural killer cell granule protein-7 (NKG7) gene expression was decreased in non-responding patients. Functional assays revealed that reduced NKG7 levels compromised cytolytic granule localization and release. Furthermore, transfection of CD8⁺ T cells with NKG7 mRNA promoted tumor cell killing both in vitro and in vivo. Thus, we identify NKG7 as critical for response to anti-PD-1 treatment, demonstrate the efficacy of NKG7 mRNA as a therapeutic strategy for improving cancer immunotherapy, and provide a model for translating scRNA-seq findings into mRNA-based therapy.

Key words: cancer immunotherapy; anti-PD-1 treatment; scRNA-seq; NKG7

15. Correlation between tregs and glycolysis in pancreatic cancer: a mini-review

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Regulatory T cells (Tregs) are a subset of T cells that control the autoimmune response and maintain the immune homeostasis. Tregs could acquire an activated phenotype and enhanced immunosuppressive function after being reprogrammed within the tumor microenvironment (TME). Pancreatic ductal adenocarcinoma (PDAC) is a heterogenous neoplasm with highly immunosuppressive. Tregs infiltration is one of the significant features of PDAC. The relative increase in the number of Tregs is closely related to the immunosuppression and disease progression of pancreatic cancer patients. Notably, enhanced glycolysis is increasingly considered to be a key hallmark of pancreatic cancer. Recent studies revealed that glycolysis promoted the pancreatic cancer progression and enhanced chemotherapy resistance. The deterioration of glycolysis has a positive effect on Tregs differentiation and function, while reducing the Tregs clonal expansion and migratory capacity. Understanding the role of glycolysis in Tregs activities will aid us explore how metabolic reprogramming modifies Tregs to meet their energy demands. Investigation of the association between Tregs and glycolysis would offer a new insight for pancreatic cancer immunotherapy.

Key words: Glycolysis; Immunotherapy; Pancreatic ductal adenocarcinoma; Regulatory T cells; Tumor microenvironment

16. 肺癌患者 ABO 血型，血管性血友病因子及血栓风险的关联

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目的: 探讨肺癌患者血浆 vWF 水平与 O 型/非 O 型血以及血栓风险的关联性。

方法: 回顾性分析 2017-2018 年天津市肿瘤医院收治的 82 例肺癌患者, 17 例正常健康者的血凝常规指标 vWF, D-D 含量以及 CEA, CA19-9 浓度。采用两独立样本资料的 t 检验分析比较两组研究变量的差异。再将病例组和对照组按血型分为 O 型血和非 O 型血, 分析比较两组 vWF 是否有差异。

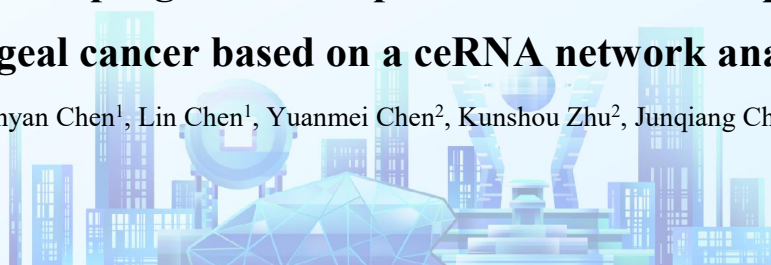
结果: 病例组的肺癌患者 D-D, vWF 水平高于健康对照组, 结果有显著性差异, $P < 0.05$ 。病例组和对照组中的非 O 型血人 VWF 水平高于 O 型血人, $P < 0.05$ 。病例组中的肺癌患者 vWF 水平高于对照组, 其 CEA, CA19-9 水平亦高于正常人, $P < 0.05$ 。

结论: 肺癌患者比正常健康人患血栓的风险更高, 非 O 型血的人存在血浆中 vWF 水平升高的风险。而 vWF 水平升高容易导致肺癌的发生和转移。

关键词: D-二聚体; 血栓; 肺癌; 血管性血友病因子 vWF; 血型

17. LIMD2 is a prognostic and predictive marker in patients with esophageal cancer based on a ceRNA network analysis

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Background: Globally, esophageal cancer (ECA) is the seventh most common cancer and sixth most common cause of cancer-associated mortality. However, there are no reliable prognostic and predictive molecular markers for ECA; in addition, the pathogenesis of ECA are not fully elucidated. This study was to explore the potential prognostic and predictive markers of ECA, as well as investigate the mechanisms of ECA.

Methods: The expressions of circular RNAs (circRNAs), microRNAs (miRNAs), and messenger RNAs (mRNAs) of ECA and control groups were obtained from the RNA-sequencing (RNA-seq) data of our hospital, the Gene Expression Omnibus (GEO) and The Cancer Genome Atlas (TCGA) datasets. Analyses of differentially-expressed genes, the circRNA-miRNA-mRNA competing endogenous RNA (ceRNA) network, and functional/pathway enrichment were conducted. The key targets in the ceRNA network that showed significant results in survival Cox regression analyses were selected. Furthermore, analyses of immune infiltration and autophagy genes related to the key targets were performed.

Results: Seven circRNAs, 22 miRNAs, and 34 mRNAs were identified as vital genes in ECA; the nuclear factor- κ -gene binding (NF- κ B) and phosphatidylinositol-3 kinase/protein kinase B (PI3K-Akt) signaling were identified as the most enriched pathways. In addition, LIM domain containing 2 (LIMD2) was an independent predictor of prognosis in ECA patients, and closely associated with immunity and autophagy. Moreover, quantitative reverse-transcription polymerase chain reaction (qRT-PCR) revealed significant upregulation of LIMD2 expression in ECA tissues.

Conclusions: ECA may be closely correlated with NF- κ B and PI3K/Akt signaling. In addition, LIMD2 could be a potential prognostic and predictive marker of ECA. Our study may provide novel insights into the prognosis and treatment of ECA by its pathogenesis.

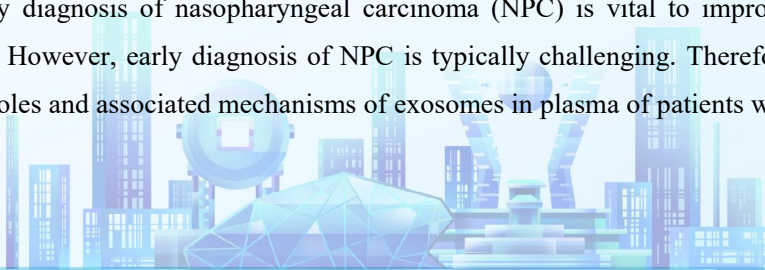
Key words: Esophageal cancer (ECA); competing endogenous RNA (ceRNA); LIM domain containing 2 (LIMD2); prognostic; predictive

18. Identification of potential plasma biomarkers in early-stage nasopharyngeal carcinoma-derived exosomes based on RNA sequencing

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Background: Early diagnosis of nasopharyngeal carcinoma (NPC) is vital to improve the prognosis of these patients. However, early diagnosis of NPC is typically challenging. Therefore, we explored the pathogenetic roles and associated mechanisms of exosomes in plasma of patients with early-stage NPC.



Methods: Exosomes in plasma were extracted by ultra-high-speed centrifugation. Western blot and transmission electron microscopy (TEM) were used to verify the purity of exosomes. The sequencing data (6 plasma samples from healthy volunteers vs. 6 NPC plasma samples) were analyzed by principal component analysis (PCA), DESeq2, gene ontology (GO), Kyoto encyclopedia of genes and genomes (KEGG), and TargetScan. The differentially expressed miRNAs (DEmiRNAs) were obtained from the dataset (GSE118720) downloaded from the Gene Expression Omnibus (GEO) repository. Additionally, the datasets downloaded from the GEO database (GSE12452, GSE13597, GSE53819, GSE64634) were used to predict the target genes and functions of hsa-miR-1301-3p. Quantitative reverse-transcription polymerase chain reaction (qRT-PCR) was applied to verify the differences in the expressions of hsa-miR-1301-3p between 10 normal plasma and 10 NPC plasma samples.

Results: Western blot, TEM, and Nanoparticle Tracking Analysis showed adequate purity of the extracted exosomes. RNA-sequencing (RNA-seq) analysis revealed 21 upregulated miRNAs, and 10 downregulated miRNAs in plasma exosomes of early-stage NPC patients. GO analysis showed that the target genes of DEmiRNAs were mainly enriched in DNA synthesis and transcription regulation. KEGG analysis revealed that DEmiRNAs were mainly enriched in phosphatidylinositol-3 kinase/protein kinase B (PI3K-Akt) and mitogen-activated protein kinase (MAPK) signaling pathways. Moreover, the expression of hsa-miR-1301-3p was verified to be significantly upregulated in enlarged samples of plasma exosomes.

Conclusions: We identified several DEmiRNAs extracted from tumor-derived exosomes between normal plasma and early-stage NPC plasma. Bioinformatics analyses indicated that these DEmiRNAs may be related to NPC development. Our study may provide novel insights into underlying biomarkers and mechanisms of plasma exosomes in early-stage NPC.

Key words: Nasopharyngeal carcinoma (NPC); Exosomes; Gene Expression Omnibus (GEO); Bioinformatics analysis; Kyoto encyclopedia of genes and genomes (KEGG)

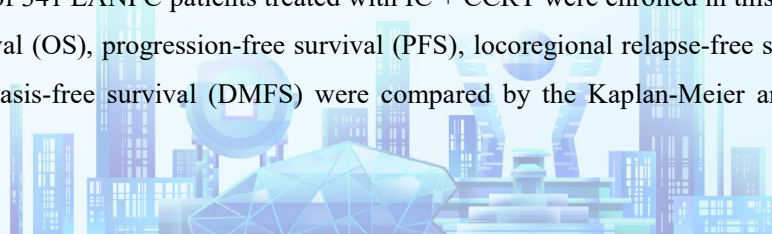
19. Prognostic value of serum uric acid and tumor response to induction chemotherapy in locally advanced nasopharyngeal carcinoma

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Background: To explore the combined predictive value of serum uric acid (SUA) and tumor response to induction chemotherapy (IC) in locally advanced nasopharyngeal carcinoma (LANPC) patients receiving IC followed by concurrent chemoradiation therapy (CCRT).

Methods: A total of 341 LANPC patients treated with IC + CCRT were enrolled in this retrospective study. Overall survival (OS), progression-free survival (PFS), locoregional relapse-free survival (LRFS), and distant metastasis-free survival (DMFS) were compared by the Kaplan-Meier analysis and the log-



rank test, and multivariable survival analysis was carried out to investigate the independent prognostic factors.

Results: Univariate analysis showed that a low SUA level and unsatisfactory tumor response to two cycles of IC both were negative predictors for OS, PFS, and DMFS in patients with LANPC. multivariable analysis demonstrated that the SUA level after two cycles of IC was an independent prognostic factor for OS ($P=0.012$) but of borderline significance for PFS and DMFS ($P=0.055$ and $P=0.067$, respectively). Furthermore, tumor response to IC was of independent significance for predicting OS, PFS, and DMFS, respectively. Finally, LANPC patients with satisfactory tumor response and a high SUA level after two cycles of IC had a better OS, PFS, and DMFS than those with unsatisfactory tumor response and a low SUA level.

Conclusion: The SUA level and the tumor response to two cycles of IC had predictive value for LANPC patients treated with IC plus CCRT. However, more aggressive therapeutic strategies are recommended for those with a low SUA level and unsatisfactory tumor response to two cycles of IC.

Key words: Nasopharyngeal carcinoma; Serum uric acid; Tumor response; Prognosis

20. 血清自身抗体检测在早期恶性肿瘤中应用的研究进展

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研究表明血清肿瘤相关抗原自身抗体直接参与肿瘤进展的观点, 即各种恶性肿瘤细胞分泌的一些抗体可以促进其增殖和转移已经得到了广泛的支持。由于肿瘤细胞产生了细胞抗原的变换, 使得细胞出现了新抗原, 从而诱导免疫系统产生自身抗体, 因此人们对建立针对肿瘤相关抗原的血清自身抗体作为新型的特异性肿瘤标志物进行了深入的研究。作为恶性肿瘤早期诊断中的肿瘤标志物, 自身抗体不仅比抗原更敏感和特异, 而且还可以在以肺癌为代表的多种癌症临床指征出现之前更好的做出提示。血清肿瘤相关抗原自身抗体在恶性肿瘤的治疗中有着较大的现实价值。本文总结了自身抗体在早期恶性肿瘤检测与诊断中的应用, 并讨论了自身抗体的检测在恶性肿瘤中潜在的价值。迄今为止的研究表明, 自身抗体不仅可以调节恶性肿瘤进展, 而且有望成为提示早期癌症的重要工具。本文特别强调了几种癌症中自身抗体特征的临床应用以及临床验证所面临的挑战。

关键词: 自身抗体; 肿瘤相关抗原; 恶性肿瘤; 诊断; 生物标志物

21. A combined strategy of TK1, HE4 and CA125 shows better diagnostic performance than Risk of Ovarian Malignancy Algorithm (ROMA) in ovarian carcinoma



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Fudan University Shanghai Cancer Center

Background: The dual marker algorithm Risk of Ovarian Malignancy Algorithm (ROMA) has been widely used in the clinic for identification of equivocal pelvic masses in ovarian carcinoma. To obtain higher diagnostic efficiency, we created a new diagnostic index Risk of Ovarian Malignancy Index (ROMI) by combining thymidine kinase 1 (TK1), HE4 and CA125.

Methods: 335 patients with pelvic masses on imaging and 46 healthy controls were enrolled. Serum TK1 was analyzed before further study. ROMI and ROMA were evaluated for diagnostic efficiency.

Results: The level of TK1 was elevated in malignant ovarian tumors compared to benign masses ($P<0.001$) and healthy controls ($P<0.001$). TK1 was positively correlated with stage, intrapelvic metastasis, lymphatic metastasis and distant metastasis (all P values <0.001). The area under the receiver operating characteristic curve (AUC) of ROMI was higher than that of ROMA for both pre- and postmenopausal women. ROMI had better sensitivity, specificity, accuracy, positive and negative predictive values than ROMA in diagnosis of all-stage or stage I+II ovarian carcinoma for both pre- and postmenopausal women.

Conclusions: TK1 is a potential biomarker in detection of ovarian carcinoma. ROMI shows better diagnostic performance than ROMA in distinguishing malignant ovarian tumors from benign masses.

Key words: Ovarian cancer; Algorithm; Thymidine kinase 1; Risk of Ovarian Malignancy Index; Risk of Ovarian Malignancy Algorithm; Tumor markers

22. Bioinformatics analysis for the role of CALR in human cancers

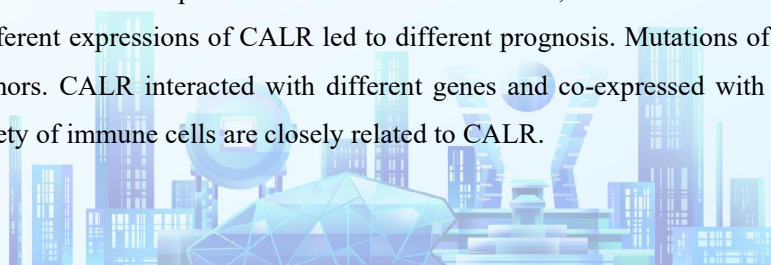
Yijun Li*, Jianjun He, Huimin Zhang

Departments of Breast Surgery, First Affiliate Hospital of Xi'an Jiaotong University

Background: Cancer is one of the most important public health problems in the world. The curative effect of traditional surgery, radiotherapy and chemotherapy is limited and has inevitable side effects. As a potential target for tumor therapy, few studies have comprehensively analyzed the role of CALR in cancers.

Methods: By using GeneCards, UALCAN, GEPIA, Kaplan-Meier Plotter, COSMIC, Regulome Explorer, String, GeneMANIA and TIMER databases, we collected and analyzed relevant data to conduct in-depth bioinformatics research on the CALR expression in Pan-cancer to assess the possibility of CALR as a potential therapeutic target and survival biomarker.

Results: We studied the CALR expression in normal human tissues, various tumors and tumor stages, and found that different expressions of CALR led to different prognosis. Mutations of CALR were widely present in tumors. CALR interacted with different genes and co-expressed with various proteins. In tumors, a variety of immune cells are closely related to CALR.



Conclusions: CALR can be used as a biomarker for predicting prognosis and a potential target for tumor molecular and immunotherapy.

Key words: CALR; cancer; immunotherapy; biomarker

23. Up-regulation of GSTT1 in Serous Ovarian Cancer Associated with Resistance to Taxol / Carboplatin

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Fudan University Shanghai Cancer Center

Serous ovarian cancer (SOC) is the most common women cancer and the leading cause of cancer-related mortality among the gynaecological malignancies. Although effective chemotherapeutics combined with surgery are developed for the treatment, the five-year survival rate is unsatisfactory due to chemoresistance. To overcome this shortcoming of chemotherapy, we established taxol and carboplatin resistant SOC cell lines for the understandings of the molecular and cellular mechanisms of chemoresistance. Here, we found that these chemoresistant cell lines showed less viability and proliferation, due to more cells arrested at G0/G1 phase. Glutathione-S-transferases-theta1 (GSTT1) was significantly upregulated in these chemoresistant cells, along with other chemoresistant genes. Meanwhile, GSTT1 expression was also significantly upregulated in the SOC patient tissues after taxol treatment, indicating this upregulation was physiologically relevant to chemotherapy. Further, suppression of GSTT1 expression by shRNA in SOC cell lines led to more sensitivity to drug treatment, through increasing divided cells and promoting cell death. Moreover, the expression of DNA topoisomerase 1 (Topo I) was in synergy with that of GSTT1 in the chemoresistant cells, and GSTT1 can bind to Topo I in vitro, which suggested GSTT1 could function through DNA repair mechanism during chemoresistance. In summary, our data imply that GSTT1 may be a potential biomarker or indicator of drug resistance in serous ovarian cancer.

Key words: GSTT1; Serous Ovarian Cancer; Drug resistance; Topo I

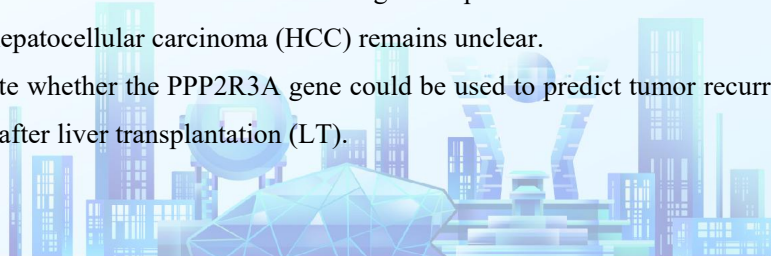
24. High expression of PPP2R3A predicts poor outcome in hepatocellular carcinoma patients after liver transplantation

Jiajia He*, Qing Zhang, Ning Jiao, Shuang Qiu

The Third Medical Center of Chinese PLA General Hospital

BACKGROUND: Protein phosphatase 2 regulatory subunit B alpha (PPP2R3A) gene has been reported in other tumors, but the influence of PPP2R3A gene expression on the occurrence, development, and prognosis of hepatocellular carcinoma (HCC) remains unclear.

AIM: To investigate whether the PPP2R3A gene could be used to predict tumor recurrence and survival of HCC patients after liver transplantation (LT).



METHODS: Collected diseased liver tissues of HCC patients after LT, as well as their clinical data and follow-up information. The immunohistochemical method was used to detect the expression of PPP2R3A protein in the tissues of 108 patients with primary liver cancer. The χ^2 test was used to analyze the relationship between PPP2R3A protein expression levels and the clinicopathological features of tumors. The Kaplan-Meier method was used to analyze overall postoperative survival. The COX proportional hazard model was used to analyze adverse prognostic factors.

RESULTS: Immunohistochemistry showed that the PPP2R3A protein was mainly expressed in the cytoplasm of HCC cells. Compared to corresponding peritumoral tissues, expression was higher in HCC tissues ($P \leq 0.001$). Correlation analysis showed that high PPP2R3A expression was correlated with preoperative serum alpha-fetoprotein (AFP) levels ($P = 0.003$), TNM- t stage ($P \leq 0.001$) and envelope invasion ($P = 0.001$). Univariate analysis showed that overall survival ($P \leq 0.001$) and recurrence-free survival ($P = 0.025$) of patients with high PPP2R3A expression (≥ 4 points) were poor compared to those with low expression (< 4 points). The overall survival rate or recurrence-free survival rate at 1, 2, and 3 years with high PPP2R3A expression were 73%, 38%, and 23%, or 31%, 23%, and 23% respectively. Multivariate analysis showed that high PPP2R3A expression (HR = 2.900, 95%CI: 1.411–5.960, $P = 0.004$) was an independent survival risk factor of HCC patients after LT, and it was also an independent predictor of postoperative tumor recurrence. This study also showed in patients with AFP ≥ 400 ng/mL, the overall survival ($P \leq 0.001$) and recurrence-free survival ($P = 0.023$) of those with high PPP2R3A expression was significantly worse compared to those with low PPP2R3A expression. When PPP2R3A expression was low, the overall survival rate ($P = 0.461$) or recurrence-free survival rate ($P = 0.072$) after LT in patients with AFP < 400 ng/mL and ≥ 400 ng/mL was no significant difference. The 1, 2, and 3- year survival rate of patients with low PPP2R3A expression and AFP < 400 ng/mL was 98%, 80%, and 69%, respectively, while patients who met Hangzhou criteria had a post-transplant 1, 2, and 3-year overall survival rate of 89%, 66%, and 55%, respectively.

CONCLUSION: High expression of PPP2R3A might be a potential marker for predicting poor prognosis of HCC after LT. Combined with serum AFP levels, PPP2R3A might enhance the accuracy of predicting HCC outcome in patients after LT and supplement the efficacy of the Hangzhou criteria.

Key words: Protein phosphatase 2 regulatory subunit B; α ; Hepatocellular carcinoma; Liver transplantation; Prognosis; Alpha-fetal protein

25. POLE2 基因通过调控 RPA3 和 WDHD1 影响膀胱癌细胞的增殖、侵袭和凋亡

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目的: 膀胱癌(bladder cancer, BCa)是常见的恶性肿瘤之一, 发病率和死亡率位居我国泌尿系统肿瘤之首, 并呈逐年上升的趋势。DNA 聚合酶 ϵ 的第二大亚基 (POLE2) 参与 DNA 复制,修复和细胞周期调控等生物功能。研究发现 POLE2 影响几种癌症发生,发展, 但是在膀胱癌中的机制尚未完全明确。我们的目的是分析 POLE2 在膀胱癌中的表达和生物学作用及其相关分子机制。

材料与方法: 收集哈尔滨医科大学附属肿瘤医院手术切除的膀胱癌和癌旁组织。通过免疫组织化学染色 (IHC), 蛋白印迹技术 (Western blot) 和实时荧光定量 PCR (qRT-PCR) 检测组织中 POLE2 的表达水平并分析相关性。检测人正常膀胱上皮样细胞 SV-HUC-1 和膀胱癌细胞系 T24,5637 中 POLE2,RPA3 以及 WDHD1 的 mRNA 和蛋白表达水平。构建沉默 POLE2 细胞系, WB 和 qRT-PCR 检测转染效率以及 POLE2, RPA3 和 WDHD1 三者之间的靶向关系。进一步分别采用 CCK-8 (Cell Counting Kit-8), 划痕实验, 克隆形成实验, Transwell 小室和流式细胞术分析沉默 POLE2 后对膀胱癌细胞增殖, 侵袭, 迁移和凋亡的影响。

结果: POLE2 基因在 25 例患者的膀胱癌组织中阳性表达率为 80.0%, 高于癌旁组织的 14.0%, 差异具有统计学意义 ($P<0.05$)。与 TCGA 数据库中 POLE2 基因在膀胱癌组织中高表达的结果相符。另外, WB 和 RT-PCR 结果证实了与正常膀胱细胞系相比 POLE2 在 T24 和 5637 膀胱癌细胞系中显著高表达。RPA3 和 WDHD1 也在膀胱癌细胞系中高表达。沉默 POLE2 基因后, RPA1 和 WDHD1 表达量下调。同时, 膀胱癌细胞的增殖减缓, 克隆数减少, 侵袭, 迁移能力明显下降, 而细胞凋亡数增加。

结论: 沉默 POLE2 基因抑制膀胱癌细胞增殖, 侵袭和迁移, 促进细胞凋亡。并可能通过靶向 PRA1 和 WDHD1 影响膀胱癌的进展。

关键词: POLE2; 膀胱癌; 增殖; 侵袭; 凋亡

26. Expression and clinical significance of PRDM2 gene methylation in ovarian cancer

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Objective: Ovarian cancer is the most fatal gynecological malignant tumor, and it is particularly important for the early diagnosis of ovarian cancer. However, the lack of specific tumor markers has become a major problem in the early diagnosis of ovarian cancer. There is increasing evidence that abnormal methylation of gene promoter plays an important role in the carcinogenic process and can silence gene expression, which is an early event in the pathogenesis of ovarian cancer. The gene promoter methylation found in tumor can be reflected in circulating cell-free DNA (cfDNA) released from tumor to peripheral blood, which is consistent with primary tumor, making cfDNA methylation a noninvasive molecular marker based on blood detection. PRDM2 is closely related to the occurrence

and development of tumor, and related research has made great progress, which has the potential as a molecular marker. Therefore, this study will explore the expression and clinical significance of PRDM2 gene promoter methylation in ovarian cancer tumor tissues and plasma cfDNA.

Methods: The tumor tissues from 56 ovarian cancer patients and 36 normal ovarian tissues were collected admitted to the affiliated Cancer Hospital of Harbin Medical University. The corresponding preoperative plasma samples were collected. The expression of PRDM2 mRNA and protein in ovarian tissues was detected by Real-time quantitative PCR (qPCR) and Western-blot, the status of PRDM2 gene promoter methylation in ovarian tissues was detected by methylation specific PCR(MSP), and the correlation between gene expression and its promoter methylation was analyzed. The status of PRDM2 gene promoter methylation in plasma cfDNA was detected by MSP, and the correlation of PRDM2 gene methylation changes in plasma cfDNA and ovarian tissues was analyzed. Moreover, to explore the relationship between PRDM2 gene promoter methylation and clinicopathological features of ovarian cancer patients, and to evaluate the diagnostic value of PRDM2 gene promoter methylation in ovarian cancer.

Results: The expression of PRDM2 was low or not present in ovarian cancer tumor tissues. However, the positive rate of PRDM2 gene promoter methylation was significantly increased, the difference was statistically significant ($P<0.05$). The frequency of PRDM2 gene methylation was 56.3% in ovarian cancer tumor tissues and 42.5% in corresponding plasma cfDNA. The promoter methylation of the PRDM2 gene is closely associated with tumor staging and lymph node metastasis. The ROC curve showed that an overall sensitivity and specificity of PRDM2 gene promoter methylation detection were 79% and 82%, respectively.

Conclusion: PRDM2 gene promoter is hypermethylated in ovarian cancer tumor tissues, but PRDM2 gene expression level is decreased. Hypermethylation of PRDM2 gene promoter is the main cause of inactivation of PRDM2 gene expression. PRDM2 gene methylation can be detected in plasma cfDNA of ovarian cancer, which is consistent with changes in tumor tissues, it provides a new pathway for noninvasive detection. Furthermore, the status of PRDM2 gene promoter methylation is associated with clinicopathological features of ovarian cancer patients, tumor staging and lymph node metastasis are important factors. And the detection of PRDM2 gene methylation has high sensitivity and specificity, it has the potential to be a molecular marker for early diagnosis of ovarian cancer.

Key words: PRDM2; gene methylation; ovarian cancer; tumor suppressor gene; diagnosis

27. Identification of a tumor-specific prognostic long non-coding RNA signature in endometrial cancer

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Objective: Long non-coding RNAs (lncRNAs) play critical roles in the development of various types of cancer. Abnormal expression of lncRNAs is associated with the prognosis of endometrial carcinoma

(EC), some of which can be further evaluated as potential biomarkers. The purpose of this study is to use bioinformatics tools to mine TCGA data, and find the specific lncRNAs that are closely related to the prognosis of EC.

Methods: edgeR package was used to identify the differentially expressed (DE) lncRNAs. Univariate and multivariate Cox regression analysis were used for survival analysis.

Results: A total of 2260 DE lncRNAs were screened in EC compared with normal tissues, of which 907 were identified as EC-specific. Seven lncRNAs (LINC01561, RP3-443C4.2, AC013463.2, AC019117.1, RP11-212I21.2, RP11-802O23.3 and RP11-259N19.1) were significantly associated with overall survival (OS). Based on these seven lncRNAs, a prognostic signature of EC was established. The patients were divided into high-risk group and low-risk group ($P<0.0001$), the survival time was significantly different.

Key words: endometrial cancer; long non-coding RNA; Cox survival analysis; prognosis; hazard ratio

28. 血清学指标在甲状腺髓样癌诊断中的应用

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目的: 探索肿瘤标志物降钙素 (CT), 癌胚抗原 (CEA), 神经元特异性烯醇化酶 (NSE), 胃泌素释放肽前体 (Pro-GRP) 和嗜铬粒蛋白 A (CgA) 在鉴别甲状腺髓样癌 (Medullary thyroid carcinoma, MTC) 中的价值。

方法: 本回顾性研究选取 2017 年 2 月至 2019 年 8 月复旦大学附属肿瘤医院检验科检测的 105 例甲状腺髓样癌, 65 例非髓样癌的甲状腺恶性肿瘤, 50 例甲状腺良性疾病, 30 例非甲状腺恶性肿瘤以及 50 例健康对照血清 CT 含量。选取其中 79 例 MTC, 30 例非 MTC 的甲状腺恶性肿瘤及 30 例健康对照者, 检测血清 CEA, NSE, Pro-GRP 和 CgA 含量。利用受试者工作曲线明确各指标区分不同组之间的曲线下面积 (AUC), 敏感性和特异性。

结果: MTC 患者 CT 含量显著高于甲状腺其他病变, 非甲状腺恶性肿瘤和健康对照。CT 区别 MTC vs. 非 MTC 患者的敏感性为 96.2%, 特异性为 99.3%, AUC 为 0.99。MTC 结节最大直径 ($>1\text{cm}$, $P=0.001$, $\text{OR}=15.74$) 与 MTC 结节个数 (>1 个, $P=0.04$, $\text{OR}=3.4$) 是 CT 升高的两个独立危险因素。CEA (AUC=0.94), NSE (AUC=0.65), Pro-GRP (AUC=0.94) 以及 CgA (AUC=0.83) 均能够区分 MTC vs. 非 MTC 的甲状腺恶性肿瘤。联合 CT, CEA, NSE, Pro-GRP 和 CgA 区分 MTC vs. 非 MTC 的甲状腺恶性肿瘤的 AUC 为 1, 敏感性 100%, 特异性 100%。

结论: CT, CEA, NSE, Pro-GRP 和 CgA 对于 MTC 的辅助诊断具有重要的意义。联合这些指标诊断 MTC 具有很高的敏感性和特异性。

关键词: 甲状腺肿瘤; 降钙素; 癌胚抗原; 神经元特异性烯醇化酶; 胃泌素释放肽前体; 嗜铬粒蛋白 A



29. 血清 N-MID 在原发性肺癌患者骨转移辅助诊断和疗效监测中的应用分析

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背景与目的: 目前临床上用于原发性肺癌患者骨转移辅助诊断的血清学标志物相对缺乏, 该研究旨在探讨血清中骨钙素 N 端中分子片段 (N-MID) 的表达水平在肺癌患者骨转移辅助诊断和疗效监测中的作用。

方法: 选取 2017 年 3 月至 2018 年 1 月在复旦大学附属肿瘤医院诊断为原发性肺癌的 231 例患者作为实验组, 其中包括 97 例肺癌合并骨转移患者以及 134 例未骨转移肺癌患者, 选取 69 例同期健康体检人员为健康对照组。利用 Logistic 多因素回归模型分析血清 N-MID、癌胚抗原 (CEA), 神经元特异性烯醇化酶 (NSE), 细胞角蛋白 19 片段 (CYFRA21-1), 碱性磷酸酶 (ALP) 等在肺癌骨转移中的相关性。

结果: 治疗前骨转移组血清 N-MID 水平明显高于无骨转移组与健康对照组 (P 均 <0.001)。Logistic 多因素分析显示, 血清 N-MID ($OR=9.265$) 和 NSE 水平 ($OR=2.688$) 是肺癌患者发生骨转移的危险因素。通过受试者工作特征 (ROC) 曲线确定血清 N-MID 的 Cut-off 值为 14.96ng/mL , 并将实验组分为 $N-MID>14.96\text{ng/mL}$ 组和 $N-MID\leq 14.96\text{ng/mL}$ 组。治疗前, 血清 $N-MID>14.96\text{ng/mL}$ 组肺癌患者的无进展生存期 (PFS) 明显低于 $N-MID\leq 14.96\text{ng/mL}$ 组患者 ($HR=2.040$)。在肺癌合并骨转移患者中, 治疗前后血清 N-MID 水平降低提示病情缓解 ($P<0.001$)。

结论: 血清 N-MID 水平与肺癌合并骨转移存在相关性, 检测治疗前后的血清 N-MID 浓度可用于肺癌患者骨转移的辅助诊断和疗效监测。

关键词: 原发性肺癌; 骨转移; 骨钙素 N 端中分子片段; 辅助诊断; 疗效监测

30. Expression of carbonic anhydrase IX and hypoxia-inducible factor 1 alpha in cystic neoplasms of the pancreas

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Background: Accurate distinction of pancreatic cystic neoplasms is essential for pancreatic cancer early detection and prevention as well as avoidance of unnecessary surgical intervention. Serous cystic neoplasms (SCNs) have no malignant potential, but mucinous cystic neoplasms (MCNs) and intraductal papillary mucinous neoplasms (IPMNs) are almost considered malignant or potentially

malignant. However, the radiologic distinction between SCNs, MCNs and IPMNs is frequently difficult. Therefore, we hypothesize that identification of biomarkers carbonic anhydrase IX (CA IX) and hypoxia-inducible factor 1 alpha (HIF-1 α) combining different clinicopathologic features will improve the differential diagnosis between cystic neoplasms.

Methods: 35 SCNs cases including 32 SCAs, 2 macrocystic SCNs and 1 VHL-associated SCN, as well as 23 MCNs cases and 14 IPMNs cases were retrospectively reviewed and analyzed. Meanwhile the expressions of CA IX and HIF-1 α in cystic neoplasms were detected with immunohistochemistry.

Results: Immunohistochemical analysis showed that CA IX was located in cytomembrane. 91.4% SCNs (32/35) were positive for CA IX, including 29 SCAs, 2 macrocystic SCNs and 1 VHL-associated SCN. 77.1% SCNs (27/35) were positive for HIF-1 α , which was located in nucleus of 24 SCAs and 2 macrocystic SCNs, but 1 VHL-associated SCN in cytoplasm. 95.7% (22/23) MCNs and 85.7% (12/14) IPMNs were positive for CA IX. Both MCNs and IPMNs with malignant were positive for CA IX. Compared to SCNs, none of MCNs and IPMNs was positive for HIF-1 α (77.1% vs. 0 and 0, all $P < 0.001$). IPMNs were significantly more common in the elderly than SCNs (median age 60 vs. 48, $P = 0.001$). MCNs occurred in women more frequently than did SCNs and IPMNs (100% vs. 91.4% and 7.1%, all $P < 0.001$). MCNs were usually larger than SCNs (median cyst size 73 vs. 37, $P = 0.003$). SCNs had a more equal distribution in the pancreas than MCNs and IPMNs. Most MCNs occurred in the body and tail of the pancreas, but IPMNs in contrast. SCNs had a benign clinical course, MCNs and IPMNs could turn into malignant variably with a high level of CA199 in serum frequently. The expressions of CA IX had negative correlation with cyst size in SCNs ($P = 0.033$). Decreased with time, the survival rate of MCNs and IPMNs gradually, the survival rate of MCNs and IPMNs was lower than SCNs, but the log-rank test demonstrated no statistical difference (Log-rank=4.870, $P = 0.088$).

Conclusions: SCNs show a dysregulation of VHL/HIF pathway but not of MCNs and IPMNs. Combining with HIF-1 α and clinicopathologic features will improve the differential diagnosis between cystic neoplasms of the pancreas.

Key words: CA IX; HIF-1 α ; cystic neoplasms; pancreas

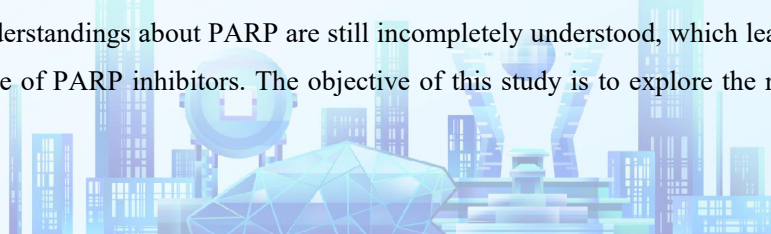
31. PARP1 is a marker for stemness suppression of platinum-resistant ovarian cancer with PARP1 inhibitor

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Objective: Although the prime mechanism underlying PARP inhibitors as anticancers drug is synthetic lethal, our understandings about PARP are still incompletely understood, which leads to a limitation of the clinical use of PARP inhibitors. The objective of this study is to explore the relationship between



PARP1 and ovarian cancer stemness, and to dig the potential use of PARP inhibitors as a stemness suppressor.

Methods: The platinum-resistant cells were established and PARP1+ platinum-resistant cells were isolated. The stemness of the cells were determined by sphere-forming capacity, the frequency of sphere-forming and tumor-initiating cells, as well as the expression of cancer stem cell markers. The ovarian cancer stem-like cells were isolated by suspension culture and magnetic-based technology with surface markers. The expression of target genes was examined by western blot and qRT-PCR, respectively. The sensitivity of the cells to platinum drugs was described by IC50 value. The target signaling was screened by qRT-PCR array. The important role of target signaling was confirmed by rescue experiment.

Results: The platinum-resistant and PARP1+ platinum-resistant cells showed enhanced stemness. The ovarian cancer stem-like cells were more resistant to platinum drugs. Overexpression of PARP1 enhanced the platinum-resistance and stemness of ovarian cancer cells and knockdown of PARP1 or PARP1 inhibitor treatment led to opposite results. PARP1 activates Hippo/YAP signaling and stabilized the protein of nuclear YAP. PARP1 did not affect the protein level or phosphorylation level of YAP in cytoplasm. Knockdown of YAP abolished the effect of PARP1 on the platinum-resistance and stemness of ovarian cancer cells.

Conclusion: PARP1 induces platinum-resistance and stemness of ovarian cancer cells by stabilization of nuclear YAP. PARP1 is a marker for suppression of platinum-resistance and stemness of ovarian cancer with PARP1 inhibitors.

Key words: Ovarian cancer; PARP1; stemness; PARP1 inhibitor; YAP

32. SEC62: 一种可能的胃癌潜在预后生物标志物

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目的: 胃癌 (GC) 在亚洲具有很高的发病率和死亡率。SEC62 是内质网膜蛋白转运装置的一部分, 参与蛋白翻译。目前已经有多项研究表明, SEC62 在多种肿瘤中高表达, 并且已经证明 SEC62 可以作为头颈部鳞状细胞癌、非小细胞肺癌、肝细胞癌等肿瘤的潜在生物标志物。但是在胃癌中, SEC62 的临床意义仍不明确。本研究旨在通过临床数据和实验室研究, 结合生物信息学方法, 探索 SEC62 在胃癌中的临床意义及预后价值。

方法: 我们通过组织芯片和免疫组化分析了 SEC62 在 220 例胃癌中的表达情况, 并针对 TCGA 数据库中的胃癌数据进行了生物信息学分析, 以此为基础探索了 SEC62 在胃癌中的表达情况以及对于预后的影响。同时, 我们对胃癌 MKN45 和 MKN74 细胞系进行 SEC62 敲低, 以观察 SEC62 对于细胞增殖和迁移的能力的影响。



结果：我们发现 SEC62 在胃癌肿瘤组织中的表达明显高于正常组织，SEC62 的表达与肿瘤大小，肿瘤浸润，淋巴结转移和疾病分期有关，SEC62 高表达患者的预后较差。多因素分析表明，SEC62 的表达和分化及疾病的分期可能会影响疾病的预后。此外，我们观察到肝癌和卵巢癌的转移灶中，SEC62 的表达明显高于原发病灶。对胃癌 MKN45 和 MKN74 细胞系进行敲低后，我们发现 SEC62 敲减显著抑制了细胞的克隆能力和迁移能力。

结论：SEC62 在胃癌中高表达，并可能促进胃癌的疾病进展和转移。SEC62 可能作为一种独立的胃癌潜在预后生物标志物。

关键词：SEC62；胃癌；预后；生物标志物

33. Identification of cerebrospinal fluid biomarkers in leptomeningeal metastasis

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Research Aim: Leptomeningeal metastasis (LM) or spread of cancer cells into the cerebrospinal fluid (CSF) presents an opportunity to study dynamic cancer cell-microenvironmental interactions in human disease. Cancer cells within the CSF disseminate throughout the nervous system, along with the infinitely dense tangle of billions of immune cell infiltrations and connections, leading to hot tumor signs in LM. The source of potential molecular biomarkers in CSF remains poorly understood. Making use of our institution wealth of patient samples and our laboratory mouse models of LM, I proposed to analyze the release of putative biomarkers into the systemic circulation, and compare CSF-derived biomarkers with those in peripheral blood and other sources to identify key molecular players and therefore effective diagnostics and therapeutic approaches in LM.

Method: My proposed study has three main significant points: First, we provided direct evidence that proinflammatory cytokines and innate immunity proteins contributes to CSF inflammatory phenotype. Second, I exploited single-cell RNA sequencing (scRNA-seq) technology, to systematically illustrate the dynamic inflammatory signaling between cancer cells and immune cells both in human disease and in mouse models. Third, the research uncovered the more concentrated proteins in this compartment, the cancer-derived innate immunity proteins served as important biomarkers in CSF within LM, which can be regulated by macrophages-derived proinflammatory cytokines.

Results: This will shed light on the roles of CSF biomarkers and their effects on the development of LM.

Conclusions: Together, these results will provide molecular insights into the microenvironmental biomarkers of leptomeningeal metastasis due to the fast accumulation of the secreted proteins by cancer cells and immune cells suggesting novel clinical diagnosis and pharmacologic targets to treat cancer cells within the leptomeningeal space.



Key words: biomarkers; cerebrospinal fluid; leptomeningeal metastasis; inflammation; tumor microenvironment

34. 消癌平注射液通过调控血管生成相关因子的表达来抑制肿瘤生长

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目的: 肝细胞癌作为全球癌症相关死亡的第三大原因, 每年至少 70 万人死亡。治疗上多以西医治疗为主, 而中医药在治疗肝细胞癌上也有一定成效。其中, 通关藤在治疗癌症方面有突出作用, 且临床上通关藤的使用多以提取物注射液的形式存在, 例如: 消癌平注射液, 但其在肝癌方面的作用机制尚未完全明确。本文主要在基因组学结果的基础上通过体内、体外实验来探讨消癌平注射液对于肝细胞癌药效及作用机制, 为中医药治疗肝细胞癌提供科学依据。

方法: 对两株肝癌细胞 MHCC97H 和 HepG2 细胞进行药物干预后收集细胞及细胞上清, 通过 CCK8 实验及 Transwell 实验来筛选后续用药浓度以及观察消癌平注射液在细胞功能学方面的影响。通过基因组学测序得到药物干预后差异基因的变化情况, 并基于肿瘤生长的相关特性对差异基因进行筛选和富集分析。随后基于差异基因富集分析结果, 通过 RT-PCR 及 Western-blot 实验进行验证。进一步进行成管实验和鸡胚尿囊膜实验, 通过肿瘤细胞上清干预内皮细胞 HUVEC 及鸡胚尿囊膜观察消癌平注射液对于血管生成的影响。体内实验建立 PDX 模型小鼠, 并进行药物干预, 观察小鼠一般情况, 包括体重、活动度等, 收集样本通过 HE 染色及免疫组化染色检测相关指标。

结果: 消癌平注射液可以抑制肿瘤细胞增殖及迁移; 同时, 消癌平注射液主要通过下调血管生成因子 VWF、VEGFA、PDGFRB 的表达来抑制肿瘤细胞生长; 此外, 消癌平注射液可以有效减少内皮细胞的成管数量、分支数量及长度; 且消癌平注射液可以抑制鸡胚尿囊膜的血管生成; 在小鼠肿瘤中, 消癌平注射液能缩小肿瘤大小, 有效扩大肿瘤内坏死面积; 且在小鼠肝脏组织样本免疫组化结果中发现, Ki67、CD31、VWF、PDGFRB 的表达均呈剂量依赖性减弱。

结论: 由于血管生成在肿瘤的发生发展中占据着重要作用, 而消癌平注射液可以通过调控 VEGFA、VWF、PDGFRB 的表达水平, 来抑制肿瘤血管生成, 从而进一步抑制肿瘤的生长。

关键词: 消癌平注射液; 肝细胞癌; 血管生成

35. 内镜黏膜下剥离术与腹腔镜切除术治疗小于 2 cm 的胃间质瘤的远期疗效临床研究

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背景与目的：腹腔镜切除术（LAP）和内镜黏膜下剥离术（ESD）常用于切除胃肠道小间质瘤（GIST）。然而，相对而言，LAP 或 ESD 哪一个术式更具优势是存在争议的。本研究主要是评估 ESD 和 LAP 对胃小间质瘤（小于 2 cm）的疗效，并提供两种方法的长期疗效对比研究。

方法：我们收集了来自中国广州南方医院的 398 例胃小间质瘤（2008 年至 2019 年）接受 ESD 或 LAP 术式的患者的所有数据。进行随访并收集有关其复发率的信息，同时也收集了其临床病理学特征和手术相关并发症的资料。

结果：398 例患者中，234 例（58.79%）接受了 ESD 治疗，164 例（41.21%）接受了 LAP 治疗。其中患者的临床病理特征无显著差异。统计学分析发现患者性别，年龄，肿瘤大小和位置在 LAP 和 ESD 两组之间没有显著性差异，患者随访时间也无显著性差异（ESD 组为 6.65 ± 1.84 年，LAP 组为 6.19 ± 1.53 年， $P=0.24$ ）。然而，两组在手术时间上有显著性差异（ 61.42 ± 32.85 min vs. 78.68 ± 39.76 min, $P=0.03$ ），失血量（ 6.58 ± 12.16 ml vs. 16.35 ± 17.06 ml, $P=0.02$ ）和住院时间（ 5.07 ± 2.15 天 vs. 9.84 ± 3.80 天, $P<0.001$ ）。并发症发生率（定义为穿孔或大出血）显示 ESD 和 LAP 组之间无显著性差异（2.14% vs. 1.22%; $P=0.85$ ）。ESD 和 LAP 组的复发率分别为 2.56% 和 1.22%; $P=0.56$ 。同时，Kaplan-Meier 曲线显示两组之间无显著性差异（ $P=0.86$ ）。

结论：长期临床随访研究显示，与 LAP 相比，ESD 可能是切除胃小间质瘤的首选术式。然而，我们还需要进行长期随机对照临床试验。

关键词：内镜黏膜下剥离术；腹腔镜切除术；胃小间质瘤

36. Long-term outcomes of endoscopic submucosal dissection versus laparoscopic resection for gastric stromal tumors less than 2 cm

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Background & Aims: Laparoscopic resection (LAP) and endoscopic submucosal dissection (ESD) is commonly used to remove small gastrointestinal stromal tumors (GISTs). However, whether LAP or ESD has more efficient outcome for small GISTs is controversial. Therefore, our Aim was to evaluate the efficacy of ESD and LAP for small GISTs and provided long-term outcomes of the two methods.

Methods: All data from 398 patients who underwent ESD or LAP for small GISTs (between 2008 and 2019) were collected from Nanfang hospital, Guangzhou, China. We made telephone calls to collect information about their recurrence rate. Clinicopathological characteristics, recurrence rate and surgical outcome were collected and blindly measured for each procedure.

Results: Among the 398 patients, 234 (58.79%) received ESD treatment, and 164 (41.21%) received LAP treatment. The clinicopathological characteristics of the patients were well balanced. There was no significant difference between LAP and ESD groups according to gender, age, tumor size and location. There was also no significant difference in follow-up time (6.65 ± 1.84 years in ESD vs. 6.19 ± 1.53 years in LAP group, $P=0.24$). However, there was a significant difference between the two groups in operating time (61.42 ± 32.85 min vs. 78.68 ± 39.76 min, $P=0.03$), estimated blood loss (6.58 ± 12.16 ml vs. 16.35 ± 17.06 ml, $P=0.02$) and hospital stay (5.07 ± 2.15 days vs. 9.84 ± 3.80 days, $P<0.001$). The complication rate (defined as perforation or massive hemorrhage) showed no significant difference among ESD and LAP group (2.14% vs. 1.22%; $P=0.85$). The recurrence rate of ESD and LAP group was 2.56% and 1.22%; $P=0.56$. Meanwhile, Kaplan–Meier curves for disease-free survival test showed no significant difference between two groups ($P=0.86$).

Conclusions: Long-term follow-up showed that ESD can be a more preferable technique for resection of small gastric stromal tumors compared with LAP. However, long-term randomized controlled trials are further needed.

Key words: endoscopic submucosal dissection; laparoscopic resection; small gastrointestinal stromal tumor

37. 胸苷激酶 1 检测在肝癌诊断及预后中的价值研究

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目的: 研究胸苷激酶-1 (TK-1) 在肝细胞肝癌 (HCC) 中的诊断及预后价值。

方法: 总共收集了 123 名 HCC 初诊患者的血清标本, 以及 80 名肝良性病变患者和 98 名健康人群对照标本, 检测并比较了不同人群的血清 TK-1 (sTK-1) 的水平, 分析 TK-1 在肿瘤诊断中的特异性和敏感性; 结合 HCC 患者的 AFP, CA19-9 等数据, 使用 ROC 曲线建立模型, 分析 sTK-1 在 HCC 中的诊断价值; 检测 HCC 患者术前、术后、术后 1 个月, 3 个月, 6 个月的 sTK-1 水平, 并随访术后 12 个月肿瘤复发情况, 分析 sTK-1 在 HCC 患者手术疗效评价和预后管理中的作用。

结果: HCC 患者 sTK-1 中位水平为 2.38 pM, 阳性率为 55.3%, 显著高于肝良性病变患者的中位水平 1.50 pM 和健康人群的 1.32 pM (P 均 <0.001); TMN III-IV 期 HCC 患者 sTK-1 中位水平 2.93 pM, 高于 I-II 期患者的 1.94 pM ($P=0.019$); HCC 患者 sTK-1 的 AUC 为 0.7983, 联合 AFP 诊断的 AUC 为 0.9221; 术前 sTK-1 阴性患者的无进展生存期 (PFS) 显著高于 sTK-1 阳性患者 ($P<0.001$); 在 HCC 患者 sTK-1 水平动态监测中, 肝癌患者术后 sTK-1 水平比术前有明显的下降 ($P<0.001$), 术后复发或转移患者的 sTK-1 水平在术后 6 个月内显著高于术后无进展患者 (P 均 <0.001)。



结论: sTK-1 能够辅助诊断 HCC, sTK-1 联合 AFP 检测可以进一步提高 HCC 诊断的特异性及敏感性。术前 sTK-1 是独立的 HCC 复发风险预测指标。术后半年内 sTK-1 水平的动态变化能够帮助肝癌患者评价手术疗效和进行预后分层。

关键词: 肝癌; 胸苷激酶-1; 肿瘤标志物; 诊断; 预后

38. 未手术肝癌患者放化疗的选择策略

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分析影响放化疗对未手术肝癌患者预后的相关因素, 为此类肝癌患者提供较佳的放化疗方式。

方法: 基于 SEER 数据库, 回顾性分析了 2015 年至 2020 年符合入排标准的 3286 例患者的临床数据资料, 组间比较采用 X² 检验, Kaplan-Meier 法绘制生存曲线, 单因素分析采用 Log-rank 检验, 多因素分析采用 COX 回归模型。

结果: 单因素分析显示, 未手术肝癌患者的预后与肿瘤分化程度, 临床分期, M 分期, 肿瘤大小, 放疗, 化疗及放疗+化疗有关($P<0.05$)。多因素分析显示, 肿瘤分化程度, 临床分期, M 分期, 肿瘤大小是影响未手术肝癌患者的独立危险因素, 放疗, 化疗及放疗+化疗是未手术肝癌患者的独立保护因素。K-M 生存分析显示选择放化疗的未手术肝癌患者比未选择放化疗的患者中位生存期(中位 OS) 较长($P<0.05$); 放疗+化疗对高分化+中分化, III+IV, M1 及肿瘤直径 $\geq 5\text{cm}$ 的患者中位 OS 较长($P<0.05$); 放疗对 M0 及肿瘤直径 $\leq 2\text{cm}$ 的患者 OS 较长($P<0.05$)。

结论: 相对于未选择放化疗的未手术肝癌患者, 选择不同放化疗方式的患者均能显著提高生存率及中位 OS。处于高分化+中分化组, III+IV 组, M1 组及肿瘤直径 $\geq 5\text{cm}$ 组的未手术肝癌患者选择放疗+化疗的预后更好。M0 及肿瘤直径 $\leq 2\text{cm}$ 的未手术肝癌患者选择放疗的预后更好。

关键词: 肝细胞肝癌; 化疗; 放疗; 预后; SEER 数据库。

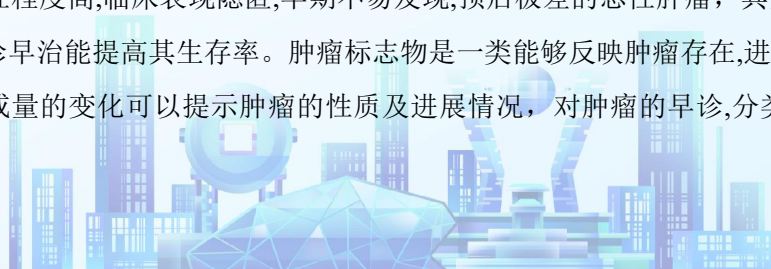
39. 胰腺癌外周血肿瘤标志物研究进展

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胰腺癌是一种恶性程度高, 临床表现隐匿, 早期不易发现, 预后极差的恶性肿瘤, 其发病率和病死率逐年升高, 早诊早治能提高其生存率。肿瘤标志物是一类能够反映肿瘤存在, 进展或预后的物质, 它们的出现或量的变化可以提示肿瘤的性质及进展情况, 对肿瘤的早诊, 分类, 预后判断及治疗



指导都有重要作用。从组织或血清中发现和鉴定具有更高灵敏度和特异性的胰腺癌相关标志物，是目前胰腺癌研究的热点领域。本文就近年胰腺癌外周血肿瘤标志物的研究现状作一综述。

关键词： 腺癌；外周血；肿瘤标志物；早期诊断

40. L1- ATP8B1 通过调控线粒体代谢促进肺鳞癌恶性进展

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背景：体细胞长散布元件-1 (LINE-1) 逆转录转座是一种基因重排过程，与基因干扰和肿瘤发生相关。我们之前的研究表明，LINE-1 逆转录转座在肺鳞癌中发生频率高，但其分子机制尚不清楚。本研究中，我们探索 LINE-1-ATP8B1 (L1-ATP8B1) 在肺鳞癌发生发展中的功能与作用机制。

方法：首先在 134 例肺鳞癌样本中分析 L1-ATP8B1 与预后及临床病理分期的相关性。通过 nCounter® PanCancer IO-360™ 比较了 24 例 L1-ATP8B1+/-肺鳞癌样本的基因表达谱。此外，在肺鳞癌细胞系 H520 和 SK-MES-1 中过表达 L1-ATP8B1，分别在体外和体内研究 L1-ATP8B1 的生物学功能。最后，我们研究了特异性逆转录抑制剂奈韦拉平 (NVR) 在体内外的抗肿瘤功效，以确定其在肺鳞癌中的治疗意义。

结果：肺鳞癌组织样本分析表明 L1-ATP8B1 与不良预后显著相关，与肿瘤 TNM 分期也明显相关。nCounter® PanCancer IO-360™ 芯片数据表明，L1-ATP8B1+组织中，代谢应激上调，并且增殖能力增强，凋亡与自噬减弱。细胞和动物实验表明，L1-ATP8B1 通过干扰 ATP8B1 基因的表达和功能，在体外调控线粒体代谢，促进 ROS 生成，进而促进肿瘤细胞增殖并抑制凋亡，在体内促进肿瘤生长和转移。此外，特异性逆转录抑制剂 NVR 能够有效的抑制肿瘤代谢应激现象，抑制 ROS 生成，进而抑制肿瘤的生长和转移。

结论：总之，L1-ATP8B1 是肺鳞癌中高频的基因组事件，可促进体外和体内肺鳞癌的发生发展，这表明 LINE-1 有望成为肺鳞癌的诊断标志物和治疗靶点。

关键词： 肺鳞癌；逆转录转座；LINE-1；ATP8B1；代谢应激；逆转录抑制剂

41. 肝细胞肝癌中肿瘤相关巨噬细胞的空间分布模式对预后的影响

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背景：肿瘤相关巨噬细胞（tumor-associated macrophages, TAMs）是肝细胞肝癌（hepatocellular carcinoma, HCC）组织中最丰富的免疫细胞之一，其特点是具有可塑性和功能的多样性。目前的测序研究显示 TAMs 在表型和基因表达水平存在高度的异质性，但是这些测序技术破坏了癌组织的空间结构，目前关于 TAMs 在 HCC 组织中的空间分布特征及其对 HCC 患者预后的影响尚无研究报道。

方法：收集 253 例 HCC 蜡块样本和包含 175 例 HCC 样本的组织芯片，同时收集患者的临床病理资料，随访患者的复发和生存情况，多色免疫荧光染色 HCC 细胞和 TAMs 表面标志物从而定位 HCC 细胞和 TAMs 的位置，利用 StrataQuest 软件分析 TAMs 与 HCC 细胞的空间分布的不同特征，分析这些特征对 HCC 患者复发生存时间和总生存时间的影响，以及与临床病理指标的关联性。

结果：在 HCC 癌组织内，TAMs 的空间分布具有异质性。根据 TAMs 的空间分布特点和浸润数量，可将 TAMs 的空间分布模式分成 4 类：分散低浸润型、分散高浸润型、环绕低浸润型和环绕高浸润型。其中，无论 TAMs 是分散型还是环绕型，TAMs 高浸润的 HCC 患者，其无复发生存时间显著低于 TAMs 低浸润的患者，而 TAMs 为环绕高浸润型的 HCC 患者的无复发生存时间和总生存时间均显著低于其他三种情况。我们鉴定出 TAMs 环绕高浸润型 HCC 的特征结构 MCTC，可有效预测 HCC 患者的复发。在本院 253 例和外院 175 例 HCC 样本中，均证实 MCTC 阳性 HCC 患者的无复发生存时间和总生存时间较 MCTC 阴性患者显著缩短，可以作为影响 HCC 患者总生存时间和无复发生存时间的独立危险因素。同时发现 MCTC 与肿瘤大小，微血管浸润，卫星结节，BCLC 分期和远处转移等临床病理指标显著相关，并且 MCTC 阳性 HCC 患者肝静脉血中 CTC 的数量明显高于 MCTC 阴性患者。

结论：在 HCC 组织内，TAMs 空间分布模式具有显著异质性，环绕高浸润型的 TAMs 分布模式与 HCC 复发显著相关。MCTC 是 TAMs 环绕高浸润型 HCC 的特征结构，不仅是 HCC 的独立预后危险因素，而且与临床侵袭特征显著相关。

关键词：肝细胞肝癌；肿瘤相关巨噬细胞；空间分布

42. The real-world research of lung cancer-associated autoantibodies and serum tumor markers

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Background: Lung cancer is one of the most common malignant tumors in the world, and it is also the main cause of death for both sexes. Early detection and treatment are considered to be the main means to reduce mortality. At present, the strategy of lung cancer screening is conducting low-dose computed tomography (LDCT), however there is risk of false positivity and radiation exposure. In order to avoid

these problems, some hematological biomarkers are used in the auxiliary diagnosis and screening of lung cancer. Currently, serum tumor markers and seven autoantibodies are widely used clinically.

Materials and Methods: Enzyme-linked immunosorbent assay (ELISA) is used to detect the expression levels and positive expression rate of seven autoantibodies (AABs) and tumor markers in serum of 354 patients with lung cancer and 108 patients with benign pulmonary diseases in the real world.

Results: Through the analysis of real-world data, the sensitivity, specificity, PPV and area under ROC curve of seven AABs were 30.0%, 84.3%, 86.3% and 0.61 respectively; the sensitivity of seven AABs combined with tumor markers was 68.6%, the specificity was 52.8%, and the area under the ROC curve was 0.72. The positive expression rate of seven AABs in patients with lung cancer was significantly higher than those with benign expression diseases (30.1% vs. 15.7%). Combined seven AABs with tumor markers, the positive rates increased to 68.6%. The positive expression of seven AABs was affected by clinical features and pathological stages, among which the expression rate of stage I was the lowest, only 17.1%.

Conclusion: Through the analysis of real-world data, the value of seven AABs as auxiliary diagnosis of lung cancer has been affirmed. However, due to its low sensitivity and susceptibility to clinical features, its application in lung cancer screening is limited. After the combination of tumor markers, although the sensitivity increased, but the specificity decreased, the false positive rate increased, and it was easily affected by clinical features, so the combination of seven AABs and tumor markers in lung cancer screening still needs further research.

Key words: Lung cancer; Seven autoantibodies; Serum tumor markers; Diagnosis; Early screening

43. 早发性胃癌临床病理分析

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目的: 分析早发性胃癌临床病理特征。

方法: 收集 2010-2019 在本院进行治疗的早发性胃癌患者 1143 例, 收集病例的临床病理包括肿瘤部位,病理类型,转移等信息, 并对相关信息进行分析。

结果: 1143 例早发性胃癌病例中, 发病年龄均小于等于 45 岁, 其中男性 494 例, 女性 649 例。按血型分类, 1143 例患者分别有 454 例 A 型 (39.7%), 87 例 AB 型 (7.6%), 182 例 B 型 (15.9%) 和 379 例 O 型 (33.6%), 另 41 例患者 (3.6%) 无血型检测记录。A 型血患者比例最高, 其次是 O 型血患者, 各种血型的男女之间无性别差异。肿瘤发生部位从多到少依次是胃体部, 胃窦部, 胃角, 胃底贲门。男性病例中胃窦部发病人数最多, 其次是胃体; 女性中以胃体部发病最多, 其次是胃窦。各种病理类型中发病人数从多到少依次是低分化腺癌, 混合型, 印戒细胞癌, 中-低分化腺癌, 中分化腺癌等。女性混合型和印戒细胞型发病率高于男性。女性早发胃癌患者的淋巴转移和远处转移率均显著高于男性。男性病例中有家族史的比例高于女性有家族史的比例,

同时男性患者烟酒生活史比例远高于女性患者。男女患者中 ERBB2 阳性率都比较低（1.4-2.0%），两者无显著差异。幽门螺旋杆菌感染阳性率男女之间无显著差异。在首次就诊的早发性胃癌病例中，17.45%患者仅出现 CA125 升高，13.2%的患者仅出现 CA724 升高，9.5%的患者仅出现 CA199 升高。

结论：本研究分析显示，早发性胃癌患者中 A 型血患者最多。女性患者胃体部发病最多，混合型和印戒细胞型高于男性，且更多出现淋巴转移和远处转移，显示早发性胃癌女性患者恶性程度高，受遗传因素影响多；早发性胃癌男性患者胃窦部发病人数最多，且烟酒生活史和家族史均高于女性，显示男性病例受环境影响甚于女性，同时遗传也是影响男性发病的重要因素。27%的早发性胃癌患者首诊检出非胃癌标志物，显示在胃癌肿标检测中，不能忽视非胃癌标志物的出现，这可能是胃癌的信号。

44. 综合分析消化系统肿瘤共同的差异表达基因特征

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目的：应用生物信息学分析技术筛选影响消化系统肿瘤的关键基因，探究其在消化系统肿瘤中的表达与功能，并分析其对患者生存预后的影响。

方法：通过 GEO2R 对 GEO 数据库中胃癌,结直肠癌,肝癌,食管癌和胰腺癌的微阵列数据集进行分析和筛选，筛选出每种肿瘤的差异表达基因，Venn 图取交集后确定五种消化系统肿瘤共同的差异表达基因作为关键基因。基于 TCGA 和 GTEx 数据库验证关键基因在消化系统肿瘤组织与正常组织中的表达差异和生存预后分析；通过 STRING 在线工具构建关键基因的蛋白相互作用 (PPI)网络，并进行 GO 功能富集分析。

结果：Venn 图显示胎盘特异性蛋白 8(PLAC8)是五种消化系统肿瘤共同的差异表达基因。与正常组织相比，PLAC8 在胃癌,结直肠癌,胰腺癌组织中高表达，在肝癌,食管癌组织中低表达。PLAC8 表达水平与消化系统肿瘤患者总生存率呈负相关，差异具有统计学意义($P<0.05$)。PPI 网络图发现 10 个蛋白与 PLAC8 相互作用密切，且相互作用分值均大于 0.9。GO 富集分析结果显示 DEGs 的生物过程富集在中性粒细胞脱粒,防御反应等，细胞组成为嗜天青颗粒腔,胞外区等，分子功能为蛋白质结合等。

结论：PLAC8 在消化系统肿瘤中存在差异表达，且高表达组患者预后不良；有望成为消化系统肿瘤患者早期诊断,治疗及判断预后的候选分子靶标。

关键词：消化系统肿瘤；胎盘特异性蛋白 8(PLAC8)；生物信息学；差异表达；生存预后

45. 基于 DNA/RNA 双测序的甲状腺癌驱动基因变异谱分析

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背景: 甲状腺癌是一类多基因病, 多种基因变异参与甲状腺癌的发生和发展, 其中最多见的变异类型是基因突变和融合。近年来随着高通量测序技术的普及, 甲状腺癌的基因变异谱研究得到越来越多的关注。甲状腺良恶性结节鉴别依赖基因变异谱的差异, 但既往多针对 DNA 开展单基因检测, 而利用高通量测序, 结合 DNA/RNA 开展双测序的工作报道不多。本研究旨在应用二代测序和生物信息学方法探究甲状腺癌与良性结节的突变谱差异, 在分子层面寻找能够辅助甲状腺良恶性结节鉴别的分子标志物。并且进一步通过对二代测序结果的统计, 确定样本中是否有驱动基因突变和融合共突变的现象。

方法: 本研究收集了 187 例甲状腺结节以及 81 例正常甲状腺样本的 DNA 和 RNA, 根据 B 超和细针穿刺活检/病理学结果将样本分为癌和良性结节。通过二代测序技术进行基因变异检测, 并且利用生物信息学方法对检测结果进行分析。统计各组突变基因的突变占比以及基因融合的发生频率, 进一步分析各突变基因以及融合与甲状腺癌临床病理特征的相关性。

结果: 共检出突变基因 40 个, 主要包括驱动基因, DNA 损伤修复基因, 免疫相关基因, 染色体重塑相关基因和激素相关基因等。其中, BRAF, ZNF717, TERT, GGT1, CHEK2, OTUD4, RET 蛋白激酶域的突变占比和基因融合的发生频率均显著高于可疑良性结节, 而且 RET 蛋白激酶域突变和 GGT1 突变均与甲状腺癌淋巴结转移呈正相关。检出融合 14 例包括 CCDC6-RET, NCOA4-RET, ETV6-NTRK3 和 TPM3-NTRK1 四种融合类型。癌组织中, BRAF 突变与融合呈显著负相关, 但在存在 ATM 突变的样本中存在 BRAF 或 RAS 突变与融合共变异的现象, 并且共变异与淋巴结转移显著相关。

结论: 甲状腺癌的基因变异特征与可疑良性结节存在明显差异, 虽然癌组织和可疑良性结节在部分基因的突变占比上差异不显著, 但是在癌组织中 BRAF, TERT, ZNF717, GGT1, CHEK2, OTUD4, RET 以及融合基因的突变占比均显著高于可疑良性结节, 这些基因或可以辅助甲状腺结节良恶性的鉴别。甲状腺癌中常见驱动基因 BRAF 或 RAS 突变和融合互斥, 但在 ATM 基因突变甲状腺癌中存在驱动基因共变异, 并与淋巴结转移显著相关。

关键词: 甲状腺癌; 甲状腺良性结节; 基因突变; 基因融合; 二代测序

46. 髓系特异性 SOCS3 基因敲除小鼠的构建及应用

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目的：运用 Cre-Loxp 基因敲除系统，构建髓系特异性 SOCS3 基因敲除的小鼠，为探索 MDSCs 促肿瘤作用机制和开发靶向 MDSCs 治疗策略提供研究基础。

方法：利用基因打靶技术构建 SOCS3^{fl/-}小鼠，将 SOCS3^{fl/-}小鼠自交获得 SOCS3^{fl/fl}小鼠，SOCS3^{fl/fl}小鼠与 Lyz2-Cre 小鼠进行杂交，获得的 SOCS3^{fl/-}-LysM-Cre 鼠再进行自交，对子代小鼠基因型进行 PCR 法鉴定，Western Blot 验证基因敲除效果，流式细胞术检测髓系特异性 SOCS3 敲除小鼠骨髓中 eMDSCs 比例及对 T 细胞的抑制作用，并在髓系特异性 SOCS3 基因敲除小鼠的基础上分别构建乳腺癌、肺癌和黑色素瘤三种 eMDSCs 高浸润的荷瘤鼠模型，流式细胞术检测肿瘤中 eMDSCs 数量。

结果：PCR 鉴定结果符合预期，获得 SOCS3^{fl/fl}-LysM-Cre 鼠，Western Blot 检测表明 SOCS3 基因在该小鼠髓系细胞中被成功敲除，流式结果表明 SOCS3 敲除的小鼠骨髓中 eMDSC 的比例升高，并具有同肿瘤原位 eMDSCs 一致的免疫抑制功能。在三种髓系特异性 SOCS3 基因敲除荷瘤鼠模型的肿瘤组织中 eMDSCs 数量显著增加。

结论：通过髓系特异性 SOCS3 基因敲除可成功构建 eMDSC 高浸润荷瘤鼠模型，可为后续研究 eMDSCs 促肿瘤作用机制和靶向 eMDSCs 治疗提供重要的动物模型。

关键词：Cre-Loxp 系统；SOCS3 基因；组织特异性；小鼠；MDSCs

47. 环状 RNA circ-CCDC85A 通过调控白介素 6 受体和 STAT3 影响乳腺癌生物学行为的机制研究

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目的：研究环状 RNA circ-CCDC85A 在乳腺癌组织和细胞中的表达及其对乳腺癌细胞增殖、迁移和侵袭能力的影响，探讨 circ-CCDC85A 通过与 miRNA 相互作用调控其下游靶基因白介素 6 受体和 STAT3 的表达进而揭示 circ-CCDC85A 在乳腺癌中发挥抑癌作用的可能机制。

方法：采用 RT-PCR 和 qRT-PCR 法检测 circ-CCDC85A 在乳腺癌组织和细胞中的表达。采用 Sanger 测序鉴定 circ-CCDC85A 的环化剪接点序列。RNase R 实验验证 circ-CCDC85A 在乳腺癌细胞中的特性。采用 CCK-8 实验、平板克隆形成实验、划痕愈合实验以及 Transwell 实验检测过表达或敲低 circ-CCDC85A 对乳腺癌细胞增殖、迁移和侵袭能力的影响。通过 CircNet 在线数据库预测可能与 circ-CCDC85A 相互作用的 miRNA 分子。采用 RIP 实验和放线菌素 D 实验验证 circ-CCDC85A 是否能与 miR-660-3p 相互作用。采用双荧光素酶报告基因实验验证 miR-660-3p 是否能与白介素 6 受体基因和 STAT3 基因相互作用。通过挽救实验检测过表达 miR-660-3p 和敲低 circ-CCDC85A 对乳腺癌细胞增殖、迁移和侵袭能力的影响。



结果: 乳腺癌患者肿瘤组织中 circ-CCDC85A 的表达明显低于癌旁正常组织, 而且 circ-CCDC85A 的表达水平与患者的病理分级、临床分期、淋巴结转移和远处转移显著相关。过表达 circ-CCDC85A 能抑制乳腺癌细胞的增殖, 迁移和侵袭能力; 敲低 circ-CCDC85A 能增强乳腺癌细胞的增殖, 迁移和侵袭能力。在乳腺癌细胞中 circ-CCDC85A 可与 miR-660-3p 互相结合。miR-660-3p 可直接靶向白介素 6 受体和 STAT3, 并至少部分通过抑制白介素 6 受体和 STAT3 的表达来发挥抑癌作用。

结论: 环状 RNA circ-CCDC85A 在乳腺癌组织中表达下调, 且能抑制乳腺癌细胞的增殖、迁移和侵袭能力, 并可通过作为 miR-660-3p 的分子贮库, 促进 miR-660-3p 对白介素 6 受体和 STAT3 的靶向调控, 从而发挥其在乳腺癌中的抑癌作用。我们的研究提供了 circ-CCDC85A 作为“miRNA 贮库”的新证据, 也为乳腺癌的研究提供了新的潜在生物标记物和治疗靶点。

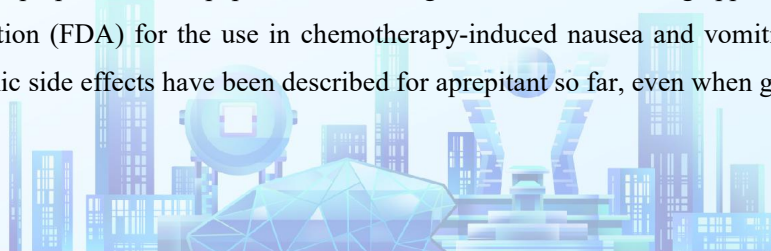
关键词: circ-CCDC85A; 白介素 6 受体; STAT3; 乳腺癌

48. Alternatively activated (M2) macrophage express SP to promote tumour growth and invasiveness and can be inhibited by aprepitant in Esophageal cancer

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Background & Aims: The role of alternatively activated (M2) macrophages on pro-tumor phenotypes have been well documented in many cancer except esophageal cancer (ECA). Considering their close relationship with chronic tissue injuries as well as enhanced tumor invasiveness and growth, we aimed to investigate the direct effect of M2 macrophages on ECA. Besides, multidrug resistance presents a major problem in ECA, and new anti-tumor strategies are desperately needed. The substance P (SP)/neurokinin-1 receptor (NK1R) complex has been discovered to be pivotal in the development of a variety of human cancers, and NK1R antagonists, such as the clinical drug aprepitant, are promising future anticancer agents. Yet, the role of the SP/NK1R complex as a potential anticancer target in ECA is still unknown. The peptide substance P (SP) is a widely distributed neuronal transmitter that, after binding specifically to the neurokinin-1 receptor (NK1R), triggers a broad variety of functions. Recently, it has become apparent that SP can induce tumor cell proliferation, angiogenesis, and migration via the NK1R, and that the SP/NK1R complex is an integral part of the cancer cell itself and its tumor microenvironment. Therefore, the use of NK1R receptor antagonists as a novel and promising approach for treating patients with cancer is currently under intense investigation. Aprepitant, a non-peptide NK1R antagonist, is a clinical drug approved by the Food and Drug Association (FDA) for the use in chemotherapy-induced nausea and vomiting. Importantly, no significant toxic side effects have been described for aprepitant so far, even when given in high doses.



Methods: M2 macrophages in 25 ECA clinical specimens were quantified using immunohistochemistry and quantitative PCR. The pro-tumour functions and the underlying molecular mechanisms of M2 macrophages in ECA were investigated in vitro co-culture system. We used the three Human ECA cell lines TE1, KYSE150, and KYSE170, as previously described. Cell proliferation was evaluated using CCK-8, We also used transwell, DAPI staining, flow cytometric to detect the growth, invasiveness and apoptosis. Human tumor samples from 25 adult with esophagus cancer were analyzed by quantitative PCR to detect the SP/NK1R.

Results: M2 macrophage express SP to promote tumor growth and invasion, therapeutic targeting with the NK1R antagonists aprepitant, led to growth inhibition, invasion weakened and apoptosis in TE1, KYSE150, and KYSE170 cells in a dose-dependent manner. Intriguingly, ECA cells predominantly expressed the truncated splice variant of NK1R. Human fibroblasts showed only dismal NK1R expression and were significantly more resistant. Stimulation of Esophagus cells with SP, NK1R's natural ligand, caused increased growth rates and abrogated the anti-proliferative effect of NK1R antagonists. Expression analysis of 25 human esophagus cancer samples confirmed the clinical relevance of NK1R, we found the expression were significantly higher for the tr-NK-1R. Most importantly the NK1R antagonists induce apoptosis in Esophagus cancer cells

Conclusions: M2 macrophages contribute to poor prognosis in ECA and promote tumour invasiveness through SP. Besides, for the first time, we describe the NK1R in its truncated splice variant as a potent target in human esophagus cancer cells and an inhibitory effect in vitro by NK1R antagonists.

Key words: M2 macrophages; Esophagus cancer; Truncated neurokinin-1 receptor; Aprepitant

49. MicroRNA-26b-3p 抑制食管癌鳞状细胞增殖和迁移的机制研究

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目的: MicroRNAs 在肿瘤的发生发展中发挥重要作用, 但 microRNA-26b-3p (miR-26b-3p) 在食管鳞状细胞癌 (esophageal squamous cell carcinoma, ESCC) 中的作用机制尚不清楚。本研究旨在检测 miR-26b-3p 在 ESCC 组织中的表达水平, 探讨其对 ESCC 细胞增殖, 侵袭和迁移能力的影响和分子机制, 及其表达的调控机制。

方法: 选取河北医科大学第四医院 2018 年 4 月 1 日~2018 年 12 月 25 日手术切除的 ESCC 组织及相应癌旁组织各 60 例, 利用实时荧光定量 PCR 检测 ESCC 组织, 癌旁组织和 ESCC 细胞中 miR-26b-3p 的表达。选取 miR-26b-3p 表达水平低的 TE1 和 KYSE150 食管癌细胞转染 miR-26b-3p mimics, 并设立阴性对照。利用细胞增殖实验, 划痕愈合实验和 Transwell 实验检测 miR-26b-3p 对 TE1 和 KYSE150 细胞增殖, 迁移和侵袭能力的影响, 荧光素酶报告基因分析检测 miR-26b-3p 与转录激活因子 3 (Activator of Transcription 3, STAT3) 的 3'UTR 的结合情况。随后同时转染

miR-26b-3p mimics 和 pcDNA3.0-STAT3, 利用细胞增殖实验,划痕愈合实验和 Transwell 实验检测 STAT3 是否可逆转 miR-26b-3p 对细胞增殖,迁移和侵袭能力的影响。荧光实时定量 PCR 和蛋白印迹法检测甲基化酶抑制剂 5-氮杂-2'-脱氧胞苷 (5-Aza-2'-deoxycytidine, 5-Aza-dC) 对 miR-26b-3p 和 STAT3 的表达的影响。

结果: miR-26b-3p 在食管鳞癌组织中的表达低于癌旁组织 ($P<0.05$)。与 miR-26b-3p NC 组相比, miR-26b-3p mimics 可显著抑制 TE1 和 KYSE150 细胞的增殖,迁移和侵袭能力 ($P<0.05$)。荧光素酶报告基因结果表明,在 TE1 和 KYSE150 中,miR-26b-3p 明显抑制了野生型 STAT3 载体的荧光素酶活性 ($P<0.05$),而突变型的荧光素酶活性不受影响。转染 pcDNA3.0-STAT3 可部分逆转 miR-26b-3p 对 TE1 和 KYSE150 细胞的增殖 ($P<0.05$),迁移 ($P<0.05$) 和侵袭能力 ($P<0.05$) 的抑制作用。经 5-Aza-dC 处理后,TE1 和 KYSE150 细胞中 miR-26b-3p 表达上调 ($P<0.05$),STAT3 mRNA 和蛋白水平降低 ($P<0.05$),miR-26b-3p 呈现去甲基化状态。

结论: MicroRNA-26b-3p 的启动子高甲基化导致 ESCC 中的表达下调,并作为抑癌因子靶向 STAT3 抑制 ESCC 细胞的增殖,侵袭和迁移能力。

关键词: 微 RNA-26b-3p; 食管鳞状细胞癌; 转录激活因子 3; 甲基化; 表达

50. 联合检测红细胞分布宽度,血小板分布宽度,癌胚抗原,糖类抗原 199 对结直肠癌诊断和分期的价值

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目的: 比较红细胞分布宽度(Red blood cell distribution width, RDW),血小板分布宽度(Platelet distribution width, PDW),癌胚抗原 (Carcinoembryonic antigen, CEA) 和糖类抗原 199 (Carbohydrate antigen 199, CA199) 在结直肠癌(Colorectal cancer, CRC)患者,结直肠腺瘤(Colorectal adenomas, CRA)患者和健康体检者之间的差异;评估 RDW,PDW,CEA,CA199 单独及联合检测对 CRC 早期筛查及分期判断的诊断价值,以挖掘血液学指标对 CRC 的临床意义。

方法: 回顾性纳入 2018 年 6 月至 2020 年 8 月就诊于贵州医科大学附属医院的 CRC 患者 165 例, CRA 患者 113 例,健康体检者 113 例。其中 CRC 患者根据国际抗癌联盟 (union for international cancer control, UICC) 2016 年第八版 TNM 分期系统进行分期,将 TNM I 期及 II 期患者定义为早期组,共 74 例;将 TNM III 期及 IV 期患者定义为晚期组,共 91 例。制定纳入标准和排除标准,详细记录所有研究对象的一般资料,RDW,PDW,CEA,CA199,病理报告和影像学资料等。按照组织病理学诊断,将患者分为结直肠癌组,结直肠腺瘤组。其中 CRC 患者根据 TNM 分期分为早期组 (TNM I 期,II 期) 及晚期组 (TNM III 期,IV 期)。比较各组间 RDW,PDW,CEA 和 CA199 水平的差异。运用受试者工作特征曲线 (Receiver

operating characteristic curve, ROC), 比较 ROC 曲线下面积 (area under the curve, AUC), 检验 RDW,PDW,CEA,CA199 单独及联合应用对 CRC 的诊断和分期的敏感性和特异性。此外, 进一步探讨 RDW,PDW 与 CRC 患者临床病理特征之间的关系。

结果: 统计学分析显示: 1.与结直肠腺瘤组及健康对照组相比, 结直肠癌组的 RDW,CEA,CA199 水平更高, 差异有统计学意义 ($P<0.05$); PDW 水平在三组间无显著差异 ($P>0.05$)。2. 晚期组的 RDW,CEA,CA199 水平高于早期组,结直肠腺瘤组及健康对照组, 差异有统计学意义 ($P<0.05$); 早期组的 RDW 水平显著高于结直肠腺瘤组及健康对照组 ($P<0.05$)。各组间 PDW 水平差异无统计学意义 ($P>0.05$)。3.运用 ROC 曲线分析各指标从所有研究对象中诊断 CRC 的效能, 当截断值为 13.35 时, RDW 诊断 CRC 的敏感度为 49.1%, 特异度为 85.2%。RDW 诊断 CRC 的诊断效能 (AUC 值 0.701) 低于 CEA (AUC 值 0.823), 高于 CA199 (AUC 值 0.655); PDW 诊断 CRC 的效能较差。两项联合检测时, RDW+CEA 诊断 CRC 的效能 (AUC=0.857)高于 RDW+CA199 (AUC=0.777) 和 CEA+CA199 (AUC=0.830)。相比单独检测, 联合检测 RDW 可以提高 CEA 和 CA199 对 CRC 的诊断效能。此外, RDW,CEA 和 CA199 联合检测对 CRC 的诊断效能最高 (AUC=0.857)。4.运用 ROC 曲线分析个指标从 CRC 患者中诊断晚期 CRC 的效能, 以 15.65 为截断值时, RDW 诊断晚期 CRC 的 AUC 为 0.637, 低于 CEA (0.701), 高于 CA199 (0.599); PDW 的 AUC 为 0.500, 对晚期 CRC 的诊断效能差。两项联合检测时, RDW+CEA 的 AUC 为 0.710, RDW+CA199 的 AUC 为 0.713, 均高于 CEA 或 CA199 单独检测时对晚期 CRC 的诊断效能。此外, RDW,CEA 和 CA199 三者联合检测对晚期 CRC 的诊断效能最高, AUC 为 0.742。5. 进一步分析发现, RDW 水平升高可能与淋巴结转移, 远处转移,分期较晚有关;而 PDW 水平与 CRC 患者临床病理特征无关。

结论: ①结直肠癌组的 RDW,CEA,CA199 水平明显高于结直肠腺瘤组, 也高于健康对照组; ②早期 CRC 患者的 RDW 水平已明显升高, 且随着肿瘤进展进一步升高, 而 CEA,CA199 在 CRC 晚期才显著升高。③RDW 对 CRC,晚期 CRC 的诊断效能低于 CEA, 高于 CA199; ④联合检测 RDW 可以提高 CEA 和 CA199 对 CRC 和晚期 CRC 的诊断效能。⑤RDW 水平的升高可能与 CRC 患者发生淋巴结转移, 远处转移和分期较晚有关。⑥PDW 对 CRC 诊断和分期的诊断效能较差。

关键词: 结直肠癌; 红细胞分布宽度; 血小板分布宽度; 肿瘤标志物; 联合检测;

51. Construction and Investigation of circRNA-miRNA-mRNA ceRNA regulatory network in breast cancer

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Background: Circular RNAs (circRNAs) have drawn lots of attention in tumorigenesis and progression. However, circRNAs as crucial regulators in multitudinous biological processes have not been systematically identified in breast cancer (BC). Our research aims to explore novel circRNAs in BC and their mechanisms of action.

Methods: The circRNA expression profile data, as well as RNA-sequencing data of BC, were downloaded from public database, respectively. The differentially expressed circRNAs, miRNA, and mRNA were determined via fold change filtering. The competing endogenous RNAs (ceRNAs) network were established on the foundation of the relationship between circular RNAs, miRNAs and mRNAs. GO and KEGG analysis of the overlapped genes were performed to predict the potential functions and mechanisms of circRNAs in BC. The CytoHubba was used to determine the hub genes from the PPI regulatory network. Moreover, we further used Kaplan–Meier plotter to perform survival analysis of these hub genes. Real-time PCR was used to validate the expression of the circRNAs in BC tissues.

Results: A total of seven differential expressed circRNAs were screened. After the predicted target miRNA and DE miRNA were intersected, four circRNA-miRNA interactions including three circRNAs and four miRNAs were determined. Furthermore, the Venn diagram was used to intersect the predicted target genes and the downregulated differentially expressed genes, and screened 149 overlapped genes. Moreover, we constructed a PPI network, and selecting six hub genes, including DGAT2, ACSL1, ADIPOQ, LPL, LEP, PCK1. Moreover, the survival analysis results revealed that low expression of ADIPOQ, LPL, LEP were obviously correlated with poor prognosis of BC patients. The real-time PCR results demonstrated that, the levels of circ_0028899, circ_0000375, and circ_0000376 were significantly down-regulated in breast cancer tissues.

Conclusions: Our study constructed and analyzed a circRNA-associated ceRNA regulatory network and discovered that circ_0028899, circ_0000375, and circ_0000376 may function as ceRNAs to serve key roles in BC.

Key words Breast cancer; circRNA; ceRNAs; GEO; TCGA

52. Gemin6 通过稳定 c-Myc 蛋白进而促进 NSCLC 的进展

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目的: 肺癌是全球癌症死亡的主要原因, 根据组织学特征, 约 85% 的患者被归为非小细胞肺癌 (NSCLC)。我们前期通过 NSCLC 转录组芯片分析发现 Gemin6 作为一个在核糖核蛋白复合体 (RNPs) 生物发生中发挥重要作用的运动神经元 (SMN) 复合体的组成部分, 在 NSCLC 癌组织和细胞系中高表达, 并且其高表达与较差的总体生存率相关。Gemin6 在肿瘤中的研究尚未见报道, 解析其在 NSCLC 中的功能与机制对未来 NSCLC 新肿瘤标志物的挖掘和治疗策略的创新有着一定意义。



方法：我们通过结合 TCGA 数据库分析和 NSCLC 临床组织芯片验证前期 Gemin6 在 NSCLC 中的表达水平和患者预后的相关性。随后，通过体外生化实验、体内成瘤实验和药物筛选实验解析 Gemin6 在 NSCLC 中的功能与机制并寻找可靶向其信号轴的 FDA 已批准药物。

结果：我们证实了 Gemin6 在 NSCLC 患者中高表达且与预后呈负相关。其高表达是由其启动子区域附近的低甲基化水平引起的，并且我们在 NSCLC 癌组织中发现了许多 Gemin6 突变。除此之外，我们还发现敲降 Gemin6 在体外抑制了肿瘤细胞的增殖、迁移和细胞周期的转变，在体内抑制了异种移植瘤的形成。药物筛选发现 Sertindole 可抑制 Gemin6 表达，与 DDP 协同促进细胞凋亡。机制研究表明，Gemin6 敲低降低了 AURKB mRNA 的成熟和蛋白的表达，从而导致 c-Myc 不稳定性增加，从而抑制肿瘤进展。

结论：我们的研究结果揭示了 Gemin6 在 NSCLC 进展中的致癌作用，此外利用 Sertindole 阻断 Gemin6 可能在未来被用作一种新的治疗策略。

关键词：Gemin6; c-Myc; NSCLC; Sertindole; AURKB

53. Circulating C-reactive protein increases lung cancer risk: results from a prospective cohort of UK Biobank

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Chronic inflammation has been associated with the development of lung cancer. In this study, we examined the association between CRP and lung cancer in a prospective cohort study and use Mendelian randomization (MR) to clarify the causality. We included 420 977 participants from the UK Biobank in the analyses; 1892 thereof were diagnosed with lung cancer during the follow-up. Hazards ratios (HRs) of CRP concentrations were estimated by Cox proportional hazard models and two approaches of MR analysis were performed. Besides, we added CRP concentrations to previously established risk model of lung cancer to evaluate its pre-diagnostic role through time-dependent ROC analysis. Elevated CRP levels were associated with a 22% increased lung cancer risk per 1 standard deviation increase (HR=1.22, 95%CI: 1.18 to 1.26). Positive associations were observed in small cell lung cancer (HR= 1.21, 95%CI: 1.10 to 1.33), lung adenocarcinoma (HR=1.17, 95%CI: 1.11 to 1.24) and lung squamous cell carcinoma (HR=1.22, 95%CI: 1.14 to 1.31). No genetical association of circulating CRP levels and lung cancer risk was observed in MR analysis. When added to established risk model of lung cancer, CRP improved the performance of model as long as 6 years (previous model: AUC=0.79 [95%CI: 0.77 to 0.81]; CRP model: AUC=0.80 [95%CI: 0.77 to 0.82]; P non-adjusted=0.003, P adjusted=0.015). Our results did not support the causal association of circulating



CRP with lung cancer risk. However, circulating CRP could be a pre-diagnostic marker of lung cancer across various histological types as long as 6 years in advance.

Key words: C-reactive protein; Chronic inflammation; Lung cancer; Mendelian randomization; Pre-diagnostic marker

54. CDH1 germline mutations in a Chinese cohort with hereditary diffuse gastric cancer

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Purpose: Germline mutations in CDH1 are associated with hereditary diffuse gastric cancer (HDGC) and have been identified in multiple ethnicities. However, CDH1 germline mutations have seldom been documented in Chinese patients with HDGC, and their frequency remains unclear. Here, we aimed to examine the frequency of CDH1 germline mutations in Chinese patients with HDGC. In total, 285 patients who met the International Gastric Cancer Linkage Consortium 2015 testing criteria of HDGC for CDH1 germline mutations were recruited.

Methods: All 16 CDH1 exons, including neighboring intronic sequences, were amplified using polymerase chain reaction and screened using Sanger sequencing. Variants were analyzed using Mutation Surveyor V4.0, SIFT, and PolyPhen-2 software.

Results: Three nonsense and nine missense CDH1 germline mutations were identified in 21 of 285 index cases (7.4%). Two CDH1 germline mutations, N405Y (Asn405Tyr) and W409X (Trp409Ter), were identified as new variants. In addition, up to 28.6% of CDH1 mutations in the 21 indicated patients were identified as c.1775G>C (E551Q). The frequency of CDH1 mutations was 6.5% (7/108) in HDGC and 7.9% (14/177) in early onset diffuse gastric cancer (EODGC). The mutation detection rates of CDH1 in males and females were 6.7% (4/60) and 8.5% (10/117) in EODGC and 4.6% (3/65) and 9.3% (4/43) in HDGC, respectively.

Conclusion: These data reveal, for the first time, the type and frequency of CDH1 germline mutations in Chinese HDGC and demonstrate that germline CDH1 mutations are a noteworthy contributor to the high frequency of HDGC in Chinese.

Key words: CDH1; mutation screening; E-cadherin; hereditary diffuse gastric cancer; germline mutation.

55. piR-9994 对胃癌细胞增殖,迁移及侵袭的影响及机制研究

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目的: 探讨 piR-9994 对胃癌细胞生物学行为的影响及可能的机制。



方法：采用 qRT-PCR 检测 piR-9994 在胃癌细胞系（MGC803 和 AGS）和正常胃上皮细胞（GES-1）中的表达情况；构建过表达、敲低 piR-9994 的 MGC803 胃癌细胞株，MTT、克隆形成实验检测 piR-9994 表达变化对细胞增殖能力的影响，划痕创伤愈合实验和 Transwell 侵袭实验检测对细胞迁移侵袭能力的影响。qRT-PCR 和 Western-Blot 检测对细胞增殖和 EMT 相关基因表达的影响。

结果：piR-9994 在胃癌细胞 MGC803 中表达水平显著高于正常人胃黏膜上皮细胞 GES-1 ($P < 0.05$)。MTT 和克隆形成实验结果显示，piR-9994 过表达促进胃癌细胞增殖，敲低抑制胃癌细胞增殖。划痕创伤愈合实验和 Transwell 侵袭结果显示，piR-9994 过表达促进胃癌细胞侵袭和转移，敲低抑制胃癌细胞侵袭和转移。流式细胞术检测结果显示，piR-9994 表达与细胞周期密切相关，特别是在 S 期。qRT-PCR 和 Western-Blot 结果显示，piR-9994 过表达促进增殖相关基因 PCNA、CyclinD1(CCND1)、BCL-2 表达，抑制凋亡基因 c-PARP 表达，促进 EMT 相关基因 N-cadherin、MMP7、Twist 和 Vimentin 表达及抑制 E-cadherin 表达；piR-9994 敲低抑制了上述增殖相关及 EMT 相关基因的表达。促进凋亡基因以及 E-cadherin 表达。

结论：piR-9994 异常表达影响胃癌细胞增殖、侵袭、转移及 EMT 进程。piR-9994 可能是胃癌的新的标志物和治疗靶点。

关键词：胃癌；piR-9994；增殖；侵袭；EMT

56. SNHG8 promotes the progression of EBVaGC via miR-512-5p /TRIM28 axis

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SNHG8, a family member of small nucleolar RNA host genes (SNHG), has been reported to act as an oncogene in gastric carcinoma (GC). However, its biological function in Epstein-Barr virus (EBV)-associated gastric cancer (EBVaGC) remains unclear. This study investigated the role of SNHG8 in EBVaGC. 61 EBVaGC cases, 20 non-EBV-infected gastric cancer cases (EBVnGC) and relative cell lines were studied for the expression of SNHG8 and BHRF1 (BCL2 homolog reading frame 1) encoded by EBV with Western blot and qRT-PCR assays. The relationship between the expression levels of SNHG8 and the clinical outcome in 61 EBVaGC cases was analyzed. Effects of BHRF1, SNHG8 and TRIM28 on cell proliferation, migration, invasion and cell cycle and the related molecules were determined by the manipulation of gene expression, qRT-PCR, Western blot and MTT, colony assay, wound healing assay, transwell invasion assay and flow cytometry. The interactions among SNHG8, miR-512-5p and TRIM28 were determined with Luciferase reporter assay, RNA immunoprecipitation (RIP), pull-down assays and Western blot assay. The in vivo activity of SNHG8 were assessed with SNHG8 knockdown tumor xenografts in Zebrafish. Results demonstrated that: (1)

BHRF1 and SNHG8 was over-expressed in EBV-encoded RNA 1 positive EBVaGC tissues and cell lines. BHRF1 up-regulated the expressions of SNHG8 and TRIM28 in AGS;(2) SNHG8 overexpression had a significant correlation with tumor size and vascular tumor thrombus. Patients with high SNHG8 expression had poorer overall survival (OS) compared to those with low SNHG8 expression; (3) SNHG8 overexpression promoted EBVaGC cell proliferation, migration and invasion in vitro and in vivo, cell cycle arrested at the G2/M phase via the activation of BCL-2, CCND1, PCNA, PARP1, CDH1, CDH2, VIM and Snail; (4) Results of dual-luciferase reporter assay, RNA immunoprecipitation and pull-down assays indicated that SNHG8 sponged miR-512-5p, which targeted on TRIM28 and promoted cancer malignant behaviors of EBVaGC cells. Our data suggest that BHRF1 triggered expression of SNHG8, which sponged miR-512-5p and up-regulated TRIM28 and a set of effectors (such as BCL-2, CCND, CDH1, CDH2, Snail and VIM, etc) to promote EBVaGC tumorigenesis and invasion. SNHG8 could be an independent prognostic factor for EBVaGC and serve as target for EBVaGC therapy.

Key words: EBVaGC; SNHG8; miR-512-5p; TRIM28; cell proliferation; migration; invasion

57. 非小细胞肺癌组织中 circ_0006692 的表达及其对肺癌细胞增殖转移的调控机制

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目的: 探讨非小细胞肺癌 (NSCLC) 中 circ_0006692 的表达与临床病理特征的关系以及相关的机制。

方法 收集 50 对 NSCLC 癌和癌旁组织, qRT-PCR 法检测癌和癌旁组织中 circ_0006692 的表达, 并分析其与临床病理特征之间的关系。构建过表达, 敲低的 circ_0006692 的 A549 肺细胞株, MTS, 克隆形成实验, 划痕创伤愈合实验和 Transwell 侵袭实验检测 circ_0006692 表达变化对细胞增殖, 迁移和侵袭能力的影响。qRT-PCR 和 Western-blot 检测 circ_0006692 表达变化对 EMT 相关基因表达的影响。

结果: 非小细胞肺癌组织中 circ_0006692 表达水平高于癌旁组织 ($P<0.05$), 其的表达水平与肿瘤大小, TNM 分期及肺膜侵犯密切相关 ($P<0.05$)。circ_0006692 敲低抑制细胞增殖, 侵袭和转移, 过表达促进细胞增殖, 侵袭和转移。同时, qRT-PCR 和 Western-Blot 结果显示 circ_0006692 敲低抑制 A549 肺癌细胞 EMT 相关基因 CDH2 和 MMP7 促进 CDH1 表达。

结论: 非小细胞肺癌组织中 circ_0006692 的表达上调与肿瘤大小, TNM 分期及肺膜侵犯密切相关; circ_0006692 表达可调节 A549 肺癌细胞增殖, 侵袭, 转移以及 EMT 进展。

关键词: circ_0006692; 非小细胞肺癌; 增殖; 转移; EMT



58. Potential diagnostic significance of Hsp90 α and Neutrophil to Lymphocyte Ratio in Gestational Hypertension and Preeclampsia

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Objective: The objective of this study was to evaluate the differences and the potential diagnosis significance of Hsp90 α and Neutrophil to Lymphocyte Ratio (NLR) in normal pregnant women and patients with gestational hypertension (GH) or preeclampsia (PE).

Methods: We recruited 131 normal pregnant women, 61 patients with GH and 97 patients with PE. The plasma concentration of Hsp90 α was determined by enzyme-linked immunosorbent assay (ELISA), and complete blood counts were measured by an automated hematology analyzer Sysmex XN-9000. The NLR was calculated as the absolute neutrophil count divided by the absolute lymphocyte count. A receiver operating characteristic (ROC) curve was employed to assess the diagnostic performance of Hsp90 α and NLR.

Results: Our study indicated that Hsp90 α and NLR were increased in the middle and the third trimester of normal pregnancy than the first trimester of normal pregnancy; However, the level of Hsp90 α but not NLR in the third trimester was significantly higher than the middle trimester of normal pregnancy. Hsp90 α and NLR were increased in GH and PE compared to the normal pregnancy (NP). More importantly, Hsp90 α and NLR served as the diagnostic biomarkers for GH and PE, the AUCs for GH were 0.749 and 0.658, for PE were 0.886 and 0.775, respectively. Moreover, their combination significantly elevated the diagnostic efficiency for GH and PE, possessing the AUC of 0.792 and 0.941, respectively.

Conclusions: The new inflammatory marker Hsp90 α and NLR might be the promising and effective markers for GH and PE.

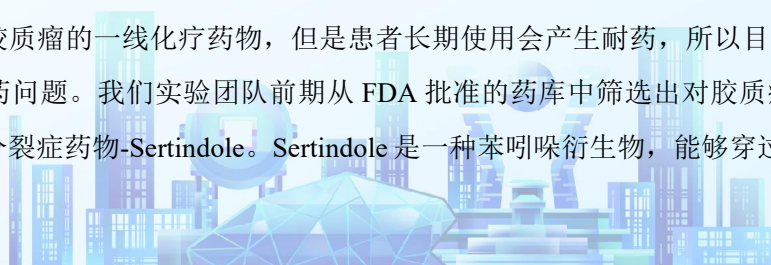
Key words: Hsp90 α ; neutrophil-to-lymphocyte ratio; gestational hypertension; preeclampsia

59. Sertindole 通过阻断自噬流进而抑制胶质瘤的进展

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目的: 多形性胶质母细胞瘤 (GBM) 是成人中最常见和最具侵袭性的原发性脑肿瘤, 其目前的标准治疗方法主要有两种: 最大程度的安全手术切除和联合放化疗。替莫唑胺 (TMZ) 是最广泛的被用于治疗胶质瘤的一线化疗药物, 但是患者长期使用会产生耐药, 所以目前迫切寻找新的药物去解决耐药问题。我们实验团队前期从 FDA 批准的药库中筛选出对胶质瘤杀伤能力较为显著的抗精神分裂症药物-Sertindole。Sertindole 是一种苯吡啶衍生物, 能够穿过血脑屏障 (BBB),



但 Sertindole 在胶质瘤中的研究尚未见报道, 因此解析其在胶质瘤治疗中的功能与机制对未来胶质瘤的治疗创新有着一定意义。

方法: 我们通过磺酰罗丹明 B(SRB)比色法检测胶质瘤细胞系和人正常星形细胞对 Sertindole 的药物敏感性。随后, 选取 U87 和 U251 两株胶质瘤细胞系进行体外增殖, 免疫荧光, 透射电子显微镜 (TEM), 流式细胞术等实验和体内裸鼠成瘤实验解析 Sertindole 在胶质瘤中的功能和机制。

结果: 我们证实了 Sertindole 在胶质瘤中有抑制其增殖的能力。另外, Sertindole 在体外将胶质瘤细胞的周期阻滞在 G0/G1 期, 在体内抑制了异种移植瘤的形成, 并且联合替莫唑胺抑制移植瘤的能力更强。除此之外, Sertindole 是通过阻断自噬流的通畅而抑制胶质瘤的发生发展。最后, 在胶质瘤干细胞中, Sertindole 抑制干细胞的成球能力和干性标志物的表达。

结论: 我们的研究结果揭示了 Sertindole 在胶质瘤进展中的抑癌作用, 此外 Sertindole 和替莫唑胺联合用药可能在未来被用作一种新的治疗策略。

关键词: 胶质瘤; Sertindole; 自噬; 干细胞

60. Ivacaftor inhibits glioblastoma stem cell maintenance

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Glioblastoma (GBM) is the most aggressive primary tumor in the central nervous system. Despite conventional clinical therapies including surgery, radiotherapy, chemotherapy, and immunotherapy, the median survival of GBM patients remains less than 15 months after diagnosis. It has been well recognized that GBM was initiated by a subpopulation of cells termed as glioblastoma stem cells (GSCs), which are characterized by sustaining abilities of self-renewal, multilineage differentiation and resistance to current therapeutic strategies. Radiotherapy and chemotherapy are cytotoxic to highly proliferative tumor cells, but fail to eliminate the relatively quiescent GSCs, which is the major cause leads to GBM recurrence. Temozolomide (TMZ) is an orally alkylating agent that commonly used for the standard glioma clinical treatment via triggering DNA damage. However, more than 50% of glioma patients received TMZ treatment show resistance to TMZ therapy. This is attributed to GSCs recalcitrance to TMZ therapy due to their enhanced DNA repair ability or/and high MGMT expression. Small molecule compounds, including clofotol, LLP-3, gboxin, inhibitor of dopamine receptor D4, and inhibitor of STAT3, have been documented to inhibit GSCs self-renewal ability. However, so far, none of an optimal drug was used for selectively targeting GSCs approved for GBM clinical therapy. Therefore, there is an urgent need to identify new drugs synergizing with TMZ to effectively eliminate GSCs and translate them into clinical application for GBM patients.

Ivacaftor was approved by US food and drug administration in 2019 for use in cystic fibrosis. The clinical safety of ivacaftor was confirmed by a phase III trial study. In this study, we identified ivacaftor as a

promising anti-glioblastoma drug via specifically and effectively repressing GSCs. Mechanistically, we provide evidence showing that ivacaftor inhibits GSCs stemness marker genes expressions including CD133, CD44, and SOX2. In summary, our findings reveal that ivacaftor inhibits glioblastoma progression via specifically eliminating GSCs, which opens a new avenue for GBM clinical therapy in the future.

Key words: Ivacaftor; Glioblastoma; Glioblastoma stem cell; Apoptosis

61. m6A 修饰在系统发育及肿瘤发展中的功能与机制

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N6-甲基腺苷 (m6A) 是真核 mRNA 中最普遍的修饰, 调节 RNA 稳定性, 剪接, 降解, 翻译和输出等。m6A 修饰的功能受三个同源因子的控制, 包括“writers”, “readers”和“erasers”。m6A“writers”: 可以催化 RNA 上腺苷的 m6A 修饰, 主要包括甲基转移酶样 3 蛋白 (METT13), 甲基转移酶样 14 蛋白 (METT14) 和 WT1 相关蛋白 (WTAP)。m6A“writers”还含有 RNA 结合域蛋白 15/15B (RBM15/15B), 甲基转移酶样 16 (METTL16), 含锌指 CCCH 型 13 (ZC3H13), 以及 Vir 样 m6A 甲基转移酶 (VIRMA, 又称 KIAA1429), 等等。m6A“erasers”: 主要包括 FTO 和 ALKBH5。这些蛋白质可以从 RNA 中除去甲基化, 这意味着 m6A 修饰是动态和可逆的。m6A“readers”: 选择性 RNA 结合蛋白, 其可以识别 m6A, 其主要包括含 YT521-B 同源性 (YTH) 结构域蛋白家族 (包括 YTHDF1/2/3 等 YTHDFs, 以及 YTHDC1/2 等 YTHDCs)。另外的 reader 包括胰岛素样生长因子-2 mRNA 结合蛋白 (包括 IGF2BP1/2/3 的 IGF2BPs), 不均一核糖核蛋白 (HNRNP) 家族 (包括 HNRNPA2B1, HNRNPC 和 HNRNPG) 和 NF- κ B-相关蛋白 (NKAP) 和真核转换起始因子 3 (eIF3)。最近的研究表明, m6A 修饰的调控因子在正常生理过程以及病理过程发挥重要的功能。在本文中, 我们系统总结了 m6A 修饰在生殖系统, 造血系统以及神经系统发育中的功能与机制。此外, 我们系统总结了 m6A 修饰异常在上述三种系统相关肿瘤发生发展中的功能与机制。本文将扩充我们对 m6A 修饰在疾病中的功能与见解, 为进一步理解系统发育与疾病发生提供了理论指导, 并未将来靶向 m6A 调控因子设计药物提供了参考。

关键词: m6A 修饰; 造血系统; 生殖系统; 神经系统; 肿瘤发生

62. 高原低氧适应基因 RETSAT 在黑色素瘤发生发展中的功能与机制研究

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低氧通常发生在高原和深海环境，此外，低氧在实体瘤的发生发展中也扮演了重要功能。低氧相关的信号通路通常与肿瘤的不良预后紧密相关。我们课题组近期利用遗传进化生物学、发育生物学、肿瘤学交叉学科的研究特点和优势，筛选出许多在高原哺乳动物低氧等极端环境进化适应的关键候选基因，其中有一个基因 **RETSAT**，我们课题组先前研究表明基因视黄醇饱和酶 (**RETSAT**) 的一个氨基酸位点在所有 4 个高原物种中都发生了谷氨酰胺(Q)到精氨酸(R)的突变，并且该突变是受正选择趋动。体内实验发现，高原突变(R)敲入小鼠比野生型小鼠拥有更快的心跳、更高比例的射血分数、更大的主动脉直径和更高的肝血氧饱和度等，并能在低氧环境中存活更长时间。而进一步的研究发现，与野生型小鼠相比，**RETSAT** 高原突变型能够显著抑制黑色素瘤生长，下调肿瘤的体积和重量，并且 **RETSAT** 高原突变型展现出更长的存活时间。进一步的机制研究表明，**PIN1** 作为 **RETSAT** 下游直接调控的靶蛋白，**RETSAT** 突变能够下调 **PIN1** 的蛋白表达，并进一步抑制 **AKT** 信号通路，进而抑制肿瘤的进展。总之，该研究表明，利用进化生物学和肿瘤学交叉学科，寻找新的高原低氧适应基因，并进一步解析其在实体瘤发生发展的分子机理，为低氧实体瘤的诊断与治疗提供了理论指导。

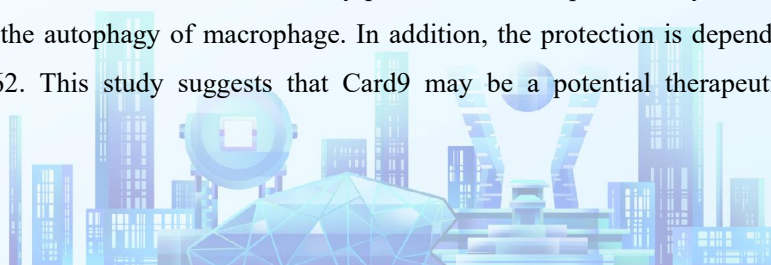
关键词：高原低氧；视黄醇饱和酶；皮肤癌；**PIN1**

63. Card9 protects fungal peritonitis through regulating autophagy in macrophage

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Fungal peritonitis (FP) is a common and serious complication of peritoneal dialysis that results in high morbidity and mortality. Autophagy of macrophages plays a protective role in peritonitis. Card9, an adapter protein, plays a critical role in anti-fungal immunity. However, the role of Card9 in autophagy of macrophage remains unknown. In this study, we demonstrate that phenotype of zymosan-induced peritonitis was exacerbated in Card9^{-/-} mice, displaying multiple organs injury and increased systemic inflammation. The number of macrophages was significantly increased in spleen of Card9^{-/-} mice. Autophagy of peritoneal macrophages was impaired in peritonitis of Card9^{-/-} mice. Moreover, the autophagy agonist, rapamycin, ameliorated peritonitis in Card9^{-/-} mice. The result of microarray analysis indicates Malt1 was significantly decreased in Card9^{-/-} mice. Notedly, Card9 mediated the interaction of Malt1 and autophagy protein P62 in macrophages under zymosan stimulation. Furthermore, we demonstrate that Malt1 mediates the function of P62 to clear ubiquitinated proteins. Together, our results indicate that Card9 may protect the development of zymosan-induced peritonitis by regulating the autophagy of macrophage. In addition, the protection is depended on interaction of Malt1 and P62. This study suggests that Card9 may be a potential therapeutic target for fungal peritonitis.



Key words: autophagy; Fungal peritonitis; Card9

64. LncRNA SNHG3 对乳腺癌骨转移微环境的影响及作用机制

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目的: 本研究拟在肿瘤微环境中探讨乳腺癌细胞中的 lncRNA SNHG3 对 BMSCs 成骨分化能力的影响及作用机制。

方法: 利用 TCGA 数据库分析 lncRNA SNHG3 在乳腺癌组织中的表达水平。采用实时荧光定量 PCR 检测乳腺癌组织和细胞系中 lncRNA SNHG3 的表达水平。构建敲低 lncRNA SNHG3 的稳转 MDA-MB-231 细胞株并通过实时荧光定量 PCR 验证。采用 ALP 染色和 ALP 活性检测实验以及 OPG,OSX,RUNX2,BMP2 与 BMP3 的 Western blot, 验证骨髓间充质干细胞 (BMSCs) 的体外成骨作用。分别提取对照组和 MDA-MB-231/shSNHG3 组的外泌体进行鉴定和测序, 并通过 miRNA 的实时荧光定量 PCR 验证分析了 lncRNA SNHG3 的靶向 miRNA。采用生物信息学预测并利用双荧光素酶报告基因分析法观察 miR-1273g-3p 分别与 lncRNA SNHG3 和 BMP3 的结合位点。

结果: LncRNA SNHG3 在乳腺癌组织中高表达, 同时其表达水平与乳腺癌骨转移呈正相关。ALP 染色, 活性检测以及 Western blot 结果表明, 下调乳腺癌细胞 lncRNA SNHG3 的表达可明显提升 BMSCs 的成骨能力。在提取的细胞上清液中检测到外泌体的存在。在乳腺癌细胞与 BMSCs 的细胞间相互作用中, lncRNA SNHG3 / miR-1273g-3p / BMP3 轴正向调控骨形态发生蛋白 3 (BMP3) 的表达。

结论: 敲低乳腺癌细胞中的 lncRNA SNHG3, 通过 lncRNA SNHG3 / miR-1273g-3p / BMP3 轴促进乳腺癌骨微环境中 BMSCs 成骨分化。以上结果提示 lncRNA SNHG3 可能是乳腺癌骨转移的潜在治疗靶点。

关键词: 乳腺癌; 骨转移; lncRNA SNHG3; miRNA-1273g-3p; BMP3

65. Fusobacterium nucleatum is a risk factor for metastatic colorectal cancer

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Background: Increasing evidence has indicated that there is a correlation between the abundance of *Fusobacterium nucleatum* (*F. nucleatum*) and poor prognosis of colorectal cancer (CRC). Moreover, tumor metastasis plays a decisive role in the prognosis of CRC patients. Therefore, we hypothesized that the abundance of *F. nucleatum* in CRC tissue affected tumor metastasis.

Methods: *F. nucleatum* DNA from 141 resected CRC samples was quantified by qPCR to analyze whether there were differences in *F. nucleatum* abundance between the groups with and without CRC metastasis. Moreover, in vitro experiments (electron microscopy as well as migration and invasion trials) were performed with CRC cells infected with *F. nucleatum* to observe the influence of *F. nucleatum*. Additionally, a meta-analysis was carried out to comprehensively evaluate the correlation between the *F. nucleatum* abundance and CRC stage based on large cohorts.

Results: CRC tissues enriched with *F. nucleatum* had a higher risk of lymph node metastasis and distant metastasis. The receiver operating characteristic (ROC) curve indicated that *F. nucleatum* in the CRC tissue could act as an indication marker for CRC metastasis to some extent. Moreover, *F. nucleatum* was a highly invasive bacterial strain and could significantly enhance the invasion and migration capacities of SW480 and SW620 cells. Besides, the meta-analysis indicated a slight correlation between the *F. nucleatum* abundance and advanced CRC stage (RR=1.17, 95% CI: 1.00–1.37, $P=0.04$, random effect).

Conclusions: *F. nucleatum* abundance is associated with CRC metastasis, and it might serve as a metastasis biomarker for CRC patients.

Key words: *Fusobacterium nucleatum*; colorectal cancer; biomarker

66. 热带念珠菌通过激活 MDSCs NLRP3 炎性小体促进结肠癌发生的机制

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真菌能够通过 Syk/CARD9 信号通路激活 DCs 的 NLRP3 炎性小体。但是,致病性真菌-热带念珠菌能否激活 MDSCs 的 NLRP3 炎性小体及其分子机制还不清楚。我们用热带念珠菌直接处理 MDSCs 之后, RNA-seq 分析发现热带念珠菌能够激活 NOD 样受体信号通路和 C 型凝集素受体信号通路。热带念珠菌能够显著上调 NLRP3 和 *Clec4d* (*Dectin-3*) 的表达。我们推测热带念珠菌可能通过 *Dectin-3* 激活 NLRP3 炎性小体。因此, 将 *Dectin-3* 敲除之后, 热带念珠菌诱导 NLRP3 炎性小体激活显著降低, 说明 *Dectin-3* 受体能够介导热带念珠菌激活 MDSCs 的 NLRP3 炎性小体。热带念珠菌能够通过上调 MDSCs 的糖原代谢和糖酵解促进 NLRP3 炎性小体的激活。

关键词: 热带念珠菌; MDSCs; NLRP3 炎性小体

67. Prognostic signatures of alternative splicing events in esophageal carcinoma based on TCGA Splice-seq data

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The alternative splicing (AS) event is a highly complex process that plays an essential role in post-transcriptional gene expression. Several studies have suggested that abnormal AS events were primary element in the pathological process of cancer. However, few works are dedicated on the study of AS events in esophageal carcinoma (EC). In the present study, clinical information and RNA-seq data of EC patients were downloaded from the TCGA database. The percent spliced in (PSI) values of AS events were acquired from the TCGA Splice-seq. A total of 183 EC patients were enrolled in this study and 2,212 AS events were found significantly associated with the overall survival of these patients by Univariate Cox regression analysis. The prognostic signatures based on AS events were built by Multivariate Cox analysis. ROC curves displayed that the AUC of the following prognostic signatures, including ES, AT, AA, AP, AD, RI and total events, was greater than 0.8, suggesting that these seven signatures had valuable prognosis prediction capacity. Finally, the risk score of prognostic signatures was indicated as an independent risk factor of survival. GO and KEGG pathway analyses were performed to explore the function of splicing factors (SFs) that were associated with AS events. Also, the interactive network between AS events and SFs identified several hub genes and AS events which need further study. This was a comprehensive study that explored prognosis-related AS events and established valuable prognosis signatures in EC patients. The network of interactions between AS events and SFs might offer novel insights into the fundamental mechanisms of tumorigenesis and progression of EC.

Key words: Esophageal carcinoma; alternative splicing; splicing factor; TCGA; prognosis

68. 潞党参三萜类化合物及其抗炎活性研究

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目的: 研究潞党参中三萜类化学成分及其抗炎活性。

方法: 对潞党参甲醇提取液的石油醚萃取部位采用反复硅胶柱色谱技术进行分离纯化, 通过核磁共振波谱 (NMR) 和质谱 (MS) 技术鉴定化合物的结构。建立脂多糖 (LPS) 诱导的小鼠巨噬细胞 RAW264.7 炎症模型, 利用 Griess 法测定一氧化氮 (NO) 含量来评价化合物的抗炎活性。

结果: 从潞党参中分离得到 3 个环阿屯烷结构母核的三萜类化合物, 分别鉴定为 24-methylenecycloartanyl linolate (1), 24-methylenecycloartan-3-ol (2), Codonoplates B (3)。化合物 1~3 在 3.75 $\mu\text{mol/L}$, 7.50 $\mu\text{mol/L}$ 和 15.00 $\mu\text{mol/L}$ 浓度下均表现出很好的 NO 抑制作用, 且抑制活性大小依次为 3 > 2 > 1。

结论: 从潞党参中分离得到的 3 种三萜类化合物对 LPS 诱导的细胞炎症模型具有良好的抗炎活性, 为深入研究潞党参的抗炎活性提供科学依据。

关键词: 潞党参; 环阿屯烷型三萜; RAW264.7 细胞; 脂多糖; 抗炎活性

69. 肿瘤标志物在非小细胞肺癌临床价值的探索与分析

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目的: 探索与分析血清铁蛋白,CEA,CYFRA21-1,SCC,NSE 对 NSCLC 的诊断以及与临床病理特征的临床价值。

方法: 2019 年 9 月至 2020 年 8 月在云南省肿瘤医院收治的患者共 212 例,其中实验组为非小细胞肺癌患者 111 例,对照组为肺良性肿瘤患者 101 例。采用电化学发光法检测两组血清铁蛋白,CEA,CYFRA21-1,NSE 和 SCC 浓度并进行比较分析。考察不同临床病理特征 NSCLC 患者的血清铁蛋白,CEA,CYFRA21-1,SCC,NSE 水平并判断 5 种肿瘤标志物单独,联合检测于非小细胞肺癌的诊断价值。

结果: ①实验组中血清铁蛋白,CEA,CYFRA21-1,SCC,NSE 比对照组明显升高,差异具有统计学意义 ($P<0.05$); ②病理分期越晚,SCC,CEA,CYFRA21-1 表达水平越高。三者联合应用对辅助临床评估患者疾病进展情况具有一定参考意义; ③铁蛋白,CYFRA21-1 在有淋巴结转移时高表达,联合检测可提高检测淋巴结转移的阳性率并可用于指导外科手术治疗; ④SCC,CYFRA21-1 水平在鳞癌中比在腺癌中表达更高,可对临床判断病理类型具有一定的参考意义; ⑤实验组血清铁蛋白,SCC,NSE,CEA,CYFRA21-1 的阳性检出率均高于对照组,差异具有统计学意义 ($P<0.05$); ⑥在鳞癌中 CYFRA21-1 阳性率最高,70.27%,在腺癌中铁蛋白阳性率最高,为 62.16%,并且在单项检测中铁蛋白的敏感性 (63.97%) 最高; ⑦5 种肿瘤标志物联合检测的 AUC,95%CI 区间,敏感性均高于任一单项检测,对辅助诊断肺癌具有重要的临床价值。

结论: 通过检测 5 种肿瘤标志物,对判断病理类型,判断患者病理分期,评估疾病进展程度,淋巴结的转移情况以及用于临床指导手术具有重要临床意义,并且 5 种肿瘤标志物联合检测对辅助诊断早期非小细胞肺癌具有重要价值

关键词: 非小细胞肺癌; 联合检测; 肿瘤标志物; 临床病理特征; 联合诊断

70. Diagnostic and Prognostic significance of Serum Tumor Markers in Patients with Lung Cancer

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Background: Tumor markers CEA, CYFRA21-1, NSE, proGRP, and SCC-Ag were routinely used for lung cancer. The objective of this study was to evaluate the diagnostic and prognostic value of these markers.

Methods: The levels of 5 serum tumor markers were measured in 255 patients with lung cancer (44 squamous cell carcinoma, 183 adenocarcinoma, 28 small cell lung cancer), 103 patients with benign lung disease, and 120 healthy controls. The relevant clinical data of the patients were collected to analyze the expression of CEA, CYFRA21-1, NSE, proGRP, and SCC-Ag in the serum of lung cancer and their correlation with prognosis.

Results: The positive rates and expression levels of CEA, CYFRA21-1, NSE, proGRP, and SCC-Ag in the lung cancer group were higher than those in patients with benign lung diseases and healthy controls. CYFRA21-1 and SCC-Ag were highly expressed in lung squamous cell carcinoma, and NSE and proGRP were highly expressed in small cell lung cancer. The expression levels of CYFRA 21-1, NSE, and proGRP in small cell lung cancer were higher than those in non-small cell lung cancer. The levels of CEA, CYFARA21-1, NSE, and proGRP were linearly correlated with the occurrence of lung cancer, while the level of SCC-Ag was not significantly correlated with the occurrence of lung cancer. What's more, the levels of CYFAR21-1 and NSE in the death group of lung cancer patients were higher than those in the survival group.

Conclusion: CEA, CYFRA21-1, NSE, proGRP, and SCC-Ag played a good role in diagnosing lung cancer. CYFRA21-1 and SCC-Ag can be used as markers for the diagnosis of squamous cell carcinoma, and NSE and proGRP can be used as markers for small cell lung cancer. Meanwhile, the combined detection of CEA, CYFARA21-1, NSE, and proGRP had the highest diagnostic accuracy for lung cancer. Furthermore, CYFAR21-1 and NSE can be used to evaluate the prognosis of lung cancer patients.

Key words: Lung cancer; Diagnostic significance; Prognostic significance; Tumor markers

71. Characterization of Non-histone Acetylation Score in Predicting the Prognosis and Immunotherapy Response of Liver Cancer

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Objective: Acetylation and deacetylation play an important role in post-translational modification. At present, 13 acetylases (KAT) and 18 deacetylases (KDAC) have been identified. They are involved in key steps in the physiological and pathological processes. and their role in liver cancer has not been fully elucidated.

Methods: Comprehensively evaluate the modification patterns of acetylase and deacetylase genes, including expression, mutation and CNV using TCGA, ICGC and GEO databases. The 26 KAT and



KDAC gene expression profiles were clustered consistently to obtain KAT+KDAC.clusterA/KAT+KDAC.clusterB and KAT+KDAC related genes, and then obtain KAT+KDAC.geneclusterA, KAT+KDAC.geneclusterB and KAT+KDAC.geneclusterC by performing the consistent clustering. Then construct KAT+KDAC.score to quantify the KAT+KDAC modification pattern of a single sample, and evaluate the patients prognosis and immunotherapy response.

Results: Most of KAT and KDAC are highly expressed in liver cancer, which can distinguish liver cancer samples from normal controls. Consistent clustering results in KAT + KDAC.clusterA/KAT + KDAC.clusterB, and there are significant differences in prognosis. The prognosis of the three groups of KAT + KDAC.geneclusterA, KAT + KDAC.geneclusterB and KAT + KDAC.geneclusterC were significantly different. The KAT+KDAC.score high group has a better prognosis than the KAT+KDAC.score low group, and it is related to the P53 mutation status, stage, and TNM staging. The low KAT+KDAC.score group is resistant to Cisplatin and Gemcitabine, and the TIDE score is low. KAT+KDAC.score can effectively predict the response of patients to immunotherapy.

Conclusion: We demonstrate that evaluating the KAT+KDAC modification pattern within a single tumor can predict patient prognosis and immunotherapy response. In summary, KAT+KDAC modification plays an important role in tumorigenesis and development.

Key words: Acetylation and deacetylation; Consistent clustering; Immunity; Prognosis

72. Clinical value of assessing serum levels of inflammatory cytokines in the early diagnosis of patients with primary liver carcinoma: an observational study

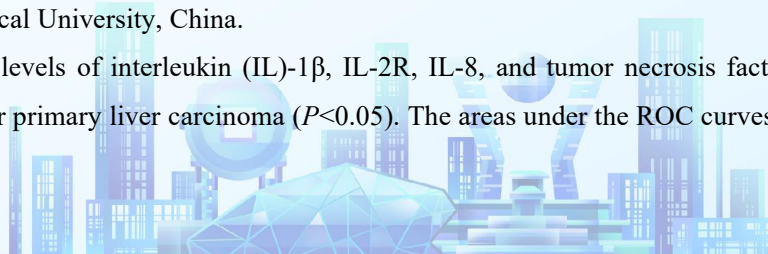
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Objective: Routine immunological tests based on six cytokine combinations were used to identify potential early diagnostic markers for hepatitis B progression to primary liver carcinoma.

Methods: This retrospective observational study included 899 patients with hepatitis B progressing to primary liver carcinoma, including 666 patients in the liver carcinoma group with HBsAg+, HBeAb+, HBcAb+ liver carcinoma and 233 patients in the liver carcinoma group with HBsAg+, HBeAg+, HBcAb+ liver carcinoma were recruited. To compare with them, the hepatitis B control group and the healthy control group were also recruited from the outpatients or physical examinees of Changhai Hospital. Receiver operating characteristic (ROC) curves were used to evaluate the efficiency of the different cytokine combinations in the diagnosis of hepatocellular carcinoma in patients with hepatitis B. This study was approved by the Institutional Review Board of Changhai Hospital, Naval Military Medical University, China.

Results: Changed levels of interleukin (IL)-1 β , IL-2R, IL-8, and tumor necrosis factor (TNF)- α were all risk factors for primary liver carcinoma ($P < 0.05$). The areas under the ROC curves (AUCs), sensitivity,



specificity, positive predictive value, negative predictive value, and Youden index for the diagnosis of primary liver carcinoma using the combination of IL-1 β , IL-2R, IL-8, and TNF- α were 0.938, 79.2%, 96.7%, 96%, 82.0%, 0.759, respectively. The serum alpha-fetoprotein (AFP) concentration level of patients with primary liver carcinoma was positively correlated with IL-2R ($r=0.3502$, $P<0.001$), IL-8 ($r=0.1558$, $P=0.0273$), and TNF- α ($r=0.2544$, $P<0.001$) levels. The final obtained fitting equation fitted to the results was $\text{logit}(P)=0.086+0.01\times\text{IL-2R}-0.001\times\text{IL-8}-0.033\times\text{TNF-}\alpha-0.041\times\text{IL-1}\beta$.

Conclusion: Our study establishes a novel, potentially valuable diagnostic model using based on four cytokines related to the early diagnosis stages of liver carcinoma.

Key words: cytokine; early diagnosis; primary liver carcinoma; clinic value; diagnostic model; hepatitis B

73. The effect of down-regulation of PPP2R3A expression on proliferation and metastasis of Hepatocellular Carcinoma

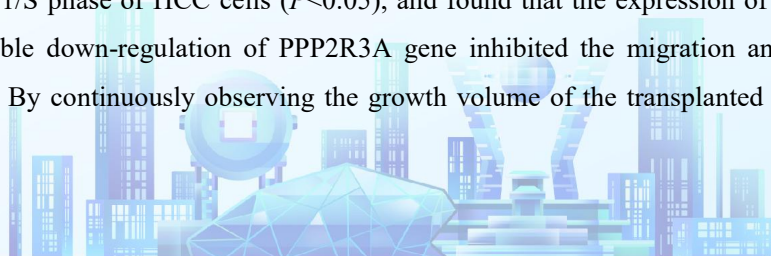
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Purposes: Exploring the effect of down-regulating the expression of PPP2R3A gene on the biological behavior of liver cancer cells in vitro and in vivo. To explore the effect of abnormal expression of PPP2R3A gene on the biological behavior of hepatoma cells.

Method: Immunohistochemical (IHC) special staining assay was used to detect the expression and localization of PPP2R3A gene in human hepatocarcinoma tissues, and to explore its difference in expression intensity from adjacent tissues. The viral vector-mediated RNA interference technology was used to construct hepatocellular carcinoma cells (HCCs) stably down-regulating PPP2R3A. HCCs were tested for knockdown of hepatocellular carcinoma cells by q-PCR and Western blot, respectively. PPP2R3A knockdown of HCCs was explored by proliferation, cycle, migration and invasion experiments in vitro, respectively. The effect of learning behavior. The transplanted tumor model was constructed in nude mice to explore the effect of PPP2R3A knockdown on the growth of HCCs in vivo. The possible mechanism of PPP2R3A affecting the behavior of hepatoma cells was explored by protein electrophoresis, such as P53 related signal protein.

Result: Immunohistochemistry experiments showed that the expression of PPP2R3A gene in human hepatocarcinoma tissues was mainly localized on cytoplasm and cell membrane, and the expression intensity of PPP2R3A gene in cancer tissues was higher than that in adjacent tissues. The hepatocellular carcinoma cells stably down-regulating PPP2R3A gene was successfully constructed by using lentiviral vector. Stable down-regulation of PPP2R3A gene inhibited the proliferation ($P<0.05$), arrested the G1/S phase of HCC cells ($P<0.05$), and found that the expression of P53 protein in cells increased. Stable down-regulation of PPP2R3A gene inhibited the migration and invasion of HCC cells ($P<0.05$). By continuously observing the growth volume of the transplanted tumor, it was found



that the growth of hepatocarcinoma cells in the animals was inhibited after the stable down-regulation of PPP2R3A gene, and the volume was significantly reduced compared with the control group ($P<0.01$).

Key words: PPP2R3A; Hepatocellular carcinoma; Proliferation; Metastasis

74. MLH1 与 TP53 在乙肝相关性肝癌中的表达及意义

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目的: 探讨 MLH1 与 TP53 在乙型肝炎病毒 (hepatitis B virus ,HBV) 感染相关性肝癌 (hepatocellular carcinoma,HCC) 中的表达及意义。

方法: 选取施行了原位肝移植手术的 238 例 HBV 相关性 HCC 伴肝硬化患者, 应用免疫组化的方法检测肝癌组织和癌旁组织中 MLH1 与 p53 的表达情况, 并以 25 例正常肝组织和良性肝病组作为对照。

结果: MLH1 在肝癌组织的阳性表达率为 31.09% (74/238), 癌旁组织的表达阳性率为 26.05% (62/238), 良性肝病对照组阳性表达率为 48.00% (12/25), 各组表达的差异无统计学意义 ($P=0.053$)。相关性分析显示, MLH1 基因的表达与患者肝移植术前 AFP 含量 ($r=0.221$, $P=0.001$) 及术后的复发 ($r=-0.159$, $P=0.014$) 有相关性, 与 HCC 组织病理学 Edmondson 分级 ($P=0.060$) 及 TNM 分期 ($P=0.065$) 有相关趋势。TP53 在肝癌组织的表达阳性率为 47.06% (112/238), 在癌旁组织的表达阳性率为 0.84% (2/238), 良性肝病对照组均为阴性, p53 蛋白的表达在癌组织中明显高于其在癌旁及良性肝病中的表达 ($P=0.000$); p53 表达情况与患者肝移植术前 AFP 含量有相关性 ($r=0.172$, $P=0.008$), 与血管侵犯有相关趋势 ($P=0.053$)。

结论: MLH1 蛋白表达下调可能与 HBV 相关性肝癌的发生及术后的复发有关, 并且 MLH1 与 p53 蛋白在肝癌中的表达有一定的关联性。

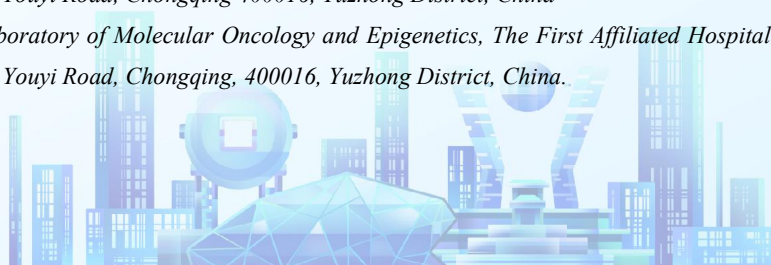
关键词: 肝细胞肝癌; 乙型肝炎病毒; MLH1; TP53

75. ZBTB28 induces autophagy by regulation of FIP200 and Bcl-XL facilitating cervical cancer cell apoptosis

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Background: Among the common preventable cancers of women, cervical cancer has the highest morbidity. It is curable if detected at an early stage. However, reliable diagnostic and prognostic markers, which relate to physiologic and pathologic regulation of cervical cancer, are not available. In this study, one such potential marker, ZBTB28, was evaluated for its potential usefulness in cervical cancer assessment.

Methods: Public database analysis, reverse-transcription polymerase chain reaction (PCR), and methylation-specific PCR were employed to analyze ZBTB28 expression and promoter methylation. The importance of ZBTB28 in cervical cancer cells was assessed by cellular and molecular analysis *in vitro* and *in vivo*.

Results: This study assessed the anti-tumor effects of the transcription factor, ZBTB28, which is often silenced in cervical cancer due to CpG methylation of its promoter. We found ZBTB28 to directly affect cervical cancer cell proliferation, apoptosis, autophagy, and tumorigenesis. Also, it increased cancer cell chemosensitivity to Paclitaxel, Cisplatin, and 5-fluorouracil. Ectopic ZBTB28 expression inhibited the growth of cervical cancer xenografts in nude mice. Furthermore, electron microscopy demonstrated ZBTB28 to induce autophagosomes in cervical cancer cells. ZBTB28 induced cellular autophagy by the degradation of Bcl-XL, reduction of the Bcl-XL-BECN1 complex, and by interaction with the autophagy-related gene FIP200. ZBTB28-induced autophagy of cervical cancer cells was shown to mediate cellular apoptosis through the regulation of FIP200.

Conclusion: These findings identify ZBTB28 as a tumor suppressor gene that can induce autophagy-related apoptosis in cervical cancer cells. As such, ZBTB28 may be a target for the treatment of uterine cervical carcinoma. Further, ZBTB28 promoter methylation analysis may offer a new objective strategy for cervical cancer screening.

Key words: ZBTB28; Cervical cancer; Autophagy; Apoptosis; BECN1; FIP200

76. 非小细胞肺癌差异表达基因的生物信息学分析

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目的: 应用生物信息学方法分析非小细胞肺癌 (NSCLC) 基因芯片数据, 筛选差异表达基因 (DEGs), 探讨与 NSCLC 预后相关的生物标志物, 为 NSCLC 的治疗提供新靶点。

方法: 在 GEO 数据库下载 NSCLC 相关的基因芯片数据, 运用 GEO2R 工具和 FunRich3.1.3 软件筛选出两个数据集共同的 DEGs。应用 DAVID 数据库对 DEGs 进行 GO 分析及 KEGG 分析, 并通过 STRING 数据库及 Cytoscape 3.8.0 软件构建蛋白质-蛋白质相互作用 (PPI) 网络, 分析筛



选出前 20 个枢纽基因。运用 Kaplan-Meier plotter 对 20 个枢纽基因进行预后分析，并通过多个外部数据库对枢纽基因的表达及其与预后的关系进行验证。

结果：从两个数据集中筛选出共同的 DEGs 159 个。构建 PPI 网络并进行分析，以连接度前 20 位的基因为本研究的枢纽基因。生存分析及多个外部数据库验证结果表明：SPP1 基因在 NSCLC 肿瘤组织中高表达，并且与患者的不良预后显著相关（ $P < 0.05$ ）。亚组分析结果显示，SPP1 可能通过影响淋巴结转移导致患者预后不良。

结论：SPP1 基因可能成为评价 NSCLC 患者预后的生物标志物，为 NSCLC 靶向治疗提供新思路。

关键词：非小细胞肺癌；差异表达基因；生物信息学分析；预后

77. SIX4 is induced by C-JUN/IL-6/STAT3 feedback loop and activates TP63/SOX2 signal axis to facilitate inflammation mediated carcinogenesis

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Inflammatory cancer transformation is one of the crucial driving factors of tumorigenesis. Colitis-associated colon cancer (CAC) evolved from inflammatory bowel disease (IBD) is an important subtype of colon cancer, but its inflammatory to cancer transformation mechanism remains to be elucidated. Here, we successfully established the animal models of chronic colitis and CAC, and found the expression of SIX4 is up-regulated in enteritis and colon cancer tissues. Inhibition of SIX4 alleviates intestinal inflammation and reduces adenoma formation in mice. The preliminary mechanism shows that inflammation activates the expression of SIX4 through IL-6/STAT3, while SIX4 induces its own expression by recruiting C-JUN to activate the IL-6/STAT3 signal, forming a positive feedback loop. Further studies revealed that upregulated SIX4 promotes the stemness of colon cancer cells via regulating TP63/SOX2 signal axis and facilitates tumorigenesis of CAC. This study demonstrates the important role of SIX4 in inflammatory cancer transformation for the first time, intends to provide new prevention and treatment strategies for CAC patients.

Key words: Colitis-associated colon cancer; IL-6/STAT3; C-JUN; tumorigenesis

78. 基于琥珀酰化修饰酶相关免疫评分构建的肾透明细胞癌预后预测模型

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目的：晚期或复发性透明细胞肾细胞癌（ccRCC）现有治疗手段及疗效有限。开发全新的 ccRCC 预后标志物，针对预后较差的患者采取更积极的治疗对于提高患者生存具有重要意义。琥珀酰化修饰是近年来新发现的一种发生于赖氨酸残基的翻译后修饰，主要受琥珀酰基转移酶 CPT1A 和 KAT2A, 去琥珀酰化酶 SIRT5 和 SIRT7 的动态可逆性调控。目前针对琥珀酰化修饰的研究均为一种特定的琥珀酰修饰酶在某一肿瘤中对下游靶蛋白的调控机制，尚无纳入 4 种琥珀酰化修饰酶的综合分析。因此，本研究拟探讨琥珀酰化修饰酶在 ccRCC 中的综合作用及可能机制。

方法：1.利用泛癌 RNA-seq 转录组数据分析 4 种琥珀酰化修饰酶在 10 种常见肿瘤中预后作用；利用 TCGA 肾透明细胞癌（ccRCC）转录组数据进行详细分析。2.利用“ConsensusClusterPlus”R 包对训练集进行一致性聚类分析。3.使用“Limma”R 包进行各 cluster 间差异表达基因筛选，利用“clusterprofiler”R 包进行 GO 和 KEGG 富集分析。4.利用 CIBERSORT 进行不同 cluster 间的免疫浸润特征分析。5.利用 LASSO 回归筛选免疫相关预后预测因子，并计算 RS_immune 评分。

结果：1.琥珀酰化调节酶在 ccRCC 中具有独特的预后价值。Cox 单因素回归分析结果显示，在 10 种常见肿瘤中，仅 ccRCC 患者的 OS 与 4 种琥珀酰化修饰酶表达均相关，提示琥珀酰化修饰酶在 ccRCC 中具有重要的作用。2.基于琥珀酰化修饰酶的一致性聚类分析建立 ccRCC 的 3-cluster 亚型。利用一致性聚类的方法分析 4 种琥珀酰化修饰酶的表达相似性，可将训练集中的 ccRCC 患者分为表达模式不同的 3-cluster 亚型。其中，cluster2 亚型 OS 最短，cluster3 亚型 OS 最长。这些结果提示基于琥珀酰化修饰酶的一致性聚类分析可以将 ccRCC 患者很好地分为生存和临床病理学特征显著不同的 3 个 cluster 亚型。3.琥珀酰化修饰酶可能通过调节免疫途径促进 ccRCC 进展。利用 cluster2 和 cluster1 分别与 cluster3 的差异基因进行 GO 分析的结果显示，cluster1 和 cluster2 中上调的大多数通路都与免疫调节有关，提示琥珀酰化调节酶可能通过调节免疫途径促进 ccRCC 进展。4.琥珀酰化调节酶参与调节 ccRCC 免疫细胞浸润。利用 CIBERSORT 分析不同 cluster 患者间免疫细胞浸润差异的结果显示，Tregs 细胞, M0 巨噬细胞及静息性肥大细胞在不同 cluster 中表现出浸润差异；Kaplan-Meier 分析显示，仅 Tregs 浸润与 OS 预后不良相关（HR=1.820, $P=0.011$ ）。进一步分析 4 种琥珀酰化修饰酶与 Tregs 细胞关键标志物基因 FOXP3 的相关性，结果显示，FOXP3 的表达与 SIRT7 呈正相关，与 SIRT5 和 CPT1A 呈负相关。这些结果提示琥珀酰化修饰酶 SIRT7, SIRT5 及 CPT1A 可能通过促进 Tregs 的浸润诱导免疫抑制微环境，从而促进 ccRCC 进展。5.利用基于琥珀酰化修饰酶相关的免疫评分模型预测 ccRCC 患者预后。针对进一步筛选出的 cluster2 和 cluster1 中高表达的 34 个与 ccRCC 不良预后相关的免疫相关基因，进行 LASSO Cox 回归分析，最终筛选出 6 个免疫相关基因。按公式（ $RS\_immune=0.148 \times EXP[Aggr]+0.066 \times EXP[IGLV3-21]+0.038 \times IL20RB]+0.283 \times EXP[LTB4R]+0.223 \times EXP[NFKBIZ]+0.018 \times EXP[SAA1]$ ）计算各样本的 6 基因免疫评分，并以中位数为界将患者分为 RS_immune 高、低两组。结果发现，High-



RS_immune 组患者 OS 远远短于 Low-RS_immune 组患者 (HR=4.232, $P<0.001$), 提示琥珀酰化修饰酶与免疫基因的表达密切相关, 6 基因免疫评分可很好地预测 ccRCC 患者预后。

结论: 琥珀酰化修饰酶在 ccRCC 中具有独特而重要的预后预测价值; 琥珀酰化调节剂可能通过调控 Tregs 细胞浸润和免疫相关基因表达促进 ccRCC 恶性进展; 基于琥珀酰化修饰酶相关免疫基因构建的 6 基因免疫模型具有较好的 ccRCC 患者预后价值。

关键词: 肾透明细胞癌; 琥珀酰化; 免疫评分; 预后预测

79. SII (系统性免疫-炎症指数) 预测首程治疗老年结直肠癌患者的预后

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目的: 结直肠癌是威胁我国居民生命健康的主要恶性疾病之一。老年结直肠癌患者意味着生理机能的降低和伴有内科合并症, 其影响着预后和对治疗的耐受性。本研究旨在探讨 SII (系统性免疫-炎症指数) 在首程治疗的老年结直肠癌患者预后中的预测价值。

方法: 回顾性地分析了四川省人民医院 2014 年 1 月至 2014 年 12 月 103 名首程治疗的老年结直肠癌患者。根据 ROC 曲线分析确定治疗前 SII 的界值: $1060 \times 10^9/L$ 。根据 SII 的界值分为高 SII 组和低 SII 组。卡方检验用于分析治疗前 SII 与 1 年生存率之间的相关性。Kaplan-Meier 生存分析用于探讨 SII 和累积生存概率之间的相关性。

结果: 低 SII 的老年结直肠癌患者有更好的 1 年生存率 ($\chi^2 = 6.012$, $P=0.014$) 和更高的累积生存概率 ($P=0.010$)。

结论: 对于首程治疗的老年结直肠癌患者而言, 治疗前的 SII 值有可能成为预测其生存预后的指标。

关键词: SII (系统性免疫-炎症指数); 首程治疗; 老年结直肠癌患者; 预测价值

80. C. tropicalis promotes chemotherapy resistance in colon cancer through increasing lactate production to regulate the mismatch repair system

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Background: Due to chemotherapeutic drug resistance, tumor recurrence is common in patients with colorectal cancer (CRC) and drug-resistant patients are often accompanied by defects in the mismatch repair system (MMR). “Warburg effect” is a metabolic feature of most tumor cells and is a potential cause of chemotherapy resistance. However, whether lactate, the main glycolysis product, can participate in CRC chemoresistance by regulating MMR has not been reported. Previous studies have shown that *Candida tropicalis* (*C. tropicalis*) is closely related to the development of CRC, but whether this conditional pathogenic fungus is involved in chemotherapy needs further investigation.

Methods: In this paper, a mouse CRC xenograft tumor model was established. The effect of oxaliplatin in *C. tropicalis* treated and non-treated groups was evaluated by comparing tumor weight and tumor volume, we also detected the expression of main functional proteins of MMR and glycolysis flux in tumor tissues. Furthermore, we stimulated the colon cancer cell line SW480 with *C. tropicalis* to explore the mechanism by which *C. tropicalis* affects the glycolysis and regulates MMR to induce chemotherapy resistance in CRC cells.

Results: We found that *C. tropicalis* promoted CRC chemotherapy resistance to oxaliplatin, it also can markedly up-regulate the glycolysis level and restrain the expression of functional MMR proteins in tumor tissues. Furthermore, inhibition of lactate production can reverse the chemotherapy resistance notably caused by *C. tropicalis*. Mechanistically, we found that lactate can regulate the function of the MMR through the GPR81-cAMP-PKA-CREB axis to facilitate the chemotherapy resistance of CRC to oxaliplatin.

Conclusion: This study clarified that the conditional pathogenic fungus *C. tropicalis* can prompt CRC chemoresistance by increasing production of lactate to inhibit the MMR, and provided novel ideas for improving CRC chemotherapy effect.

Key words: *Candida. tropicalis*; chemoresistance; glycolysis; lactate; mismatch repair

81. Combination of three DNA methylation markers as a novel approach for the diagnosis of non-small cell lung cancer

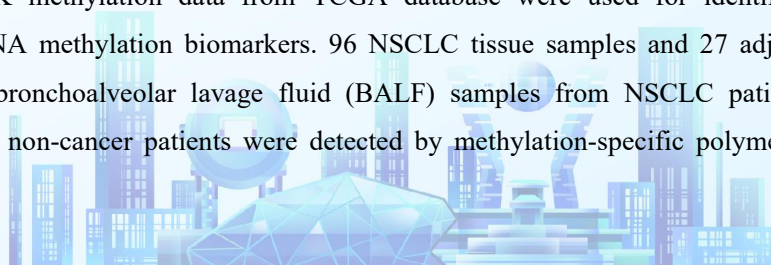
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Clinical Medical College and The First Affiliated Hospital of Chengdu Medical College

Purpose: For patients with suspected non-small cell lung cancer (NSCLC) who are difficult to diagnose, liquid biopsy can bring evidential support. Our aim is to establish an approach of liquid biopsy for the diagnosis of NSCLC based on novel DNA methylation biomarkers in sputum and plasma samples.

Methods: Our RNA sequencing (RNA-seq) and targeted bisulfite sequencing data, combined with RNA-seq and 450K methylation data from TCGA database were used for identification of NSCLC diagnostic DNA methylation biomarkers. 96 NSCLC tissue samples and 27 adjacent normal tissue samples, 72 bronchoalveolar lavage fluid (BALF) samples from NSCLC patients and 17 BALF samples from non-cancer patients were detected by methylation-specific polymerase chain reaction



(MSP). 44 sputum samples and 25 plasma samples were analysed by MethyLight droplet digital PCR (ddPCR).

Results: Three DNA methylation biomarkers C2orf40, FIBIN and GRP were identified as diagnostic biomarkers of NSCLC through high throughput data. Their mRNA expressions were all negatively correlated with methylation levels, and were closely correlated with clinical T stage and prognosis. MethyLight ddPCR was used to detect body fluid samples after these three DNA methylation markers were verified to have a good diagnostic efficacy in tissue and BALF samples. In sputum samples, the diagnostic sensitivities of C2orf40, FIBIN and GRP was 92.3%, 92.3%, and 80.8% with the specificity of 55.6%, 61.1%, and 72.2%, respectively. The sensitivity and specificity were 92.3% and 77.8% by combination of these three biomarkers. In plasma samples, the diagnostic sensitivities of C2orf40, FIBIN, and GRP was 63.6%, 72.7%, 54.5%, and 81.8%. The specificity was 64.3%, 71.4%, and 85.7%, respectively. The sensitivity and specificity of the combined panel was 72.7% and 85.7%, respectively.

Conclusion: Combination of three DNA methylation biomarkers C2orf40, FIBIN and GRP has a good diagnostic efficiency by using MSP or MethyLight ddPCR method in NSCLC. It is a convenient and economical approach and has potential as a novel application in liquid biopsy diagnosis of NSCLC.

Key words: Non-small cell lung cancer; diagnosis; biomarkers; methylation; MethyLight

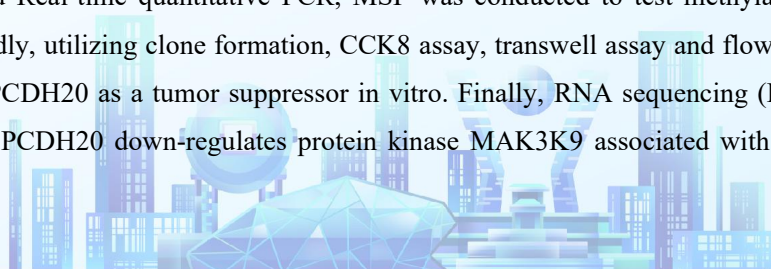
82. Inactivation of PCDH20 by aberrant promoter hypermethylation contribute to esophageal cancer progression

Junhao Mu*

Chongqing Medical University

Background: Protocadherin (Pcdh) is the largest mammal subgroup of the cadherin superfamily, which play important roles in mediating intercellular adhesion, aberrant expression of protocadherin has been found closely related to invasion and metastasis among multiple tumors. Recent studies have shown that PCDH20 acts as a tumor suppressor gene in a variety of solid tumors mainly by antagonizing Wnt/ β -catenin pathway but is frequently down-regulated may due to promoter methylation. However, the mechanism of PCDH20 in esophageal squamous cell cancer (ESCC) remains elusive. Therefore, this study mainly focused on the effects of PCDH20 on the esophageal cancer and underlying molecular mechanisms.

Methods: Firstly, the expression of PCDH20 in esophageal cancer tissues and cells were detected by Real-time PCR and Real-time quantitative PCR, MSP was conducted to test methylation of PCDH20 in ESCC. Secondly, utilizing clone formation, CCK8 assay, transwell assay and flow cytometry to verify functions of PCDH20 as a tumor suppressor in vitro. Finally, RNA sequencing (RNA-Seq) was used to found that PCDH20 down-regulates protein kinase MAK3K9 associated with activation of WNT



pathway. Western blot and Co-immunoprecipitation were carried out to study the molecular mechanism of PCDH20 in ESCC.

Results: PCDH20 expression was significantly down-regulated in esophageal cancer tissues and cells due to frequently promotor methylation. Ectopic expression of PCDH20 suppressed ESCC cells by inhibiting cell growth, migration and invasion, inducing cell cycle arrest and promoting cell apoptosis. Furthermore, we investigated the core molecular mechanism of PCDH20 in esophageal cancer, the results indicated that PCDH20 exerts anti-tumor effect by down-regulating MAP3K9 to suppress the Wnt/ β -catenin pathway in ESCC.

Conclusion: Our study identified PCDH20 act as a tumor suppressor gene, antagonizing Wnt/ β -catenin signaling pathway by downregulating MAP3K9 in ESCC.

Key words: PCDH20; esophageal squamous cell cancer; MAP3K9; Wnt/ β -catenin pathway

83. 肺部菌群失调影响早期肺癌的复发

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研究目的: 人体内的微生物在潜移默化地影响着人类的健康。微生物菌群的失调可能通过影响代谢,炎症或免疫通路,在多种水平的致癌过程中发挥重要作用。而肺部菌群与肺癌复发的关系尚不明确。

材料与方法: 我们分别对 29 例 3 年内存在复发和 29 例无复发的肺癌患者的肿瘤及配对癌旁组织进行了 16s 测序。通过多样性分析,差异分析等探索肺部菌群与早期肺癌复发的关系。

结果: 复发组和无复发组在菌群组成上存在差异,门水平,复发组中厚壁菌门($P=0.036$)增加,变形菌门($P<0.001$)和放线菌门($P<0.001$)减少。在属水平,双歧杆菌,罗氏菌属和粪杆菌属丰度较高,且在两组的肿瘤组织中存在差异。物种组成上,复发组和无复发组的癌旁组织菌群构成存在差异($P=0.001$)。无复发组的肿瘤和正常组织 α 多样性明显高于复发组($P<0.001$)。同时, α 多样性可以区分无复发生存时间(RFS),高多样性组 RFS 时间明显长于低多样性组($P<0.001$)。此外,LEfSe 分析发现罗氏菌属,双歧杆菌等是很好的复发相关微生物标志物。

结论: 早期肺癌复发与肺部微生物失调相关,罗氏菌属,双歧杆菌等是很好的复发相关微生物标志物。

关键词: 肺癌; 复发; 微生物; 标志物

84. PKMYT1AR promotes β -catenin stabilization and cancer stem cell maintenance in non-small cell lung cancer

Yaomei He*, Cuiping Yang, Yongbin Chen



Non-small cell lung cancer (NSCLC) is the most common type of human lung cancers, which has diverse pathological features. Although many signaling pathways and therapeutic targets have been defined to play important roles in NSCLC, limiting efficacies have been achieved. We identified a long non-coding RNA termed PKMYT1AR that is highly expressed in NSCLC, especially is increased in cancerous cell lines compared to that in normal human bronchial epithelium cell line. We found that PAKMYT1AR high expression correlates with worse clinical outcome, and knockdown of PKMYT1AR inhibits tumor cell proliferation, migration and xenograft tumor formation. Bioinformatics analysis and a luciferase assay demonstrated that PKMYT1AR directly interacts with MicroRNA to attenuate its binding to the 3'-untranslated region of PKMYT1, leading to upregulation of PKMYT1. Furthermore, we show that MicroRNA is downregulated in both cancerous cell lines and peripheral blood serum isolated from NSCLC patients. Consistently, forced expression of MicroRNA inhibits the proliferation and migration abilities of tumor cells. Mechanistic study showed that PKMYT1AR/MicroRNA/PKMYT1 axis promotes cancer stem cells (CSCs) maintenance in NSCLC, which in turn leads to reduced tumorigenesis. In summary, our findings reveal the critical role of PKMYT1AR/ MicroRNA /PKMYT1 axis during NSCLC progression, which could be used as novel therapeutic targets in the future.

Key words: PKMYT1AR; MicroRNA; PKMYT1; non-small cell lung cancer; cancer stem cells (CSCs)

85. Systematic profiling of alternative splicing in *Helicobacter pylori*-negative gastric cancer and their clinical significance

Chuan Liu^{*1}, Chuan Hu², Zhi Li¹, Jing Feng¹, Jiale Huang¹, Bowen Yang¹, Ti Wen¹

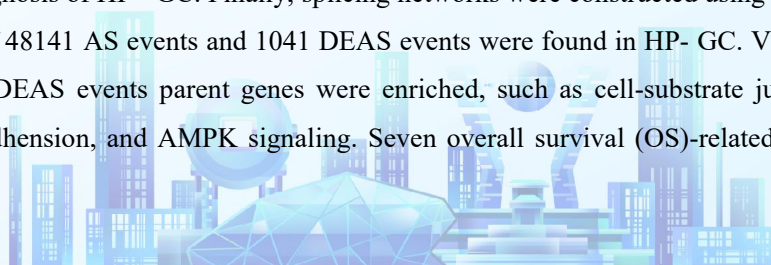
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Background: Alternative splicing (AS) may cause structural and functional variations in the protein to promote the proliferation of tumor cells. However, there is no comprehensive analysis of the clinical significance of AS in *Helicobacter pylori*-negative gastric cancer (HP-GC).

Methods: The clinical, gene expression profile data and AS events of 138 HP-GC patients were obtained from the database named the cancer genome atlas. Differently expressed AS (DEAS) events were determined by a comparison of the PSI values between HP-GC samples and adjacent normal samples. Unsupervised clustering analysis, proportional regression and Kaplan-Meier analysis were used to explore the association between clinical data and immune features and to establish two nomograms about the prognosis of HP-GC. Finally, splicing networks were constructed using Cytoscape.

Results: A total of 48141 AS events and 1041 DEAS events were found in HP-GC. Various functions and pathways of DEAS events parent genes were enriched, such as cell-substrate junction, cell leading edge, focal adhesion, and AMPK signaling. Seven overall survival (OS)-related and seven disease-



free survival (DFS)-related AS events were used to construct the prognostic signatures. Based on the independent prognostic factors, two nomograms were established and showed excellent performance. Then, splicing regulatory networks among the correlations suggested that splicing factors were significantly associated with prognostic DEASs. Finally, the unsupervised clustering analysis revealed that DEAS-based clusters were associated with clinical characteristics, tumor microenvironment, tumor mutation burden, and immune features.

Conclusion: Seven OS-related and seven DFS-related AS events have been found to be correlated with the prognosis of HP–GC and can be used as prognostic factors to establish an effective nomogram.

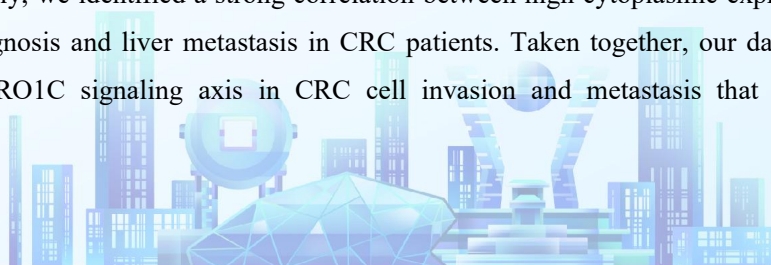
Key words: Alternative splicing; Helicobacter pylori-negative gastric cancer; Immune cells; Prognosis

86. Cytoplasmic RAD23B interacts with CORO1C to induce invadopodia formation and promote colorectal cancer progression and metastasis

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Colorectal cancers (CRCs) are characterized by diffuse infiltration of tumor cells into the regional lymph nodes and metastasis to distant organs, and its highly invasive nature contributes to disease recurrence and poor patient outcomes. The molecular mechanisms underlying CRC cell invasion remain incompletely understood. Here, we identified the upregulation of DNA damage repair-related protein RAD23B in CRC cells and tissues and showed that it associates with CORO1C to facilitate invasion. We found that knockdown of RAD23B expression significantly inhibited the proliferation, invasion, and migration abilities of CRC cells both in vitro and in vivo, and suppressed the Talin1/2/integrin/FAK/RhoA/Rac1/CORO1C signaling pathways. Mechanistically, overexpression of RAD23B and/or CORO1C further increased invadopodia formation and matrix degradation in SW480 and HCT8 CRC cells. Conversely, silencing of RAD23B expression suppressed tumorigenesis and liver metastasis in xenotransplant murine models. Furthermore, we found that RAD23B was significantly overexpressed in paired tumor tissue compared to adjacent non-tumor tissues of CRC patients. Finally, we identified a strong correlation between high cytoplasmic expression of RAD23B, and poor prognosis and liver metastasis in CRC patients. Taken together, our data highlight a novel RAD23B-CORO1C signaling axis in CRC cell invasion and metastasis that may be of clinical significance.



Key words: invasive protrusion; invadopodia formation; liver metastasis; Talin1/2/integrin/FAK/RhoA/Rac1/CORO1C signaling pathway

87. Aberrantly High Activation of a FoxM1-STMN1 Axis Contributes to Progression and Tumorigenesis in FoxM1-Driven Cancers

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Fork-head box protein M1 (FoxM1) is a transcriptional factor which plays critical roles in cancer development and progression. However, the general regulatory mechanism of FoxM1 is still limited. STMN1 is a microtubule-binding protein which can inhibit assembly of microtubule dimer or promote depolymerization of microtubules. It was reported as a major responsive factor of paclitaxel resistance for clinical chemotherapy of tumor patients. But the function of abnormally high level of STMN1 and its regulation mechanism in cancer cells remain unclear. In this study, we used public database and tissue microarrays to analyze the expression pattern of FoxM1 and STMN1 and found a strong positive correlation between FoxM1 and STMN1 in multiple types of cancer. Lentivirus-mediated FoxM1/STMN1-knockdown cell lines were established to study the function of FoxM1/STMN1 by performing cell viability assay, plate clone formation assay, soft agar assay in vitro and xenograft mouse model in vivo. Our results showed that FoxM1 promotes cell proliferation by up-regulating STMN1. Further ChIP assay showed that FoxM1 up-regulates STMN1 in a transcriptional level. Prognostic analysis showed that a high level of FoxM1 and STMN1 is related to poor prognosis in solid tumors. Moreover, a high co-expression of FoxM1 and STMN1 has a more significant correlation with poor prognosis. Our findings suggest that a general FoxM1-STMN1 axis contributes to cell proliferation and tumorigenesis in hepatocellular carcinoma, gastric cancer and colorectal cancer. The combination of FoxM1 and STMN1 can be a more precise biomarker for prognostic prediction.

Key words: FoxM1; transcriptional regulation; STMN1; cell proliferation; cell mitosis

88. COL14A1 promotes self-renewal of human liver cancer stem cells through activation of ERK signaling

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Objective: Liver cancer stem cells (CSCs) are the culprits of hepatocellular carcinoma metastasis and recurrence. Only by eliminating tumor stem cells can malignant tumors be fundamentally cured. This study aimed to identify the role and underlying mechanism of aberrant Collagen Type XIV Alpha 1 Chain (COL14A1) overexpression in liver CSCs, and improve understanding of the molecular basis of hepatocellular carcinoma metastasis and recurrence.

Methods: First, quantitative real-time polymerase chain reaction was used to confirm aberrant high-expression of COL14A1 in liver CSCs. Next, interference experiments were performed to determine the key role of COL14A1. To explore the mechanism of COL14A1 overexpression in liver CSCs, putative microRNA (miRNAs) targeting COL14A1 were analyzed using the miRTarBase database. Next, quantitative real-time polymerase chain reaction, western blotting, and luciferase reporter assays were performed to verify the interaction between miR-7108-3p and COL14A1. Lastly, key target proteins of the COL14A1-extracellular-regulated signal kinase (ERK) signaling pathway were identified through western blotting analysis. This study was approved by the Ethics Committee of Shanghai Fourth People's Hospital, Tongji University School of Medicine, China (approval No. 2019tjdx17) on February 21, 2019.

Results: COL14A1 is abnormally highly expressed in liver CSCs, which is necessary for liver CSCs to maintain their self-renewal capability. Mechanistically, COL14A1 is post-transcriptionally regulated by miR-7108-3p in a negative manner. Low expression of miR-7108-3p increased translation of COL14A1, which subsequently activated ERK signaling, ultimately maintaining the self-renewal and stem cell-like properties of liver CSCs.

Conclusion: COL14A1, which is negatively regulated by miR-7108-3p, was found to play a crucial role in maintaining the self-renewal and stem cell-like properties of liver CSCs through activation of ERK signaling.

Key words: COL14A1; ERK signaling; hepatocellular carcinoma; miR-7108-3p; liver cancer stem cells

89. Activation of PI3K/AKT pathway is revealed as a mechanism of chemoresistance in small cell lung cancer

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Purpose: There is an urgent need to elucidate mechanisms involved in chemoresistance in SCLC. Here we have investigated the mechanisms of chemoresistance in SCLC, focusing on comparing the genotype and phenotype in tumor samples of chemo-resistant and chemo-sensitive SCLC.

Methods: We conducted whole-exome sequencing (WES) on paired tumor samples at diagnosis and relapse collected from 11 patients with SCLC treated with standard chemoradiation to investigate mechanisms of chemoresistance. Additionally, we performed targeted sequencing of 1,021 cancer-related genes on cell free DNA (cfDNA) obtained at baseline from 9 additional patients and paired relapsed samples. Furthermore, we performed label-free mass spectrometry- (MS-) based proteomics on tumor samples derived from 28 chemo-resistant and 23 chemo-sensitive patients with SCLC.

Results: We found that numerous previously reported mutated genes were identified both in treatment-naïve and post-treatment SCLCs in our cohort, while numerous relapse-specific mutations and copy number variants (CNVs) were also identified. At relapse, genes in the PI3K/ATK signaling pathway were enriched for acquired somatic mutations or high frequency acquired CNVs. Pathway analysis found that genes with differentially upregulated expressed proteins were enriched in HIF-1 signaling pathway. Interestingly, 12 of 96 PI3K/AKT pathway genes containing acquired somatic copy number amplification were enriched in HIF-1 pathway, and most of them were located upstream of HIF-1. Furthermore, in vitro-derived chemo-resistant SCLC cell lines demonstrate reversal of chemotherapy resistance upon PI3K.

Conclusions: Overall, our findings point to an important role for PI3K/AKT pathway activation in SCLC chemoresistance. PI3K/ATK pathway targeting could be a viable strategy to reverse chemoresistance.

Key words: small cell lung cancer; whole-exome sequencing; mechanism of chemoresistance; PI3K/AKT pathway

90. 线粒体呼吸链受损条件下肿瘤细胞二氢乳清酸生物合成的调控机制研究

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目的: 乏氧和线粒体呼吸链受损的条件下肿瘤细胞依赖于谷氨酰胺到二氢乳清酸(DHOA)的代谢途径以存活和增殖, 本研究旨在探究线粒体呼吸链受损条件下肿瘤细胞中谷氨酰胺多余的碳和氮合成 DHOA 的调控机制。

方法: 分别在常氧,缺氧及 Ant A 条件下培养宫颈癌 HeLa 细胞并提取总 RNA 进行转录组测序筛选差异表达 mRNA 并进行差异及富集分析; 运用生物信息学分析, 研究肿瘤细胞 DHOA 合成代谢过程中相关蛋白 CAD,UMPS,DHODH 及 GOT1 在肿瘤组织中的表达及对患者预后的影响;



利用 Western Blot 技术检测 MCF-7 和 HeLa 细胞在呼吸链受损条件下 DHOA 代谢过程中蛋白的动态变化。运用免疫共沉淀(Co-IP)技术初步探究 DHOA 合成相关蛋白之间的相互作用。

结果: 转录组学分析发现 Anti-A vs. Normoxia 及 Hypoxia vs. Normoxia 不同条件下 mRNA 表达存在明显不同, 相较于常氧, 在 Ant A 条件下, CAD mRNA 表达明显上调, UMPS 表达则明显下调, 而在缺氧条件下 CAD 与 UMPS 表达并无显著变化。生信分析结果发现 CAD 和 GOT1 在乳腺癌和宫颈癌中表达升高且二者高表达均与乳腺癌不良预后呈正相关。DHODH 在乳腺癌中表达下降但在宫颈癌中表达无明显变化且与预后无相关性。Ant A 可以下调 UMPS 蛋白表达, 并以磷酸化的方式激活 CAD; Ant A 可上调 AMPK α 和 mTOR 蛋白表达。Rot 可使 HeLa 细胞 CPS2 蛋白表达升高; 苯乙双胍可使 MCF-7 细胞 CPS2 表达升高, 并以磷酸化方式激活 CAD; 寡霉素不能上调 HeLa 细胞 CPS2 表达但可降低 DHODH 及 UMPS 蛋白表达。三种抑制剂作用下 DHOA 合成相关蛋白表达变化不一, 需要与代谢物检测相结合以进一步研究。Co-IP 实验初步证明在常氧和 Ant A 条件下 CAD 都能够与 UMPS 结合。

结论: Ant A 所诱导的线粒体呼吸链受损条件下, CAD 表达上调并以磷酸化方式被激活从而调控肿瘤细胞 DHOA 的大量合成, 而 UMPS 表达被抑制, 导致 DHOA 并没有生成下游的 UMP。AMPK 和 mTOR 两大信号可能在这一代谢过程中发挥了重要的调控作用。

关键词: 二氢乳清酸; 线粒体呼吸链受损; 肿瘤细胞; 调控机制

91. The effect of PRL-3 regulated PI3K/Akt/mTOR signal pathway on the death of acute myeloid leukemia cell and its mechanism

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fujian medical university

Background: PRL-3, an oncogenic dual-specificity phosphatase, is relevant to the occurrence and development of a wide range of malignant tumors. Studies have shown that PRL-3 is overexpressed in about 47% of acute myeloid leukemia (AML) patients, and is an independent negative prognostic factor in AML, both for overall survival and event-free survival. Li et al. find that PRL-3 can change the characteristics of ovarian cancer cells through PI3K/Akt/mTOR pathway. mTOR is the key regulator of autophagy in this pathway. PRL-3 is both the activator and the substrate of autophagy. Inhibition of autophagy dramatically reduced the ovarian cancer cells growth induced by PRL-3. Whether PRL-3 affects the death of AML cells through PI3K/Akt/mTOR pathway is unclear. In the current study, we investigated that (1)PRL-3 affected the characteristics and PI3K/Akt/mTOR pathway of AML cells, (2) the combination of PRL-3 inhibitor and mTOR inhibitor promoted the death of AML cells.

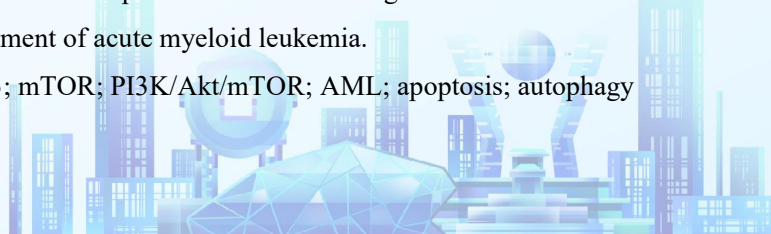


Methods: After exposure to pentamidine (a kind of PRL-3 inhibitor), cell proliferation inhibition was tested by MTS, cell cycle and apoptosis were measured by FCM, autophagy and PI3K/Akt/mTOR pathway were detected by Western blot. A recombinant lentiviral vector was constructed to change the expression of PRL-3. then, autophagy and PI3K/Akt/mTOR pathway were detected by Western blot. Combined pentamidine with rapamycin (a kind of mTOR inhibitor), apoptosis and autophagy were detected by Western blot.

Result : After exposure to pentamidine, the mRNA and protein expression of PRL-3 and mTOR were both significantly down-regulated ($P<0.05$) in K562 and U937 cells. Compared with the control groups: the growth of K562 and U937 cells was ere inhibited ($P<0.05$); the proportion of K562 and U937 cells in the G2/M phase were increased significantly ($P<0.05$), the proportion of K562 and U937 cells in the S phase were reduced significantly ($P<0.05$) and the total apoptosis rate were as increased ($P<0.05$) ; the expression of autophagy related protein ATG5 in K562 and U937 cells were both increased ($P<0.05$) , the ratio of LC3II/LC3I was decreased significantly ($P<0.05$) and the expression of Beclin-1 did not change significantly ($P>0.05$) ; the expression of Akt did not change significantly ($P>0.05$) ; while the expression of p-Akt, mTOR, and p-mTOR were decreased significantly ($P<0.05$) , respectively. After c Constructed a specific shRNA lentiviral vector targeting PRL-3 in K562 cells ,and a PRL-3 overexpression lentiviral vector, compared with theK562-NC group, PRL-3-silencing dramatically increased the expression of p-Akt, mTOR and p-mTOR in the K562-KD group ($P<0.05$), compared with the control group, the expression of Akt in the K562-KD group did not change significantly ($P>0.05$) , the expression of p-Akt, mTOR and p-mTOR were all decreased significantly ($P<0.05$) , and the expression of ATG5 was increased significantly($P<0.05$), the ratio of LC3II/LC3I was decreased significantly ($P<0.05$), and the expression of Beclin-1 did not change ($P>0.05$) . After constructed a PRL-3 overexpression lentiviral vector; the expression of Akt in the U937-OE group did not change significantly ($P>0.05$), the expression of p-Akt, mTOR, p-mTOR were all increased significantly ($P<0.05$), the expression of ATG5, Beclin-1 did not change significantly ($P>0.05$), the ratio of LC3II/LC3I was increased ($P<0.01$). Different results were observed in the U937-OE group. The expression of p-Akt, mTOR, p-mTOR were all increased significantly ($P<0.05$), the expression of ATG5, Beclin-1 did not change significantly ($P>0.05$), the ratio of LC3II/LC3I was increased significantly($P<0.01$), except the expression of Akt did not change significantly ($P>0.05$).

Conclusion: Pentamidine, an inhibitor of PRL-3, can inhibit PI3K/Akt/mTOR signaling pathway, which can inhibit cell proliferation, arrest cell cycle, promote apoptosis and reduce autophagy. The expression of PRL-3 and mTOR had a similar trend, and can regulate PI3K/Akt/mTOR signaling pathway, then affect the autophagy level of cells. Combined pentamidine with rapamycin two kinds of inhibitor can reduce the protective autophagy induced by rapamycin, and in turn promote the death of AML cells. PRL-3 is expected to be a new target for AML treatment.PRL-3 may represent a novel target for treatment of acute myeloid leukemia.

Key words: PRL-3; mTOR; PI3K/Akt/mTOR; AML; apoptosis; autophagy



92. 人工智能在硫代乙酰胺所致实验动物肝脏病变中的应用

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材料与方法：我们构建了硫代乙酰胺诱导的胆管病变模型，并利用分子氢(H₂)干预胆管纤维化进程。

硫代乙酰胺导致的动物肝脏病变有三个特征：肝脏边缘呈波浪状,肝纤维化和疑似胆管癌。为了客观,定量地评价肝脏病变，我们开发了一种基于卷积神经网络(CNNs)的肝脏病变自动检测框架。首先使用 Otsu 阈值算法从整个幻灯片图像中提取组织区域，然后进行形态学操作，计算相应的组织区域 tissue。随后，提出了基于深度学习的病变自动检测框架，从组织区域中检测和定位纤维化和癌症区域。该框架包括一个补丁级分类和一个后处理过程，以生成损伤似然图的 WSI。我们以滑动窗口的方式在组织区域运行 patch-wise CNN 分类器。对于每个 patch，分类器被用来给出一个损伤概率。然后累积概率，得到 WSI 的似然图。然后，对似然图进行归一化，使每个像素具有从 0 到 1 的连续似然。为了得到病变区域，Alesion 对 0.9 的似然图进行阈值化，去除低似然区域。已知 WSI 的整个组织面积(tissue area, tissue)和病变面积(A/lesion, A/lesion)，我们可以通过 $ratio = \frac{A/lesion}{tissue}$ 计算比值。

结果：我们开发了一个基于深度学习卷积神经网络(CNNs)的病变自动检测框架。该 AI 算法清晰显示了 WSIs 中肝脏病变的位置和数量。TAA 组 AI 识别纤维化病变的比例为 $19.6\% \pm 9.01$ ，明显高于 TAA + H₂ 组($7.53\% \pm 11.0$)。我们还在光学显微镜下计算了显微镜下“肠型”CCA。TAA 组所有大鼠(100%，9/9)均发生显微镜下胆管纤维化，显微镜下平均为 12 ± 10.1 只。令人惊讶的是，在 TAA + H₂ 组中，只有 57.1%(4/7)的大鼠发生了显微镜下的胆管纤维化，每只大鼠 2.9 ± 5.4 个病变，而其他 42.9%的大鼠没有任何可检测到的胆管纤维化。TAA 组胆管纤维化发生率明显高于 TAA + H₂ 组($P=0.0487$)。

结论：实验动物的肝脏病变评估方法完全可以由人工转变为机器化。其优点在于：①可视化，非专业人士都能够看得懂；②计量化，精准到小数点后三位；③整体化，能够看到整个肝脏切面的变化，减少误差；④真实化，杜绝了造假。

关键词：人工智能；硫代乙酰胺；肝脏病变

93. 利用自动组织学分类技术研判富氢水预防硫代乙酰胺诱导大鼠胆管上皮癌前病变的应用性研究

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研究目的：动物原位成瘤模型是研究疾病发生和药物干预的极佳手段。胆管纤维病变是一种有争议的肝内胆管病变，先于胆管癌的发展。在这里，我们构建了硫代乙酰胺诱导的胆管病变模型，并利用分子氢(H₂)干预胆管纤维化进程。

材料与方法：首先利用正常大鼠评价分子氢(H₂)的安全性和生活质量。而后，在硫代乙酰胺(TAA)诱导的胆管纤维化大鼠的整个过程中给予 H₂。其次，给予大鼠 TAA 3 个月，然后进行 H₂ 干预。采集大鼠肝脏，用光镜和卷积神经网络进行评估。采用 RNA-seq 分析这些动物模型的遗传变化。

结果：富氢水的持续使用是安全的，改善了生活质量。肝胆管纤维化发生率和平均数目：TAA 组 (100%，12.0±10.07) 高于 H₂ 组 (57.1%，2.86±5.43)。人工智能算法显示，TAA 组 Alesion/Aliver(19.6%±9.01)高于 H₂ 组(7.54%±11.0)。RNA-seq 分析显示，H₂ 导致糖酵解下降。在第三个实验中，长期使用 H₂ 后，可疑肿瘤的发生率和肝脏病变的比例较未治疗组(100%，0.98%±0.73)下降 (12.5%，0.57%±0.45)。使用 H₂ 后，肠道微生物群发生变化，包括 clostridiaceae-1, ruminococcus, turicibacter, coriobacteriales, 放线菌 actinobacteria 和 firmicutes-bacterium。

结论：人工智能技术可以精准识别肝脏病变，并予以可视化和计量化，从整体上反映了富氢水的干预效果，防止人为所致的计量偏差。可视化结果显示，富氢水可以防止肝损伤和胆管纤维化，并通过调节肠道菌群的组成部分改善生活质量。

关键词：自动组织学分类；富氢水；硫代乙酰胺；胆管上皮癌

94. 病理人工智能的三阶段学说

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近年来，病理切片数字化技术结合人工智能技术为病理学科打开了一扇新的大门。人工智能是指研究、开发用于模拟、延伸和扩展人的智能的理论、方法、技术及应用系统的一门新的技术科学。人工智能扩展了数字病理学的范畴，由最初的数字化过程进化成为数字化图像检测、分割、诊断和分析方法。目前，人工智能已用于探索基于病理图像的细胞学初筛、定量分析、组织病理诊断和判断预后等方面。

1. 病理人工智能的三阶段学说

基于病理在癌症管理中的重要性及医学自身的发展规律，我们把基于数字病理图像识别的人工智能分为 3 个阶段：第一阶段即诊断和辅助诊断，明确诊断是肿瘤诊治的最核心环节，也是目前病理人工智能期待解决的热点和难点；第二阶段即精准医疗，肿瘤确诊之后，治疗方案的选择

是重点，基于人工智能提取的病理特征有助于指导治疗方案的选择；第三个阶段即生命探索，肿瘤自然演进或药物诱导下的进化是肿瘤患者治疗失败的主要原因，病理人工智能有助于探索肿瘤进化史，为防治肿瘤提供建议。

2. 人工智能与基因组学

基于数字病理的人工智能第3个阶段就是整合生物医学领域和病理形态学，利用计算机程序可视化和量化肿瘤异质性和肿瘤微环境，甚至识别导致肿瘤细胞增殖和转移的异常基因和信号通路等，助力研究肿瘤进化、筛选新的靶点、开发新的药物等，最终开发精准、有效的个体化治疗方案。人工智能通过病理信息探索肿瘤发生和肿瘤进化有助于推动医疗进步，反哺精准医疗。然而如何将病理特征和组学特征相融合值得思考。近年出现的空间转录组能够将病理 H-E 切片与 RNA 测序相对应，观察病理切片上的某一区域的基因表达情况，这是人工智能-病理-组学交叉融合的一个创新性尝试，有助于我们通过病理切片就能够知道肿瘤更多的信息。

3. 贯穿病理人工智能三阶段的镜子理论

肿瘤的诊断不单单是诊断出是否存在肿瘤细胞，还要判断肿瘤细胞的分化程度、浸润程度、神经侵犯、癌栓、肿瘤间质比和肿瘤浸润淋巴细胞等肿瘤微环境中的信息。

为了实现数字病理人工智能3个阶段的跨越式发展，我们提出了“镜像拓画”标注理论。本方法能够根据病理科医师、肿瘤科医师和科技人员的需求快速地产生产高质量和高容量的数据库，助力人工智能研发高度准确性的诊断、预后和疗效预测辅助系统，降低病理人工智能研究的入门门槛，扩展了病理人工智能的应用范围，彻底改变了病理人工智能的生态环境。

关键词：人工智能；病理；镜像拓画

95. GTF2E2 is a novel recurrence biomarker after surgery and promotes progression via miR-139-5p/GTF2E2/FUS axis for esophageal squamous cell carcinoma.

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Background: Esophageal squamous cell carcinoma (ESCC) is one of the most lethal gastrointestinal malignancies with high mortality. Recurrence develops within only a few years after curative resection and perioperative adjuvant therapy in 30–50% of these patients. Therefore, it is of great significance to find promising biomarkers with the early detection of recurrence in order to select following surveillance and therapeutic strategies. The general transcription factor II E subunit beta (GTF2E2) is a crucial component for transcription initiation and promoter opening. However, the biological function and the molecular mechanism of GTF2E2 in the aggression and recurrence of ESCC remain ambiguous.



Methods: GTF2E2 expression in paired ESCC specimens and postoperative recurrence specimens were determined by immunohistochemistry (IHC). quantitative real-time PCR (qRT-PCR) was used to measure mRNA and microRNA (miRNA) expression level. Cell migration, invasion and proliferation ability were evaluated by transwell, CCK8, colony formation, EdU and apoptosis assay. Bioinformatics analysis was used to predict miRNAs targeting GTF2E2. Dual luciferase reporter assay and anti-Ago2 immunoprecipitation assay were performed to confirm the binding between GTF2E2 mRNA and miRNA-139-5p. Tumorigenesis and metastasis mouse model were used to explore the role of GTF2E2 in vivo. ChIP-seq and RNA-seq were found that GTF2E2 was directly regulated for the transcription of FUS, and it was confirmed by ChIP-PCR and dual luciferase reporter assay. Rescue assays were conducted to illustrate the role of FUS in GTF2E2-mediated ESCC progression.

Results: In this study, we found that GTF2E2 was highly expressed in ESCC and elevated GTF2E2 expression predicted early recurrence after surgery for ESCC patients. GTF2E2 promoted mobility and proliferation of ESCC cells in vitro and in vivo. We further revealed that the expression of miR-139-5p was negatively correlated with GTF2E2 and found that miR-139-5p repressed GTF2E2 expression by downregulating its mRNA through binding with Argonaute 2 (Ago2) in ESCC. Moreover, GTF2E2 was positively interacted with FUS, and the phenotype changes caused by GTF2E2 manipulation were recovered by rescuing FUS expression in ESCC cells.

Conclusion: GTF2E2 may serve as a novel recurrence biomarker after surgery and potential therapeutic target for ESCC patients, and promotes the ESCC progression via miR-139-5p/GTF2E2/FUS axis.

Key words: ESCC; recurrence biomarker; GTF2E2; miR-139-5p; FUS

96. An Immune Cell Signature is Associated With Disease-Free Survival and Adjuvant Chemosensitivity of Patients With Resectable Gastric Cancer

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Increasing evidence has indicated that current tumor-node-metastasis (TNM) stage alone cannot predict prognosis and adjuvant chemotherapy benefits accurately for stage II and III gastric cancer (GC) patients after surgery. In order to improve the predictive ability of survival and adjuvant chemotherapy benefits of GC patients after surgery, this study aimed to establish an immune signature based on the composition of infiltrating immune cells. Twenty-eight types of immune cell fractions were evaluated based on the expression profiles of GC patients from the Gene Expression Omnibus (GEO) database using single-sample gene set enrichment analysis (ssGSEA). The immunoscore (IS) was constructed using a least absolute shrinkage and selection operator (LASSO) Cox regression model. Through the

LASSO model, an IS classifier consisting of eight immune cells was constructed. Significant difference was found between high-IS and low-IS groups in the training cohort in DFS ($P < 0.0001$) and OS ($P < 0.0001$). Multivariate analysis showed that the IS classifier was an independent prognostic indicator. Moreover, a combination of IS and TNM stage exhibited better prognostic value than TNM stage alone. Further analysis demonstrated that low-IS patients who had more tumor-infiltrating lymphocytes had better response to adjuvant chemotherapy. More importantly, we found that patients with high-IS were more likely to benefit from a Xeloda plus cisplatin regimen after surgery. Finally, we established two nomograms to screen the stage II and III GC patients who benefitted from adjuvant chemotherapy after surgery. The combination of IS classifier and TNM stage could predict disease-free survival (DFS) and overall survival (OS) of GC patients. The IS model has been proven as a promising tool that can be used to identify the patients with stage II and III GC who may benefit from adjuvant chemotherapy.

Key words: Immunoscore; gastric cancer; adjuvant chemotherapy; prognosis; XP

97. 一线 EGFR-TKIs 联合血管生成抑制剂对比 EGFR-TKIs 单药在晚期 EGFR 突变非小细胞肺癌中的 meta 分析

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目的: 表皮生长因子受体酪氨酸激酶抑制剂 (EGFR-TKIs) 是 EGFR 突变晚期非小细胞肺癌 (non-small cell lung cancer, NSCLC) 一线治疗的标准方案。血管生成抑制可以通过阻断血管内皮生长因子受体 (VEGFR) 信号通路来增加 EGFR-TKIs 抗肿瘤作用。本文旨在比较一线 EGFR-TKIs 联合血管生成抑制剂对比 EGFR-TKIs 单药治疗晚期 EGFR 突变 NSCLC 的疗效和安全性。

方法 对 PubMed, Embase, Web of Science 和 Cochrane Library 数据库以及欧洲医学肿瘤学会 (ESMO), 美国临床肿瘤学会 (ASCO) 中会议摘要进行了全面的文献检索。检索时间截止至 2020 年 11 月 13 日。使用 STATA V.14.0 对相关数据进行统计分析。

结果: 本 meta 共纳入 6 个 II/III 期 RCTs (11 篇文章), 包括 1537 例符合分析条件的 NSCLC 患者。结果表明, 与 EGFR-TKIs 单药组相比, 联合血管生成抑制剂组患者的无进展生存期 (progression-free survival, PFS) 显著延长 ($HR=0.62$, 95% CI 0.54-0.70, $P<0.001$)。然而, 联合治疗并不能改善患者的总生存期 (overall survival, OS) ($P=0.536$), 客观缓解率 (objective response rate, ORR) ($P=0.186$) 和疾病控制率 (disease control rate, DCR) ($P=0.918$)。联合治疗组发生 grade 3+ 不良事件 ($RR=1.80$, 95% CI 1.46-2.22, $P<0.001$) 和严重不良事件 ($RR=1.48$, 95% CI 1.22-1.81, $P<0.001$) 的风险较 EGFR-TKIs 单药组增加。其中联合治疗组患者蛋白尿、高血压和腹泻的发生显著增加。此外, 亚组分析结果表明, 联合治疗组中 Ex19del



(OR=0.62, 95% CI 0.51-0.75, $P<0.001$) 和 Leu858Arg (OR=0.62, 95% CI 0.51-0.75, $P<0.001$) 突变的 NSCLC 患者获益相当。

结论：一线 EGFR-TKIs 联合血管生成抑制剂可以显著延长晚期 EGFR 突变 NSCLC 患者的 PFS。

尽管联合组不良反应发生率增加，但毒性尚可耐受和管理。联合治疗可作为晚期 EGFR 突变的 NSCLC 患者一线选择。

关键词：表皮生长因子受体酪氨酸激酶抑制剂；血管生成抑制剂；非小细胞肺癌；meta 分析

98. EGCG-NPs reduce the resistance of non-small cell lung cancer to EGFR-TKIs by inhibiting NF- κ B signaling pathway

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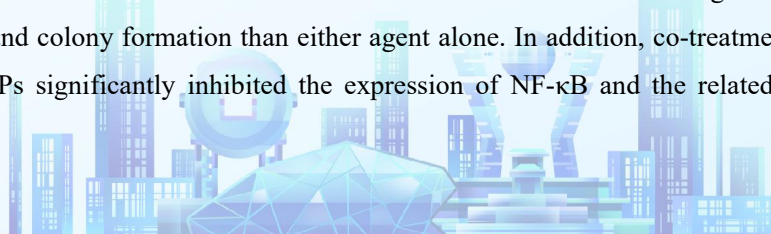
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Background: The epidermal growth factor receptor (EGFR)-specific (TKIs) tyrosine kinase inhibitors have shown efficacy in the clinic, but tumors often become resistant to these therapies. Activation of the NF- κ B promotes the resistance of Non-small cell lung cancer (NSCLC) to EGFR-TKIs. Herein, We investigated the ability of EGFR-TKIs combined with (-)-epigallocatechin-3-gallate Nanoparticles (EGCG-NPs) to inhibit cell proliferation, and NF- κ B activation in several NSCLC resistant cell lines.

Experimental Design: NCI-PC9 cell line containing EGFR del 19 mutation was induced to establish the three generation EGFR-TKIs (Erlotinib, Afatinib and Osimertinib) resistant cell lines (PC9/ER, PC9/AR and PC9/OR) by low-concentration addition method in vitro. RNA sequencing (RNA-seq) was performed on PC9, PC9/ER, PC9/AR and PC9/OR to detect differentially expressed genes and involved pathways. The result of RNA-seq was verified by RT-PCR. And protein expression of P-NF- κ B and P-EGFR was detected using Western blot. Experiments were conducted with EGCG-NPs and the EGFR-TKIs via MTT assay, colony formation assay, Western blot analysis and RT-PCR to detect the synergistic effects on NSCLC.

Results: The established PC9/ER, PC9/AR and PC9/OR cells had over 180.051, 128.15 and 269.38-fold increased resistance to Erlotinib, Afatinib and Osimertinib than its sensitive parental PC9 cells, respectively. In terms of morphology, showed irregular cell characteristics. In terms of biological characteristics, resistant cells were characterized as slow proliferation, and prolonged multiplication time. RNA-seq revealed multiple changed pathways in R-PC9 cells compared to the parental cells and one of the most changed pathways was NF- κ B signal pathway where most of gene activities were up-expression. The combination of EGFR-TKIs and EGCG-NPs resulted in greater inhibition of cell proliferation and colony formation than either agent alone. In addition, co-treatment with EGFR-TKIs and EGCG-NPs significantly inhibited the expression of NF- κ B and the related genes. Finally, the



combination of EGFR-TKIs and EGCG-NPs also have a synergistic antiproliferative effect in H1650 and H1975 cells.

Conclusion: EGCG-NPs can significantly enhance the effect of inhibiting cell proliferation in several NSCLC cell lines, including those resistant to both EGFR kinase inhibitors and those over-expressing P-NF- κ B. This effect was mostly due to the inhibition of NF- κ B signaling pathway. These data suggested that EGCG-NPs may reduce the resistance of NSCLC to EGFR-TKIs.

Key words: NSCLC; EGFR-TKIs; EGCG-NPs; resistance; NF- κ B

99. Positive feedback regulation of poly(ADP-ribose) polymerase 1 and the DNA-PK catalytic subunit alters the sensitivity of nasopharyngeal carcinoma (NPC) to etoposide

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Abstract: Etoposide (VP-16) is used to treat a wide spectrum of human cancers, including nasopharyngeal carcinoma (NPC), but cancers develop resistance to this agent by promoting DNA repair. The catalytic subunit of DNA-PK (DNA-PKcs) and poly (ADP-ribose) polymerase 1 (PARP1) mediate acquired resistance and poor survival in NPC cells treated with DNA-damaging agents. Since DNA repair is the major molecular mechanism that alters sensitivity to DNA-damaging agents and these two enzymes may function concomitantly in the response to DNA damage in vivo, we explored the relationship between DNA-PKcs and PARP1, which may affect NPC cell survival by regulating DNA repair after VP-16 treatment. We performed western blotting, quantitative real-time PCR (qRT-PCR) and ELISAs and found that DNA-PKcs knockdown downregulated PARP1 and PAR expression. Conversely, PARP1 knockdown reduced DNA-PKcs activity, indicating mutual regulation between DNA-PKcs and PARP1 in VP-16-induced DNA repair. Moreover, combination treatment with olaparib (PARP1 inhibitor) and NU7441 (DNA-PKcs inhibitor) sensitized NPC cells to VP-16 both in vitro and in vivo, suggesting that a combination therapy consisting of olaparib, NU7441 and a DNA-damaging agent may be a successful treatment in patients with NPC.

Key words: Etoposide; DNA-PKcs; PARP1; DNA repair; nasopharyngeal carcinoma

100. 结直肠癌微卫星不稳定性 (MSI) 与 PD-L1 表达的相关临床意义研究

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目的：研究结直肠癌微卫星不稳定性（MSI）与 PD-L1 表达的临床病理特征和相关临床意义。

方法：收集在宁夏医科大学总医院接受结直肠癌切除术，术后病理确诊为 CRC 的患者共 116 例，采用多重荧光 PCR 结合毛细管电泳方法检测 6 个单核苷酸重复位点（NR-21,NR-24,NR-27,BAT-25,BAT-26,MONO-27）以鉴定微卫星状态。采用免疫组化（IHC）方法进行 PD-L1 和 MMR 蛋白（MLH1,MSH2,MSH6 和 PMS2）检测。通过分析研究结直肠癌微卫星不稳定性（MSI）与 PD-L1 表达的临床病理特征和相关临床意义，并分析 PCR 与 IHC 两种方法检测结果的一致性。

结果：①在 MSI-L/MSS 的 CRC 与 MSI-H 的 CRC 之间肿瘤部位,肿瘤直径,分化程度差异具有统计学意义（ $P<0.05$ ），而浸润深度,pTNM 分期,有无神经或脉管侵犯,有无淋巴结转移之间差异无统计学意义（ $P>0.05$ ）；②免疫组化和 PCR 毛细管电泳法的检测结果经 Kappa 一致性检验,结果一致性较好（Kappa=0.674）；③CRC 组织中 PD-L1 表达在患者性别,年龄,肿瘤位置,分化程度,浸润深度,pTNM 分期,有无神经或脉管侵犯,有无淋巴结转移之间的差异均无统计学意义（ $P>0.05$ ）；④在 MSI-L/MSS 的 CRC 中，PD-L1 阳性率为 28.3%，在 MSI-H 的 CRC 中，PD-L1 阳性率为 70.0%；两组比较差异具有统计学意义（ $P<0.05$ ）。

结论：①MSI-H 型 CRC 具有位于右半结肠,肿瘤直径大,中分化的特点，基因检测位点中 BAT-26,NR21,NR27 突变率相对较高，可为结直肠癌免疫治疗的临床应用提供理论依据。②PCR 与 IHC 两种检测方法一致性较好，可以根据情况，选用简便而经济的检测方法。③PD-L1 在 MSI-H 的 CRC 阳性率显著高于 MSI-L/MSS 的 CRC，MSI-H 可以作为免疫检查点抑制剂（ICI）PD-L1 的阳性预测标志物。

关键词：微卫星不稳定；PD-L1；免疫组化，PCR—毛细管电泳

101. To explore the mechanism of danggui kushen pill in treating Esophageogastric junction cancer based on network pharmacology

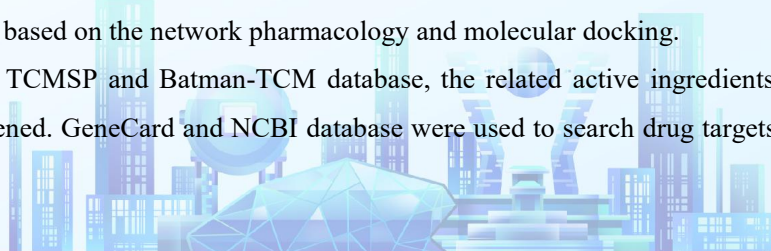
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Objective: To explore the mechanism of danggui kushen pill in the treatment of Esophageogastric junction cancer (AEG) based on the network pharmacology and molecular docking.

Methods: through TCMSP and Batman-TCM database, the related active ingredients of danggui kushen pill were screened. GeneCard and NCBI database were used to search drug targets and disease-related



genes, and common targets were obtained. The Cytoscape software were employed to construct a interaction network of drugs-components-targets. Draw up protein-protein interaction (PPI) network with String database, analyze and identify the key target proteins and active pharmaceutical ingredient. The GO and KEGG pathway enrichment analyses were performed by Metascape database. Finally, molecular docking was carried out.

Results: Thirty-four active ingredients with $OB \geq 30\%$ and $DL \geq 0.18$ were selected and obtained twelve active components by further screening. 203 drug targets in addition to 207 disease-related genes were collected, of which 35 intersection targets were acquired. A total of 10 key targets including TP53, CASP3, MYC, VEGFA, TNF, EGF, EGFR, PTGS2, IL6 and CXCL8 were identified through PPI network analysis. These targets were mainly focused on the biological processes of positive regulation of protein phosphorylation, ovarian follicle development and response to drug. The KEGG enrichment manifested that the mechanism of action of the drug were closely related to Pathways in cancer, MicroRNA in cancer, PI3K-Akt signaling pathway. TP53, CASP3, MYC and VEGFA were regarded as the most important genes, which were validated by molecular docking simulation. The autodock energy between VEGFA and luteolin was the lowest, showing a strong binding affinity.

Conclusions: Based on network pharmacological analysis, the active components of danggui kushen pill including quercetin and luteolin and 10 hub targets were identified. Danggui kushen pill plays a role in the treatment of AEG by regulating multi-components and multi-targets. This study offers a theoretical basis for the development of danggui kushen pill as the new drug againsting AEG and provides novel insight for further researches.

Key words: danggui kushen pill; adenocarcinoma of esophagogastric; network pharmacology; signaling pathway; molecular mechanism

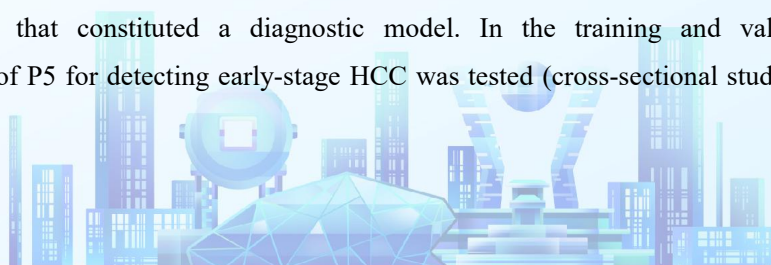
102. A panel of five plasma proteins for the early diagnosis of hepatitis B virus-related hepatocellular carcinoma in individuals at risk

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Background: To improve the early diagnosis of hepatocellular carcinoma (HCC), more effective diagnostic biomarkers are needed. A combination of biomarkers is reported to distinguish individuals with early-stage HCC from at-risk individuals.

Methods: Participants in this study were recruited from six hospitals in China. Literature review was used to choose 19 candidate proteins, a case-control study in the discovery stage was used to identify five proteins (P5) that constituted a diagnostic model. In the training and validation stages, the effectiveness of P5 for detecting early-stage HCC was tested (cross-sectional study). Finally, a nested



case-control study independent of the other stages was set up to evaluate the P5 in the preclinical diagnosis of HCC.

Findings: Between February 2013 and June 2017, a total of 1396 participants were recruited. A panel of 5 proteins (P5: OPN, GDF15, NSE, TRAP5 and OPG) showed high diagnostic accuracy when differentiating the early-stage HCC from the at-risk group, with AUCs of 0.892, 0.907 and 0.852 for the training stage, validation cohort 1 and cohort 2 data sets, respectively. In the prediction set, the sensitivity of P5 for diagnosing preclinical HCC increased with time, starting from 12 months before to the time of definitive clinical diagnosis (range, 46.15% to 86.67%).

Interpretation: The P5 panel has the potential to screen populations at high risk of developing HCC and can enable the early diagnosis of HCC.

Key words: Peripheral blood; Multi-tumor markers; Earlier detection; Liver cancer; Multi-center study

103. 高表达 HAX1 的鼻咽癌释放外泌体调节内皮细胞的翻译促进血管形成及转移

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目的: 鼻咽癌来源于鼻咽黏膜上皮细胞, 是头颈部最常见的恶性肿瘤。NPC 患者转移较为常见, 一旦发生转移预后极差。因此, 探索 NPC 患者转移的分子机制, 对于指导 NPC 的精准治疗, 改善患者预后具有重要的作用。血管生成是肿瘤生长和转移的关键环节。肿瘤来源的外泌体, 作为肿瘤微环境的重要组分, 能明显促进肿瘤血管生成。既往的研究中, 我们发现 HAX1 在 NPC 中高表达, 参与 NPC 的恶性生物学行为, 影响其预后, 同时 NPC 来源外泌体中高表达的 HAX1 是促进 NPC 血管生成的重要原因。因此, 我们提出“高表达 HAX1 鼻咽癌细胞来源的外泌体促进肿瘤相关血管的形成, 从而促进鼻咽癌的转移”的假设。

方法: 通过免疫组化观察鼻咽癌 HAX1 的表达与肿瘤微血管的关系; 使用裸鼠和斑马鱼构建转移模型, 研究 HAX1 的表达对鼻咽癌转移的影响。而后我们敲低了鼻咽癌细胞中的 HAX1, 通过鼻咽癌细胞/外泌体与内皮细胞共培等方式研究鼻咽癌细胞对内皮细胞的生物学行为的影响。在斑马鱼模型进一步研究 HAX1 对斑马鱼的血管的发育的影响。利用 cas9 技术敲除斑马鱼的 HAX1 的表达, 而后进行了转录组及 TCGA 数据库进行分析, 排除在转录水平上的调控。通过多聚核糖体分析及免疫印迹确认 HAX1 对内皮细胞的翻译起始因子 4 复合物及蛋白翻译水平的影响。接着借助核糖体印迹技术寻找 HAX1 调控的下游。最后在裸鼠模型中验证 HAX1 在鼻咽癌过程转移中的分子机制。

结果: HAX1 的表达与肿瘤微血管数量及患者预后呈正相关。动物模型中发现 HAX1 的高表达显著促进鼻咽癌的转移。在鼻咽癌细胞/外泌体与内皮细胞共培模型中表明, 高表达 HAX1 的鼻咽癌细胞分泌的外泌体可以促进内皮细胞的迁移, 血管形成, 增殖等功能。通过斑马鱼模型发现,



HAX1 被敲除后斑马鱼的血管发育受到抑制。多聚核糖体分析发现 HAX1 敲低后抑制内皮细胞的真核生物翻译起始因子 4 复合物的形成, 同时蛋白翻译受到抑制。通过核糖体印记分析, 发现整合素的翻译效率受到 HAX1 的调控, 其中影响最大的是 ITG β 6。ITG β 6 可调节 FAK 通路从而影响微血管的形成, 促进鼻咽癌的转移。

结论: 高表达 HAX1 的鼻咽癌细胞可通过外泌体将 HAX1 传递至内皮细胞, 以调节翻译效率的方式促进 ITG β 6 的表达, 进而促进 FAK 的磷酸化, 从而调节血管生成, 进而促进鼻咽癌的转移。

关键词: 鼻咽癌; 转移; 外泌体; 血管形成; 蛋白翻译

104. Circular RNA 0014715 Facilitates Cell Proliferation and Inhibits Apoptosis in Esophageal Squamous Cell Carcinoma

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Objective: Circular RNAs (circRNAs) have recently been verified to have multiple biological functions and participate in diverse biological processes in different malignant tumors, including esophageal squamous cell carcinoma (ESCC).

Materials and Methods: We investigated clinical data from sixty-seven patients under-going surgery for esophageal cancer. The clinical data were collected. And we analyzed the correlation between the clinical characteristics of these patients and the expression of circ_0014715. Besides, we explored the expression of circ_0014715 in ESCC cell lines. We used cell counting kit-8, colony formation, transwell assay, and flow cytometry to detect changes in cell proliferation, migration, apoptosis, and cell cycle progression.

Results: We found that circ_0014715 was highly expressed in esophageal squamous cell carcinoma tissues and cell lines. The correlation analysis of clinicopathological features and gene expression revealed that high expression of circ_0014715 was related to nerve invasion, vascular invasion, more advanced tumor-node-metastasis (TNM) stage and poor differentiation grade. Receiver operating characteristic (ROC) curves revealed that circ_0014715 might have diagnostic value for ESCC. Experiments with cultured cells showed that knockdown of circ_0014715 significantly restrained cell proliferation, migration, invasion, wound healing and accelerated cell apoptosis. And cell cycle arrest at G2 phase was observed via flow cytometry. Overexpression of circ_0014715 caused the opposite effects. Collectively, these studies show that circ_0014715 is closely connected with the pathogenesis and development of ESCC. The excess expression of circ_0014715 may have promoting effects on the progression of esophageal cell carcinoma.

Conclusion: Our finding revealed that circ_0014715 promoted tumor growth and cell proliferation. All of these suggest that targeting circ_0014715 has potential therapeutic value in the treatment of ESCC.



Key words: circular RNA 0014715; circular RNAs; esophageal squamous cell carcinoma; biological characteristics; cell proliferation

105. Peroxiredoxin-3 promotes the development of gastric cancer through the ERK/NRF2 signaling pathway

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Purpose: Peroxiredoxin-3 (PRDX3) is a multifunctional protein that is involved in the protection of cells against oxidative injury, regulation of proliferation, modulation of intracellular signaling, and pathogenesis of tumors. The expression and biological functions of PRDX3 in gastric cancer (GC) are not clear.

Methods: The expression and prognosis of PRDX3 in gastric cancer were detected from public databases by means of biological information. In our study, we obtained paired tissue samples from patients undergoing resection for GC, which were analyzed for PRDX3 expression using western blot analysis and Immunohistochemistry. We conducted in vitro experiments on the downregulation or overexpression of PRDX3 in gastric cancer cells. Cell Counting Kit-8 was used to determine the effect of PRDX3 on cell proliferation, flow cytometry was used to determine the effect of PRDX3 on cell cycle distribution and apoptosis, and Transwell assays were used to determine changes in cell migration and invasion.

Results: According to TCGA (The Cancer Genome Atlas) database, the PRDX3 expression in GC tissues was obviously higher than that in normal tissues. In addition, based on a survival analysis, high expression of PRDX3 indicates poor prognosis of gastric cancer patients. Based on patient specimens collected by us, the levels of PRDX3 are significantly increased in gastric cancer tissues and cell lines. PRDX3 gene knockdown inhibits cell proliferation and metastasis but increases the cell apoptosis rate. In contrast, the overexpression of PRDX3 in gastric cancer cells promotes cell growth, migration and invasion. Interestingly, the effects of PRDX3 can be exerted by activating the ERK/NRF2 signaling pathway to protect gastric cancer cells from oxidative stress.

Conclusion: In summary, these results indicate that PRDX3 functions as an oncogene and may become a potential therapeutic target for the treatment of gastric cancer in the future.

Key words: gastric cancer; metastasis; proliferation; PRDX3; ERK/NRF2

106. Upregulation of TRIP13 promotes the malignant progression of lung cancer via the EMT pathway

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Lung cancer is the most common malignant tumor type and it is associated with poor prognosis. The identification of potential biomarkers is of great significance for the early diagnosis and treatment of lung cancer. Non-small cell lung cancer (NSCLC) is the most common pathological type of lung cancer. The present study aimed to investigate the mechanism via which thyroid hormone receptor-interacting protein 13 (TRIP13) participates in the malignant progression of NSCLC. Immunohistochemistry, reverse transcription-quantitative PCR and western blotting were used to assess the expression level of TRIP13. According to The Cancer Genome Atlas data-base, TRIP13 was upregulated in NSCLC tissues compared with adjacent normal tissues. Moreover, TRIP13 knockdown increased apoptosis, induced cell cycle arrest in the S phase and inhibited the proliferation, invasion and migration of H1299 cells in vitro. Furthermore, TRIP13 upregulation was closely associated with tumor metastasis via epithelial-mesenchymal transformation. In conclusion, TRIP13 could promote the malignant progression of lung cancer, and TRIP13 may be a potential biomarker for the early diagnosis and treatment of NSCLC.

Key words: TRIP13; lung cancer; proliferation; apoptosis; EMT

107. CCDC65 as a new potential tumor suppressor induced by metformin inhibits activation of AKT1 via ubiquitination of ENO1 in gastric cancer

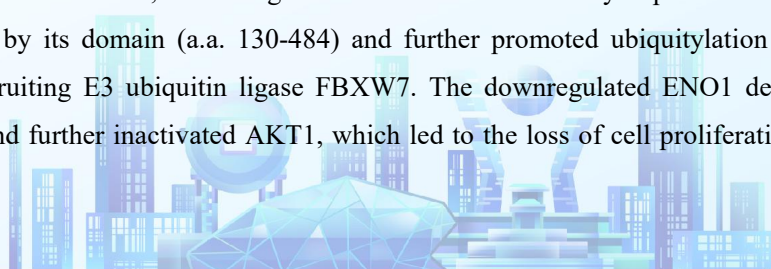
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Purpose: The coiled-coil domain containing protein members have been well documented for their roles in many diseases including cancers. However, the function of the coiled-coil domain containing 65 (CCDC65) remains unknown in tumorigenesis including gastric cancer.

Methods: CCDC65 expression and its correlation with clinical features and prognosis of gastric cancer were analyzed in tissue. The biological role and molecular basis of CCDC65 were performed via in vitro and in vivo assays and a various of experimental methods including co-immunoprecipitation (Co-IP), GST-pull down and ubiquitination analysis et al. Finally, whether metformin affects the pathogenesis of gastric cancer by regulating CCDC65 and its-mediated signaling was investigated.

Results: Here, we found that downregulated CCDC65 level was showed as an unfavourable factor in gastric cancer patients. Subsequently, CCDC65 or its domain (a.a. 130-484) was identified as a significant suppressor in GC growth and metastasis in vitro and in vivo. Molecular basis showed that CCDC65 bound to ENO1, an oncogenic factor has been widely reported to promote the tumor pathogenesis, by its domain (a.a. 130-484) and further promoted ubiquitylation and degradation of ENO1 by recruiting E3 ubiquitin ligase FBXW7. The downregulated ENO1 decreased the binding with AKT1 and further inactivated AKT1, which led to the loss of cell proliferation and EMT signal.



Finally, we observed that metformin, a new anti-cancer drug, can significantly induce CCDC65 to suppress ENO1-AKT1 complex-mediated cell proliferation and EMT signals and finally suppresses the malignant phenotypes of gastric cancer cells.

Conclusion : These results firstly highlight a critical role of CCDC65 in suppressing ENO1-AKT1 pathway to reduce the progression of gastric cancer and reveals a new molecular mechanism for metformin in suppressing gastric cancer. Our present study provides a new insight into the mechanism and therapy for gastric cancer.

Key words: Gastric cancer; CCDC65; ENO1; AKT1; Metformin

108. Whole transcriptome sequencing-based construction and integrated analysis of differentially expressed LINC01426 mediated ceRNA network in non-small cell lung cancer

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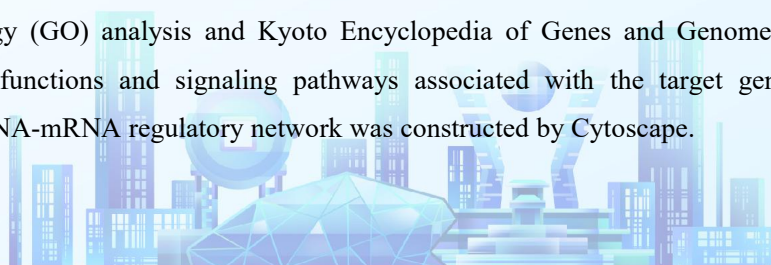
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Background: Lung cancer is the most commonly diagnosed cancer and the leading cause of cancer death globally, and non-small cell lung cancer (NSCLC) is the most common type of lung cancer. Long non-coding RNAs (lncRNAs) have emerged as novel master regulators of initiation, progression, and response to therapy in a wide variety of solid tumors and hematological malignancies. Some lncRNAs may act as microRNA (miRNA) sponge to affect miRNA activities by regulating messenger RNA (mRNA) expression. Our study aimed to describe the regulatory mechanisms in NSCLC by constructing a regulatory lncRNA-miRNA-mRNA network.

Methods: Whole transcriptome sequence was performed in five NSCLC tissues and paired adjacent normal tissues to obtain the differentially expressed lncRNAs (DELs) that play an important role in the occurrence and development of NSCLC. The expression of the selected lncRNAs were detected by quantitative real-time polymerase chain reaction (qRT-PCR). After that, the interactions between lncRNA and the targeted miRNAs were predicted by miRcode, starBase, and LncBase databases. MiRNAs and mRNAs expression profiles were obtained from TCGA database. Then, miRDB, miRTarBase and Targetscan datasets were used to search for the mRNAs targeted by the miRNA. Then, we draw a Venn diagram by R (Venn Diagram package) to find overlapped target genes of mRNA. Survival analysis of overlapped mRNAs were performed by GEPIA and LOGp in NSCLC. Gene Ontology (GO) analysis and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway revealed the functions and signaling pathways associated with the target genes. Furthermore, a lncRNA-miRNA-mRNA regulatory network was constructed by Cytoscape.



Results: A total of 559 lncRNAs ($FC > 2$, $P < 0.05$) were dysregulated in whole transcriptome sequence, of which 235 were up-regulated and 324 were down-regulated in NSCLC tissues compared with the adjacent normal tissues. Then, top five up-regulated lncRNAs were selected for further analysis. Subsequently, we were verified that LINC01426 was highly expressed in 6 NSCLC cell lines compared with BEAS-2B, and was highly expressed in 15 pairs of NSCLC tissues compared with adjacent tissues by qRT-PCR. Through the bioinformatics prediction, we gained 4 target miRNAs (hsa-miR-508-5p, hsa-miR-143-3p, hsa-miR-125b-5p, hsa-miR-1258) and 48 relative mRNAs were connected with the LINC01426. GO analysis revealed that differentially expressed genes were classified into three functional groups: molecular function group, biological process group and cellular component group. In the biological process group, genes mainly enriched in urogenital system development, centrosome cycle and microtubule cytoskeleton organization involved in mitosis. In the molecular function group, genes mainly enriched DNA-binding transcription activator activity, RNA polymerase II-specific and DNA-binding transcription activator activity. In the cellular component group, genes mainly enriched in chromosomal region and mitotic spindle. Meanwhile, KEGG pathway analysis revealed that differentially expressed genes were mainly linked to Cell cycle, p53 signaling pathway, Cellular senescence, Regulation of actin cytoskeleton, Transcriptional misregulation in cancer and Citrate cycle. Furthermore, the lncRNA-miRNA-mRNA regulatory network were constructed based on lncRNA LINC01426, 4 miRNAs and 48 mRNAs, allowing us to better understand its underlying mechanisms in NSCLC.

Conclusion: The study constructed a lncRNA-miRNA-mRNA ceRNA regulatory network associated with NSCLC. This network demonstrates a new mechanism based on whole transcriptome sequence, which is of great significance for the study of the tumorigenesis and progression of NSCLC.

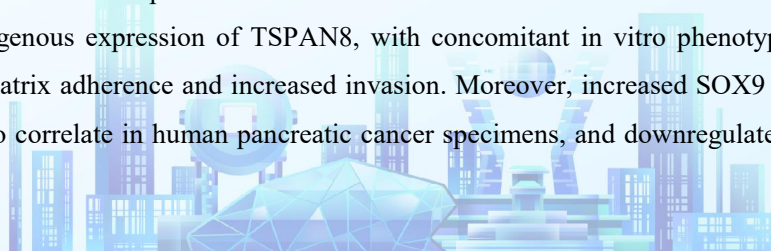
Key words: NSCLC; LINC01426; miRNA; bioinformatics; ceRNA

109. SOX9 is a critical regulator of TSPAN8-mediated metastasis in pancreatic cancer

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Pancreatic ductal adenocarcinoma (PDAC) is the deadliest cancer mainly due to its proclivity to early metastasis and the lack of effective targeted therapeutic drugs. Hence, understanding the molecular mechanisms underlying early invasion and metastasis by PDAC is imperative for improving patient outcomes. The present study identified that upregulation of TSPAN8 expression in PDAC facilitates metastasis in vivo and in vitro. We found SOX9 as a key transcriptional regulator of TSPAN8 expression in response to EGF stimulation. SOX9 modulation was sufficient to positively regulate endogenous expression of TSPAN8, with concomitant in vitro phenotypic changes such as loss of cell-matrix adherence and increased invasion. Moreover, increased SOX9 and TSPAN8 levels were shown to correlate in human pancreatic cancer specimens, and downregulated in vitro by EGFR



tyrosine kinase inhibitors. High expression of SOX9 and TSPAN8 has been associated with tumour stage, poor prognosis and poor patient survival in PDAC. In conclusion, this study highlights the importance of the EGF-SOX9-TSPAN8 signalling cascade in the control of PDAC invasion and implies that TSPAN8 may be a promising novel therapeutic target for the treatment of PDAC.

Key words: SOX9; TSPAN8; metastasis; PDAC

110. 敲低 C17orf64 对乳腺癌细胞 MCF-7 凋亡的影响及可能的分子机制

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研究目的: 初步探讨 C17orf64 对乳腺癌的作用及其调控机制

材料与方法: 通过 MTT 法, 流式细胞术研究 C17orf64 敲减后对乳腺癌细胞生长的影响; 对乳腺癌细胞 MCF-7 进行 C17orf64 敲低处理后的 RNA 测序(RNA-seq), 进行了基因本体论(GO)功能分类注释, 京都基因与基因组百科全书(KEGG)途径分析; 通过质粒转染在乳腺癌细胞 BT549 中过表达 C17orf64, 用 Western blot 对调控基因进行验证。在 BT549 中过表达 C17orf64, 按 $5 \times 10^4/\text{ml}$ 的细胞数接种于 96 孔板中, 应用 CCK-8 法检测 C17orf64 过表达对细胞生长的影响; 通过生物信息学和在线数据库, 研究 C17orf64 对乳腺癌生存率的调控机制。

结果: MTT 检测结果发现 C17orf64 敲减后对细胞活力有不同程度的促进作用, 以 48h 和 72h 最为明显; 从流式凋亡检测结果发现敲低 C17orf64 后, MCF-7 细胞的凋亡率显著降低, 提示了 C17orf64 在乳腺癌细胞中可能有促进细胞凋亡的作用。流式周期结果显示, 敲低 C17orf64 后的 MCF-7 细胞与阴性对照相比, G0/G1 期细胞明显减少和 S 期细胞明显增多。这些结果显示敲低 C17orf64 基因后, 促进了 MCF-7 细胞的增殖; RNA-seq 测序共鉴定了 450 个上调和 291 个下调基因, 从中筛选了 2 个与乳腺癌相关的差异表达基因, 差异表达基因的 GO 富集分析结果主要表现在 DNA 复制, 重组修复, 维持 DNA 甲基化等。差异表达基因的 KEGG 途径分析的结果显示主要在 NF- κ B 信号通路, cAMP 信号通路, 抗坏血酸和醛酸盐代谢等; Western blot 的初步实验结果表明, 在 BT549 细胞中过表达 C17orf64 会上调 BRCA2 的表达, 与 RNA 测序结果相符。CCK8 实验发现过表达 C17orf64 对乳腺癌细胞增殖没有发生明显变化。Kaplan-Meier Plotter 分析发现, 在乳腺癌患者中 C17orf64 的高表达与乳腺癌患者的总生存期(OS) 长呈正相关, 展示了 C17orf64 的抑癌作用。对 C17orf64 的深入研究可进一步明确乳腺癌生长, 侵袭和转移的机制。

结论: C17orf64 可能是乳腺癌新的肿瘤标志物, 可望为乳腺癌防治提供新靶点。

关键词: C17orf64; 乳腺癌; 增殖; 侵袭; 调控机制



111. Interleukin-2 related mRNA profile predicts Immune Subtypes in Head and Neck Squamous Cell Carcinoma and the underlying mechanisms

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Objective: The purpose of this study is to screen important biomarkers that affect the prognosis of patients with head and neck squamous cell carcinoma by bioinformatics analysis technology, and build a new algorithm to establish a prediction model that can identify immune subtypes of patients with head and neck squamous cell carcinoma, to screen and describe the biological characteristics of immunotherapy beneficiaries more accurately.

Methods: Part I Screening of prognostic signaling pathways and construction of immune subtype prediction model for head and neck squamous cell carcinoma based on multi omics

1. In this study, the important signal pathway and biological markers that affect the prognosis of head and neck squamous cell carcinoma were screened by multi-layer histochemical prognosis analysis. The research methods are as follows: ① The data of HNSCC multi-layer histochemistry (including transcriptional data, gene mutation data, gene copy number change data and gene methylation data) and clinical prognosis data were downloaded. The transcriptional data were TCGA level3 counts, The formula is standardized to TPM data, and the proportion of expression 0 is more than 20%, or the gene with the median value of 0 is deleted, and the gene type is annotated according to Vega standard; the methylation data is annotated with VEP software; the copy number change data is evaluated by gistic2 software according to CNV. All data are normalized and standardized. ② The signal pathway and biomarkers that affect the prognosis of head and neck squamous cell carcinoma were screened by MOSClip multi-omics histography. ③ The biological function of cells was annotated by the Reactome database. ④ The clinicopathological parameters, survival status and total survival period of the patients were obtained by retrospective collection of head and neck squamous cell carcinoma patients. ⑤ The expression of IL2RG in the tumor tissues of head and neck squamous cell carcinoma was verified by immunohistochemistry. ⑥ The level of LCK methylation in tumor tissue of head and neck squamous cell carcinoma was verified by methylation specific PCR.

2. The prediction model of identifying immune subtypes was constructed by using interleukin-2 (IL-2) related genes

① The immune subtype related genes were screened by 1000 lasso logistic analysis. ② Univariate and multivariate Cox regression models were used to screen prognostic genes of head and neck squamous cell carcinoma. ③ The unsupervised cluster analysis adopts the consistent cluster analysis, which is implemented by R package ConsensusClusterPlus. ④ Single sample gene enrichment analysis (ssgsea) was used to evaluate tumor related signaling pathways and tumor immune cell infiltration abundance.

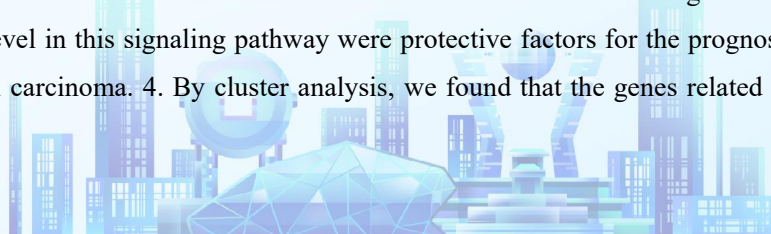


⑤ In order to verify the relationship between gene expression in tumor and microenvironment, the purity of tumor was evaluated by estimate algorithm. ⑥ Non negative matrix factorization and bootstrapping algorithm were used to construct IRIM immune subtype prediction model.

Part II Biological significance of IRIM model in tumor immunotyping of head and neck squamous cell carcinoma

Objective to evaluate the immune microenvironment of head and neck squamous cell carcinoma by IRIM algorithm, and explore the relationship between IRIM evaluation of inflammatory characteristics and different immune cell function status. ① In this study, single cell sequencing data gse103322 of head and neck squamous cell carcinoma was used. The "double cell" and low-quality cells were deleted by cell quality evaluation. ② The normalization data function in Seurat package was used to standardize the gene expression, and the inter batch difference of data was corrected by harmony package. ③ The first 25 principal components are selected for tSNE and Umap dimension reduction analysis. By DBClustdimension function, the subpopulations with less than 30 cluster cells were deleted. ④ There are two ways to annotate cell types: annotate by SingleR package; annotate by biomarkers of various types of genes. ⑤ The "Findvariablegenes" function in Seurat package was used to calculate the differential genes among different cell subpopulations. ⑥ The biological functions of cell subsets were analyzed by single cell function enrichment analysis (ssgsea). ⑦ R software was used for statistical analysis. The quantitative data of normal distribution was expressed as mean $\pm$ standard deviation. T test was used for comparison between groups. The quantitative data of non-normal distribution was expressed as median and quarterback distance. Wilcoxon test was used for comparison between groups. The mean value of quantitative variables in accordance with normal distribution is selected as cut-off value, and the median value of quantitative variables in accordance with normal distribution is selected as cut-off value. Kaplan Meier method was used to generate survival curves of each subgroup in each data set. Log rank test was used to determine the statistical significance of the differences. Landmark analysis was used for the data with intersecting survival curves. $P < 0.05$, the difference was statistically significant.

Results: 1. The prognostic factors of HNSCC were screened by multi-layer omics data, including TCGA transcriptome data, gene mutation data, methylation data and copy number change data. The results showed that there were 45 pathways associated with the prognosis of head and neck squamous cell carcinoma. These 45 signaling pathways play an important role in human immune function in head and neck squamous cell carcinoma. 2. Prognosis related pathways and gene modules in prognosis related pathways were screened according to P value. The results showed that: the signal pathway of interlinukin-2 family and its gene co-expression module 1 were most closely related to the prognosis of head and neck squamous cell carcinoma. 3. The Kaplan Meier curve was used to evaluate the signal pathway and its molecular module 1. The results showed that low gene expression and high methylation level in this signaling pathway were protective factors for the prognosis of head and neck squamous cell carcinoma. 4. By cluster analysis, we found that the genes related to the interlinukin-2



family signaling pathway could divide the head and neck squamous cell carcinoma patients into two subgroups. 5. Wilcoxon test showed that there were significant differences in T cell content, B cell content, WNT pathway score, IFNG pathway score and PD-L1 expression between the two subgroups. Based on previous studies, the two subgroups showed the characteristics of immune inflammatory type and non-immune inflammatory type respectively. 6. In order to verify the role of Interleukin-2 family signaling related genes in immunophenotyping, we tested them in imvigor210 data set. The results showed that the gene expression levels of IL21R, IL2RG, LCK, INPP5D, JAK3 and PIK3R3 could indicate that the patients were of immune inflammatory type and were related to the efficacy of immunotherapy. 7. In order to better describe the relationship between the above six key genes and immune subtypes, we designed IRIM algorithm and constructed the immune subtype prediction model of head and neck squamous cell carcinoma (IRIM model). The results showed that: in the head and neck squamous cell carcinoma, if three or more of the above six key genes play a role, the head and neck squamous cell carcinoma patients can be identified as "immune inflammatory type", AUC was 0.8146, the accuracy was 74.3%. 8. Other immune related data sets (GSE35640, GSE78220, GSE63557 and GSE91061) were used to verify the results. The results show that IRIM model has the function of indicating immune efficacy in other data sets. 9. The six key genes were found to be expressed in tumor microenvironment by estimate and correlation analysis, so we verified them in different cancer species. The results show that irim model can identify "immune inflammatory" patients in lung squamous cell carcinoma, breast cancer, cervical squamous cell carcinoma, esophageal squamous cell carcinoma and other solid tumors. 10. In order to verify the relationship between these six key genes and the prognosis of head and neck squamous cell carcinoma patients, we screened the representative genes IL2RG and LCK by principal component analysis. 11. GEPIA database analysis showed that IL2RG was a protective factor for the prognosis of head and neck squamous cell carcinoma ($P=0.015$). 12. Methods: 79 cases of head and neck squamous cell carcinoma were collected retrospectively. The overall survival status and overall survival time of the patients were followed up. The results of immunohistochemical staining of IL2RG showed that IL2RG was a protective factor for the prognosis of head and neck squamous cell carcinoma. The patients with positive results of IL2RG immunohistochemistry had a good prognosis ($P=0.0017$). MSP test was used to evaluate the methylation status of LCK in patients with head and neck squamous cell carcinoma in our center, and the relationship between the methylation status of LCK and the overall survival time of patients was analyzed by combining with the results of IL2RG immunohistochemistry. The results showed that the long-term survival time of patients with LCK unmethylation status combined with IL2RG positive was significantly better than that of patients with LCK methylation status combined with IL2RG negative, and the difference was statistically significant ($P=0.0075$). 13. The IRIM model score was closely related to T cells in head and neck squamous cell carcinoma. 14. Through T cell subgroup analysis, IRIM model score can mainly indicate the infiltrative T cell aggregation in tumor microenvironment of patients with head and neck squamous cell carcinoma. 15.



The poor prognosis of interleukin-2 family signaling pathway is mainly related to CD8 + T cell depletion.

Conclusion: 1. The signal pathway of Interlukin-2 family is a risk factor of head and neck squamous cell carcinoma. The level of IL2RG transcriptome and the level of LCK methylation are involved in the influence of Interlukin-2 family signaling on the prognosis of head and neck squamous cell carcinoma. High expression of IL2RG is a protective factor in patients with head and neck squamous cell carcinoma, and hypermethylation of LCK is a risk factor in patients with head and neck squamous cell carcinoma.

2. IRIM model is an important prediction model for the immunophenotyping of head and neck squamous cell carcinoma. It can screen the patients with inflammatory subtype of head and neck squamous cell carcinoma and effectively predict the therapeutic effect of immune checkpoint inhibitors.

Key words: head and neck squamous cell carcinoma; multi-slice omics analysis; immunophenotyping; prognostic markers

112. Immune inflamed gene model in lung squamous cell carcinoma and prediction of immunotherapy response

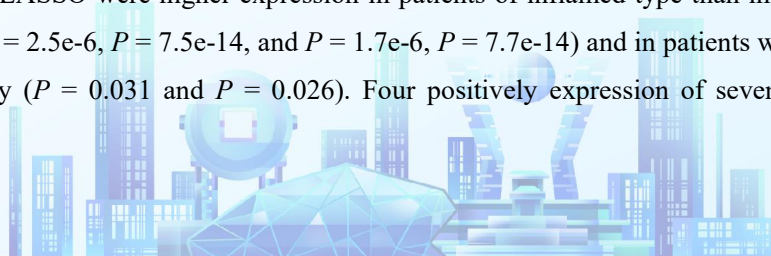
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Backgrounds: Lung squamous cell carcinoma (LUSC) is one of the most common malignant tumors around the world with limited therapy for the patients with advanced stage. Immunotherapy has been approved for treatment of LUSC, however, the response rate is unsatisfactory. Recent studies have found that patients with the inflamed type of immune environment were more likely to response to the immunotherapy. It is imperative to build a model to characterize the immune signature of LUSC and to predict the response of immunotherapy.

Methods: The gene expression of LUSC patients from the GEO and the TCGA database were performed by single-sample gene set enrichment analysis (ssGSEA), weighted gene co-expression network analysis (WGCNA), multiple linear regression, and least absolute shrinkage, and selection operator (LASSO).

Results: The immune related modules were acquired from TCGA and GSE50081, and the genes in the TCGA turquoise module were positively related to inflamed type ($r = 0.69$, $P < 1e-200$; $r = 0.93$, $P < 1e-200$; $r = 0.57$, $P = 3.5e-135$). Fifty-one hub genes were obtained by taking the intersection of TCGA and GSE50081 hub genes which were also positively correlated to inflamed type ($r = 0.38$, $P = 1.1e-18$; $r = 0.92$, $P = 4.4e-200$; $r = 0.32$, $P = 5.4e-13$). Fifty-one gene model and 7 gene model simplified by LASSO were higher expression in patients of inflamed type than immune excluded and desert type ($P = 2.5e-6$, $P = 7.5e-14$, and $P = 1.7e-6$, $P = 7.7e-14$) and in patients with response to anti-PD-L1 therapy ($P = 0.031$ and $P = 0.026$). Four positively expression of seven gene signified the



model positive. The model was validated by multiple GEO and TCGA databases and could applied on other tumors.

Conclusion: The establishment of 7 gene model provides a new way to characterized the immune microenvironment of LUSC and predicted the response of immunotherapy.

Key words: Lung squamous cell carcinoma; immune microenvironment; inflamed type; response prediction of immunotherapy; bioinformatics

113. Ad-ER α -36-Fc-GFP 的制备及鉴定

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研究目的: ER α -36 是雌激素受体 α 新亚型,在三阴性乳腺癌中高表达,与 EGFR/Src/Shc 形成复合物,介导膜启动的促有丝分裂雌激素信号通路,与细胞生长,迁移,侵袭能力相关。ER α -36 可作为三阴性乳腺癌的治疗靶点,但目前仅有小分子靶向药物研发。本研究拟根据诱饵受体“Trap”原理,采用基因治疗策略,通过腺病毒感染表达分泌型的 ER α -36-Fc 重组蛋白作为诱饵受体,结合细胞周围微环境中的已知或未知的 ER α -36 配体,以阻断配体对肿瘤细胞 ER α -36 受体的活化,从而达到抑制肿瘤细胞的目的。

材料与方法: 通过基因工程技术,将 ER α -36 受体与免疫球蛋白 IgG1 的 Fc 段融合,构建可表达由 Ig κ 信号肽引导分泌的重组融合蛋白 ER α -36-Fc 的穿梭质粒 pDC316-Ig κ -ER α -36-Fc-GFP。利用 AdMax™ 腺病毒包装系统进行对照病毒 Ad-GFP,Ad-ER α -36-GFP 及重组腺病毒 Ad-ER α -36-Fc-GFP 的包装,鉴定及纯化。通过感染三阴性乳腺癌细胞 MDA-MB-231 进行表达和分泌验证。Western Blot 检测 Ad-ER α -36-Fc-GFP 感染 MDA-MB-231 细胞后,对 EGFR/ERK 信号通路信号活化的抑制作用。

结果: 完成对照病毒 Ad-GFP,Ad-ER α -36-GFP 及重组腺病毒 Ad-ER α -36-Fc-GFP 包装,鉴定,纯化工作,均可高效感染三阴性乳腺癌细胞 MDA-MB-231。Ad-ER α -36-Fc-GFP 感染 MDA-MB-231 后,表达并分泌 ER α -36-Fc 重组蛋白,并显著抑制 p-EGFR,p-ERK 活化。带有 Fc 序列的 Ad-ER α -36-Fc-GFP 重组腺病毒对 EGFR/ERK 信号通路的阻断效果优于仅含 ER α -36 的 Ad-ER α -36-GFP。

结论: d-ER α -36-Fc-GFP 可在三阴性乳腺癌中表达并分泌 ER α -36-Fc 重组蛋白,显著抑制 EGFR/ERK 信号通路。本研究为开展 ER α -36-Fc 诱饵受体的基因治疗研究提供了工具,同时也为另一种以 ER α -36-Fc 融合蛋白作为蛋白药物进行肿瘤治疗的策略奠定基础。(浙江省自然科学基金 LQ19H160017, LY18H160006 资助)

关键词: Ad-ER α -36-Fc-GFP; 腺病毒制备; 诱饵受体; 基因治疗

114. HRP 稳定剂对改善 SCCA 酶结合物稳定性的研究



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目的: 鳞状细胞癌抗原 (SCCA) 是鳞状细胞癌相关的血清学肿瘤标志物, 研究时发现 SCCA 酶结合物 37°C 放置 10 天后, 与 2-8°C 对照试剂相比, 信号值降幅约 30%, 需要改善稳定性。

方法: 配制酶结合物稀释液, 分成四份, A 组作为对照, B 组在酶结合物稀释液中添加 1% 的 HRP 稳定剂, C 组在酶结合物稀释液中添加 5% 的 HRP 稳定剂。D 组在酶结合物稀释液中添加 10% 的 HRP 稳定剂。按照 1:5000 的稀释比例添加酶标抗体。四组试剂各取一支于 37°C 放置 10 天。稳定性到期后, 37°C 放置 10 天的试剂和 2-8°C 的试剂平行考核 SCCA 校准品及 6 份梯度临床样本。搭配磁珠使用 AutoLumo A2000 进行稳定性考核。计算 37°C 放置 10 天的试剂与 2-8°C 试剂相比的信号值变幅。

结果: 与 2-8°C 试剂相比, 37°C 放置 10 天后, A 组试剂信号值降幅 71.46%; B 组试剂信号值降幅 85.13%; C 组试剂信号值降幅 92.62%; D 组试剂信号值降幅 91.97%;

结论: 酶结合物稀释液中添加 HRP 稳定剂后有助于改善酶结合物的稳定性。添加 5% 的 HRP 稳定剂效果优于添加 1% 的 HRP 稳定剂。添加 10% 的 HRP 稳定剂效果和添加 5% 的 HRP 稳定剂效果相当。所以, 优选在酶结合物稀释液中添加 5% HRP 稳定剂, 从而改善了 SCCA 酶结合物的稳定性。

关键词: 鳞状细胞癌抗原; HRP 稳定剂; 稳定性

115. Exosomal-miR-10a Derived from Colorectal Cancer Cells Suppresses Migration of Human Lung Fibroblasts and Secretion of IL-6, IL-8 and IL-1 β

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MicroRNAs (miRs) carried in exosomes serve an important role in the pre-metastatic microenvironment and in intercellular interactions. However, the function of exosomal-miR-10a derived from primary colorectal cancer (CRC) cells on fibroblasts in the lung metastatic microenvironment of patients with CRC remains unclear. Reverse transcription-quantitative PCR was performed using samples from patients with CRC, and demonstrated that the expression levels of miR-10a were significantly lower in serum and cancer tissue samples from patients with CRC compared with in serum from healthy individuals and paired non-cancerous tissues, respectively. In addition, the expression levels of miR-10a were inversely associated [TL1] with the invasion depth of CRC. Exosomal-miR-10a derived from CRC cells reduced the proliferative and migratory activities of primary normal human lung fibroblasts (NHLFs), and the expression levels of IL-6, IL-8 and IL-1 β in NHLFs. The present study

provided insight into the phenotypic alterations of NHLFs induced by exosomal-miR-10a derived from CRC cells, which may aid understanding of the mechanism underlying the process of CRC lung metastasis.

Key words: colorectal cancer; exosome; microenvironment; lung fibroblasts; microRNA-10a

116. microRNA-10a-5p overexpression suppresses malignancy of colon cancer by regulating human liver cancer fibroblasts

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Background: The crosstalk between tumor and stroma plays a critical role in cancer metastasis. However, the function of miR-10a-5p on liver fibroblasts in the metastatic microenvironment of colon cancer (CC) and the effect of activated fibroblasts on CC cells are still unclear.

Methods: Cell proliferation, adhesion, invasion, migration and stemness were determined by the cell counting kit-8 assay (CCK-8), cell-matrix adhesion assay, transwell invasion assay, wound-healing assay and spheroid formation assay, respectively. The RNA expression and protein secretion were assessed by reverse transcription quantitative polymerase chain reaction (RT-qPCR) and enzyme-linked immunosorbent assay (ELISA). In addition, the primary cell line were established by tissue cultivation, and them were identified by morphological observation, cell immunofluorescence assay and flow cytometry assay.

Results: In our study, miR-10a-5p overexpression inhibited the proliferation, migration and IL-6/IL-8 level of LX-2 cells and primary human liver cancer fibroblasts (HLCFs). Moreover, miR-10a-5p was identified lower expression in HLCFs than in primary human liver normal fibroblasts (HLNFs). The conditioned medium (CM) from LX-2 cells with miR-10a-5p overexpression could inhibit the invasion, migration and stemness of CC cell line SW480, whereas HLCFs CM could promote these malignant phenotypes of SW480 cells.

Conclusions: Our study illustrates that miR-10a-5p suppresses the invasion, migration and stemness of CC cells by inhibiting the liver fibroblasts activation in metastatic microenvironment, which may aid the understanding of the mechanisms underlying of CC liver metastasis.

Key words: colon cancer liver metastasis; fibroblasts; miR-10a-5p; tumor microenvironment

117. 胶质母细胞瘤复发相关基因的筛选,表达和临床预后分析

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目的：研究旨在筛选胶质母细胞瘤复发相关的基因，并分析其表达、临床病理参数和预后的关系。

方法：通过对胶质母细胞瘤原发和复发病例的相关数据集挖掘，筛选原发病例和复发病例样本间的差异表达基因，行 GO 和 KEGG 分析，构架 PPI 网络，筛选 Hub 基因，行生存分析、表达和临床病理参数相关分析。

结果：GSE62153 和 GSE58399 数据集分别筛选到 40 个和 19 个差异表达基因，富集于组氨酸代谢。

ERMN、MOG 和 MOBP 高表达者预后均优于低表达组，且与 WHO 分级，IDH 状态和病理相关。

结论：ERMN、MOG 和 MOBP 可能发挥抑癌基因作用参与胶质瘤复发过程，组氨酸代谢途径可能与甲氨蝶呤治疗敏感性相关。

关键词：胶质瘤；生物信息；生存预后；复发；组氨酸代谢

118. 2 型糖尿病患者血清 9 项肿瘤标志物水平的研究

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目的：探索 2 型糖尿病患者 9 种肿瘤标志物的水平，及其与 HbA1c 的相关性。

方法：选取 2017 年 12 月到 2019 年 3 月泉州市第一医院确诊并住院进行正规治疗的 2 型糖尿病患者 197 例，选取同期健康对照组 40 例。2 型糖尿病患者根据 HbA1c 水平分为 A 组（6%~7%，47 例）、B 组（7%~8%，50 例）、C 组（8%~9%，49 例）、D 组（≥9%，51 例）。疾病各组以及健康对照组两两之间性别、年龄差异均无统计学意义。使用电化学发光法检测糖尿病组和健康对照组（40 例）血清 CA19-9、AFP、CEA、CA724、CYFRA21-1、NSE、CA125、CA153 和 HE4 的水平。Spearman 相关分析糖尿病组和健康对照组肿瘤标志物与 HbA1c 是否存在相关性；并用 logistic 线性回归分析肿瘤标志物升高的危险因素。

结果：糖尿病组血清 CA19-9（7.28~21.55 U/ml）、CEA（1.89~3.95 ng/ml）、CA125（8.60~15.80 U/ml）和 HE4（51.86~90.26 pmol/L）较健康对照组 CA19-9（2.72~7.35 U/ml， $P=0.000$ ）、CEA（1.18~2.76 ng/ml， $P=0.002$ ）、CA125（7.76~12.42 U/ml， $P=0.035$ ）和 HE4（44.21~65.48 pmol/L， $P=0.003$ ）明显升高。糖尿病四组之间 D 组 CA19-9（9.00~41.86 U/ml）、CEA（2.88~5.56 ng/ml）水平显著升高，D 组血清 CA125（10.50~19.00 U/ml）水平明显高于 A（7.36~13.16 U/ml， $P=0.000$ ）、B（7.90~14.53 U/ml， $P=0.014$ ）组，但和 C（8.67~16.94 U/ml， $P=0.064$ ）组无差异；B 组的血清 HE4（55.76~102.80 pmol/L）水平明显高于 A（48.54~80.43 pmol/L， $P=0.048$ ）组，其余组间无差异。Spearman 相关性分析显示血清 CA19-9（ $r=0.246$ ， $P=0.002$ ）、CEA（ $r=0.334$ ， $P=0.000$ ）、CA125（ $r=0.287$ ， $P=0.000$ ）与

HbA1c 水平存在相关性；血清 HE4 ($r=-0.015$, $P=0.849$) 水平变化与 HbA1c 无关。logistic 线性回归分析显示 HbA1c 水平是血清 CA19-9 ($P=0.000$), CEA ($P=0.000$), CA125 ($P=0.015$) 水平升高的独立危险因素。

结论：2 型糖尿病患者血清 CA19-9, CEA, 和 CA125 水平可出现异常升高，且水平升高与 HbA1c 水平密切相关。临床诊疗时应注意该现象与恶性肿瘤的区别。

关键词：2 型糖尿病；糖化血红蛋白；肿瘤标志物；血清 CA19-9；血清 CEA

119. 脑胶质瘤患者外周血循环肿瘤细胞与其肿瘤 WHO 分级相关性研究

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目的：通过对脑胶质瘤患者外周血循环肿瘤细胞 (circulating tumor cells, CTCs) 的检测及分型鉴定，探讨其与临床病理特征的相关性及临床应用价值。

方法：选取 2018 年 5 月至 2020 年 10 月于中山大学附属第三医院神经外科诊治 27 例脑胶质瘤患者为研究组和 10 例健康体检者为对照组作为研究对象，采用 CanPatrol 技术进行 CTCs 分离鉴定并计数，根据上皮和间质等标志物表达情况进行 CTCs 分型。分析 CTCs 数目及分型与脑胶质瘤 WHO 分级的关系。

结果：高级别胶质瘤患者 (WHO III-IV 级) 的 CTCs 阳性率高于低级别胶质瘤患者 (WHO I-II 级)，原发肿瘤组织 Ki67 高表达的患者外周血 CTCs 阳性率高于肿瘤组织 Ki67 低表达者，差异有显著统计学意义 ($P<0.05$)，发生复发的胶质瘤患者 CTC 总数及混合型 CTC 的表达比不发生复发患者的阳性率显著高，差异有统计学意义 ($P<0.05$)。

结论：CTCs 表达水平与脑胶质瘤 WHO 分级显著相关，且上皮-间质标记共表达为主的 CTCs 在预测胶质瘤复发方面具有潜在的临床应用价值。

关键词：脑胶质瘤；循环肿瘤细胞；WHO 分级

120. 乙型肝炎病毒 X 蛋白通过靶向 miR-200c 诱导 DNA 异常甲基化

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乙型肝炎病毒 x (Hepatitis B virus x, HBx) 蛋白是导致肝癌 (Hepatocellular Carcinoma, HCC) 的重要因素。但 HBx 在 HCC 形成过程中表观遗传机制尚有待于阐明。本研究发现 microRNA-200c (miR-200c) 在过表达乙型肝炎病毒的 HCC 中下调, 并且它直接靶向 DNA 甲基转移酶 3A (DNA methyltransferase 3A, DNMT3A)。此外, miR-200c 和 DNMT3A 在 HB 诱发的肝癌组织中呈现负相关。乙型肝炎病毒诱导 miR-200c 下调, 进而引起 DNMT3A 表达上调, 然后导致细胞中肿瘤相关基因的启动子超甲基化。我们对乙型肝炎病毒诱导的肝癌的表观遗传学改变进行了进一步研究, 并提出了一种基于 miRNA 的靶向治疗乙型肝炎病毒相关的肝癌的潜在方法。

关键词: miR-200c; 肝癌; DNMT3A; 乙肝病毒

121. ITGA5 predicts dual-drug resistance to Temozolomide and Avastin in glioma

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Aims: Anti angiotherapy (Avastin) is currently regarded as a promising option for glioma patients who are resistant to TMZ treatment. But ongoing clinical research failed to meet therapeutic expectations. This study aims to explore the pivotal genetic feature responsible for TMZ and Avastin resistance in glioma patients.

Methods: We downloaded transcriptomic and methylation data of glioma patients from TCGA, CGGA and GEO databases, grouped these patients into resistant and non-resistant group based on their clinical profiles. Differentially expressed genes and pathways were identified and exhibited with software in R platform. Expression of candidate gene was compared in resistant and non-resistant glioma cells, while biological function of it was investigated by CCK8 assay, western blot and PAS staining.

Results: Change of cell morphology and polarity was closely associated with TMZ mono-resistance and TMZ/Avastin dual-resistance in glioma patients. Expression level of ITGA5 was effective in determining drug resistance and glioma patients' outcome, which is regulated by methylation on two distinct sites. ITGA5 was augmented in TMZ-resistant glioma cells, while overexpressing ITGA5 altered cell promoted TMZ resistance correspondingly.

Conclusions: Both epigenetic and transcriptional levels of ITGA5 are effective in predicting TMZ and Avastin resistance, indicating that ITGA5 may serve as a predictor of treatment outcome in glioma patients.

Key words: glioma; TMZ resistant; Avastin resistant; ITGA5; vascular mimicry



122. Evaluation and characterization of HSPA5 (GRP78) expression profiles in normal individuals and cancer patients with COVID-19

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HSPA5 (BiP, GRP78) has been reported as a potential host-cell receptor for SARS-Cov-2, but its expression profiles on different tissues including tumors, its susceptibility to SARS-Cov-2 virus and severity of its adverse effects on malignant patients are unclear. In the current study, HSPA5 has been found to be expressed ubiquitously in normal tissues and significantly increased in 14 of 31 types of cancer tissues. In lung cancer, mRNA levels of HSPA5 were 253-fold increase than that of ACE2. Meanwhile, in both malignant tumors and matched normal samples across almost all cancer types, mRNA levels of HSPA5 were much higher than those of ACE2. Higher expression of HSPA5 significantly decreased patient overall survival (OS) in 7 types of cancers. Moreover, systematic analyses found that 7.15% of 5,068 COVID-19 cases have malignant cancer coincidental situations, and the rate of severe events of COVID-19 patients with cancers present a higher trend than that for all COVID-19 patients, showing a significant difference (33.33% vs 16.09%, $P < 0.01$). Collectively, these data imply that the tissues with high HSPA5 expression, not low ACE2 expression, are susceptible to be invaded by SARS-CoV-2. Taken together, this study not only indicates the clinical significance of HSPA5 in COVID-19 disease and cancers, but also provides potential clues for further medical treatments and managements of COVID-19 patients.

Key words: cancer; HSPA5; prognostics; SARS-CoV-2; transcriptomics

123. eEF2K: 胃癌预后判断的新型分子标志物

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研究目的: 胃癌是消化系统最常见的肿瘤之一, 对胃癌的早期诊断及治疗可以有效的提高患者的 5 年生存率。近年来, 真核延伸因子 2 激酶 (eukaryotic elongation factor-2 kinase, eEF2K) 被报道成为多种肿瘤的潜在致癌因素, 已成为肿瘤治疗和肿瘤标志物筛选的新热点, 但尚未有研究报道其作为胃癌的临床预后生物标志物的作用。本文主要探讨胃癌患者正常组织及癌组织中 eEF2K 的表达及其与胃癌临床病理特征的关系。

材料与方法: 下载癌症基因组图谱 (The Cancer Genome Atlas, TCGA) 和基因表达总库 (Gene Expression Omnibus, GEO) 数据库胃癌临床及基因表达数据, 利用 R 语言 edge R 软件包分析 540 名胃癌患者的数据, 以确定公共数据库中 eEF2K 的表达。收集 2011 年 10 月 01 日至 2017



年 8 月 31 日哈尔滨医科大学附属肿瘤医院病理科胃癌组织标本 96 例, 正常组织标本 96 例, 搜集并整理患者临床资料, 通过免疫组织化学 (Immunohistochemistry, IHC), Western blots 和实时聚合酶链反应 (Reverse Transcription-Polymerase Chain Reaction, RT-PCR) 检测胃癌组织及正常组织中 eEF2K 表达情况, 根据其表达情况及临床病例数据分析 eEF2K 在胃癌组织的临床意义。

研究结果: 与正常组织相比, eEF2K 在胃癌组织中的表达水平明显增高 ($P<0.05$)。单因素分析显示, eEF2K 的高表达水平与患者年龄、性别、肿瘤大小无关 ($P>0.05$), 与淋巴结转移明显相关 ($P=0.002$)。此外, 多因素分析显示, eEF2K 是手术切除的 STAD 患者总生存期 (Overall Survival, OS) (风险率[hazard ratio, HR]=1.72, 95%置信区间[confidence interval, CI]=1.06-2.79; $P=0.03$) 和无病生存期 (Disease Free Survival, DFS) (HR=1.66, 95%CI=0.997-2.765; $P=0.052$) 的一个独立指标。K-M 生存分析显示, 胃癌患者中 eEF2K 高表达者预后不良 ($P<0.05$)。

研究结论: 在胃癌组织中 eEF2K 高表达, 其高表达与胃癌患者淋巴结转移相关,并可导致胃癌患者预后不良。eEF2K 可作为潜在的胃癌预后预测的分子标志物。

关键词: eEF2K; 胃癌; 预后; 分子标志物

124. 血清胸苷激酶 1 在晚期非小细胞肺癌疗效评估中的意义及临床价值

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目的: 通过动态监测血清胸苷激酶 1 水平的变化, 探讨血清胸苷激酶 1 在晚期非小细胞肺癌患者疗效评估中的临床意义。

方法: 纳入我院 70 例已确诊的晚期非小细胞肺癌初治患者, 入组患者预估生存时间大于 3 个月, 所有患者均有可测量的客观病灶, KPS 评分 70-100 分。所有入组患者在治疗前 (包括放疗、化疗、靶向治疗及免疫治疗) 及每个周期治疗后分别采集血清标本送至我院核医学科检测 CEA, CYFRA21-1, SCC, CA125, NSE 水平, 以及送至我院肿瘤细胞学实验室检测血清胸苷激酶 1 的水平。记录患者复发转移时间。年龄、血清胸苷激酶 1 水平等计量指标采用 ($\bar{x} \pm s$) 表示, 组间比较采用 t 检验; 多因素分析采用 Logistic 回归分析法。以 $P<0.05$ 为差异有统计学意义。

结果: 肺鳞癌与肺腺癌组患者血清胸苷激酶 1 的水平无统计学差异; 男性与女性患者血清胸苷激酶 1 的水平无统计学差异; 血清胸苷激酶 1 的水平与 Ki67 表达高低无关; 治疗后的动态评估中, 疗效评价为 PR (部分缓解) 的患者血清胸苷激酶 1 的水平较前明显下降, 差异具有统计学意

义 ($P<0.05$)；疗效评价为 SD（疾病稳定）的患者血清胸苷激酶 1 的水平较前变化不明显 ($P>0.05$)；疗效评价为 PD（疾病进展）的患者血清胸苷激酶 1 的水平较前明显升高，差异具有统计学意义 ($P<0.05$)。

结论：血清胸苷激酶 1 水平的变化与患者治疗疗效相关，通过动态监测血清胸苷激酶 1 水平的变化可早期判断治疗疗效。

关键词：非小细胞肺癌；血清胸苷激酶 1；复发；转移

125. Tead4 在实体瘤中研究进展

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近年来研究发现 TEAD4 是 Hippo 信号通路中具有保守性的主要下游转录因子，是肿瘤发生的关键因子，在癌症状态下经常处于失衡状态，能够脱离 YAP 直接控制下游相关基因表达，在乳腺癌、口腔癌、直肠癌等肿瘤中具有促癌作用，加重肿瘤患者病情。本文就 TEAD4 在肿瘤的作用机制进行归纳及分析，为以 TEAD4 研究重点的肿瘤治疗提供一定参考意义。

关键词：Tead4；Hippo 信号通路；作用机制；肿瘤

126. 胃肠外营养通过影响 MUC2 蛋白引起肠粘膜屏障功能障碍的研究进展

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肠粘膜杯状细胞（goblet cell, GC）的数量及其分泌的黏蛋白 2（mucin 2, MUC2）对于维持肠道稳态都具有重要作用，是肠粘膜屏障的重要组成部分。胃肠外营养（parenteral nutrition, PN）可导致肠粘膜屏障功能障碍，造成肠源性感染，进一步加重原发疾病且诱发全身炎症反应综合征，这一过程复杂且对临床治疗意义重大，本文就 PN 对 MUC2 的影响引起的肠粘膜屏障功能障碍的研究进展进行综述。

关键词：胃肠外营养；黏蛋白 2；肠粘膜屏障



127. COVID-19 disease and malignant cancers: The impact for the furin gene expression in susceptibility to SARS-CoV-2

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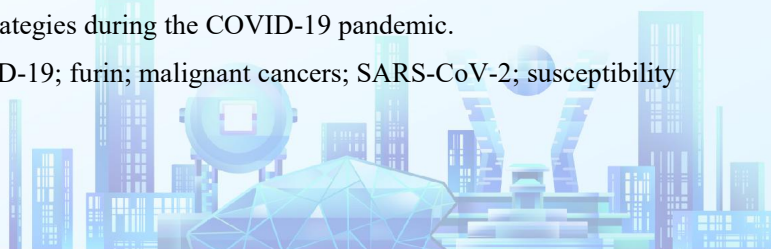
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Furin is a proprotein convertase that activates different kinds of regulatory proteins, including SARS-CoV-2 spike protein which contains an additional furin-specific cleavage site. It is essential to foretell the cancer patients' susceptibility to SARS-CoV-2 and the disease outcomes through evaluating furin expressions in tumor tissues. In this study, we analyzed the furin expression, methylation, mutations, functional enrichment, survivals and COVID-19 outcomes in normal and tumor tissues through online databases and IHC. As results, furin presented the biased expression profiles in normal tissues, showing 12.25-fold higher than ACE2 in the lungs. The furin expressions in tumors were significantly increased in ESCA and TGCT; decreased in DLBC and THYM, indicating furin may play critical roles for COVID-19 viral entry in these cancer patients. Line with furin over/downexpression, furin promoter hypo-/hyper-methylation may be the regulatory mechanism and in pathogenesis of ESCA and THYM. Furthermore, usage of FURIN-201 isoform with functional domains (P_proprotein, Peptidase_S8 and S8_pro-domain) is the highest in all cancer types, demonstrating this isoform role in tumorigenesis and SARS-Cov-2 entry into tumor tissues. Meanwhile, furin mutation frequency was highest in UCES, and its mutation elevated ACE2 expression in LUAD and UCEC, reduced ACE2 expression in COAD; elevated HSPA5 expression in PAAD; elevated TMPRSS2 expression in BRCA. These results showed that furin mutations mostly increased expression of ACE2, HSPA5 and TMPRSS2 in some cancers, indicating the possible network roles of furin mutation for COVID-19 viral entry for cancer patients. In addition, high expression of furin was significantly reverse correlated with long overall survival (OS) in LGG; significantly correlated with long OS in COAD and KIRC, indicating that it may serve as a favorable prognostic marker for those cancer patient's survivals. Moreover, GO and KEGG demonstrated that furin was mostly enriched in the genes for metabolic and biosynthetic processes, retinal dehydrogenase activity, tRNA methyltransferase activity, and diseases mainly include COVID-19, demonstrating its roles for COVID-19 and cancer metabolism. Altogether, furin highly expression not only implies the susceptibility to SARS-CoV-2, severity of COVID-19 symptoms in cancer patients, but also highlights the values of combating cancers by targeting therapeutic strategies during the COVID-19 pandemic.

Key words: COVID-19; furin; malignant cancers; SARS-CoV-2; susceptibility



128. 有核红细胞与感染的关系的研究进展

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有核红细胞是未成熟的红细胞。除新生儿期外,有核红细胞极少出现在正常人的外周血中。外周血中出现有核红细胞往往提示病理状态。感染时,患者机体存在炎症反应,组织细胞缺氧刺激促红细胞生成素的合成,导致有核红细胞释放增加。近年来,多项研究揭示了外周血有核红细胞与感染的关系。有核红细胞的数量与阶段分类对于各类疾病感染及其严重程度的辅助诊断与预后判断有重要的意义。现将国内外有核红细胞与感染的关系的研究综述如下。

关键词: 有核红细胞; 感染

129. Comparative analysis of QS3D and droplet digital PCR for detection of plasma EGFR T790M mutation at disease progression

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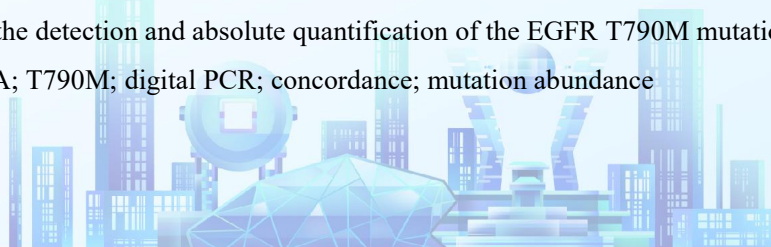
Objectives: Numerous studies have demonstrated the ability of QuantStudio™ 3D (QS3D) and droplet digital PCR (dPCR) platforms in the successful detection of EGFR mutations from plasma. However, no prospective data on quantitative comparative analysis of the two methods are available. Here we directly compared the performance of the two platforms in the detection of the EGFR T790M mutation in cell-free DNA (cfDNA) samples from lung cancer patients.

Methods: cfDNA was isolated from plasma samples of 72 non-small cell lung cancer patients who initially received tyrosine kinase inhibitor treatment and acquired drug resistance. Identical cfDNA samples were subjected to T790M mutation analysis using QS3D and droplet dPCR in parallel.

Results: The T790M mutation was detected in 15/72 (20.8%) cfDNA samples by QS3D dPCR and 21/72 (29.2%) cfDNA samples by droplet dPCR. The overall concordance between the two methods was 91.7% (66/72). The median allele frequency of the T790M mutation detected by QS3D dPCR and droplet dPCR was 2.01% and 2.62%, respectively. The partition number of QS3D dPCR is much higher than that of droplet dPCR, while the mutation abundance detected by the two platforms is similar. Furthermore, a strong correlation was observed in allele frequencies and copy numbers between the two methods, with R^2 of 0.98 and 0.97, respectively.

Conclusion: Our study demonstrated a high level of concordance between the QS3D and droplet dPCR platforms for the detection and absolute quantification of the EGFR T790M mutation in cfDNA.

Key words: cfDNA; T790M; digital PCR; concordance; mutation abundance



130. 肿瘤患者放化疗后外周血细胞形态改变的研究进展

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恶性肿瘤现如今在中国的发病率和死亡率仍然高居不下,除了手术以外,主要的治疗手段有放射治疗以及化学药物治疗。当其杀死肿瘤细胞的同时对正常组织和细胞也会造成不良影响。主要影响之一的骨髓抑制可以通过观察外周血细胞形态来发现,其主要的异常形态有细胞体积巨型变或小型变,中毒颗粒,核右移,核左移,低分叶,未成熟细胞,退行性变化,异型淋巴,核分叶异常及大颗粒淋巴,破碎细胞,有核红细胞,红细胞形态异常,大血小板。而形成骨髓抑制的机制有损伤 DNA 导致细胞凋亡,衰老以及骨髓细胞周期异常;损伤造血微环境中的微血管,造血生长因子(HGF)及骨髓基质细胞。通过观察外周血细胞形态出现的异常改变可以发现骨髓抑制损伤情况并为临床医生提供参考依据做出相应的改善治疗措施。

关键词: 放化疗; 外周血; 细胞形态; 骨髓抑制; 机制;

131. 肺癌患者下呼吸道病原菌分布特征与耐药性分析

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目的: 了解肺癌患者下呼吸道病原菌分布及耐药性,以指导临床经验治疗及合理使用抗菌药物。

方法 收集 2015 年至 2019 年上海交通大学附属胸科医院肺癌患者的痰培养资料,对病原菌进行鉴定和体外药物敏感性实验,并分析其分布特点和耐药情况。

结果: 2015-2019 年共收集 4753 份痰培养,有 672 份痰培养检出病原菌 720 株,检出率为 14.1%,其中革兰阴性菌,革兰阳性菌,真菌分别占 71.5%,6.9%,21.5%。在所有病原菌中排名前 5 的分别是肺炎克雷伯菌(21.0%),铜绿假单胞菌(16.8%),白色念珠菌(16.5%),鲍曼不动杆菌(11.0%)和金黄色葡萄球菌(5.0%)。肺炎克雷伯菌,铜绿假单胞菌,鲍曼不动杆菌对氨苄西林/舒巴坦,左旋氧氟沙星,环丙沙星,头孢他啶,妥布霉素,庆大霉素均较为敏感。白色念珠菌对常用的抗真菌药物两性霉素 B,氟康唑,伊曲康唑,伏立康唑,5-氟胞嘧啶均敏感。未发现对替加环素,万古霉素,利奈唑胺,奎奴普汀/达福普汀耐药的金黄色葡萄球菌。

结论: 肺癌患者下呼吸道病原菌种类复杂,以革兰阴性菌为主。临床对于下呼吸道感染的肺癌患者可以根据耐药监测结果进行经验治疗,并根据具体药物敏感性试验结果进行针对性治疗。

关键词: 肺癌; 下呼吸道; 病原菌



132. 高敏心肌肌钙蛋白在急性冠脉综合征诊断中的应用价值

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随着日常生活和工作压力的不断升高,以及作息和饮食习惯的改变,心血管疾病的发病率和死亡率呈不断上升趋势,且正朝着年轻化的趋势发展。在我国,冠状动脉疾病也成为城市人群的主要疾病和死亡原因之一。急性冠脉综合征(ACS)作为心血管内科发病率较高的疾病之一,具有发病较急且病情变化快,同时临床表现较复杂的特点,若得不到早期精准的诊断常会致死,该疾病目前正严重威胁人类的生命健康。随着医学水平的快速进步,血浆肌钙蛋白凭借其组织特异性强,灵敏度高的优势,成为诊断ACS的重要指标,经过不断地更新换代,高敏心肌肌钙蛋白检测法(hs-cTn)横空出世,较普通肌钙蛋白检测灵敏度,精密度更高,并已被广泛应用于临床。本文就hs-cTn在ACS中的诊断应用与价值进行综述。

关键词: 高敏肌钙蛋白;急性冠脉综合征;诊断

133. 肺移植术后病原菌感染的分布和耐药特征及风险因素

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目的: 回顾性分析肺移植术后感染的病原菌的分布和耐药特征及增加感染风险的因素,为指导临床合理选择抗菌药物,调整抗感染治疗方案提供依据。

方法: 分析2007年9月~2019年8月行肺移植手术的50例患者术后病原菌分布情况,发生时间,耐药特征和增加感染的危险因素,采用VITEK2 COMPACT全自动微生物鉴定与药敏系统鉴定菌株和检测药物敏感性,使用SPSS 22.0软件系统处理数据。

结果: 肺移植术后受者感染率74%(37/50),单一病原菌感染9例(24.3%),两种及以上病原菌混合感染28例(75.7%)。引起感染的主要病原菌是革兰阴性菌(铜绿假单胞菌,鲍曼不动杆菌,嗜麦芽窄食单胞菌和肺炎克雷伯菌),铜绿假单胞菌对头孢类,氟喹诺酮类和复方新诺明耐药率66.7%~94.1%;鲍曼不动杆菌对多种抗菌药物高耐药,耐药率72.7%~100%;嗜麦芽窄食单胞菌对头孢他啶耐药率50%;肺炎克雷伯菌对碳青霉烯类, β 内酰胺类,头孢类和氟喹诺酮类耐药率44.4%~71.4%。其次是革兰阳性菌(金黄色葡萄球菌,溶血葡萄球菌和粪肠球菌),对利奈唑胺,达福普汀,替加环素和万古霉素敏感,可作为抗感染治疗的首选药物。单因素分析结果显示性别,年龄,入住重症加强护理病房(Intensive Care Unit, ICU),氧分压,血红蛋白水平,血清白蛋白水平,他克莫司水平,吻合口瘘/支气管狭窄,机械通气和阻塞性细支气管炎综合征是术后肺部病原菌感染的危险因素($P < 0.05$)。



结论： 移植物本身的性质,患者营养状态和外界环境因素是造成肺移植受者不同时间段感染的危险因素,以革兰阴性菌尤其是非发酵菌感染为主,对多种抗菌药物表现为高耐药,临床需根据药敏结果选择抗菌药物和剂量,以提高患者生存年限。除病原菌的识别,控制和治疗至关重要外,术后营养支持,康复护理,环境消毒隔离亦扮演重要角色,直接影响移植物的功能和免疫抑制剂的应用。

关键词： 关键词：肺移植；细菌感染；耐药性；危险因素

134. Identification of MXD1 as a Key Gene for Esophageal Squamous Cell Carcinoma

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Identification of novel biomarkers is crucial for the diagnosis and treatment of esophageal squamous cell carcinoma (ESCC). The clinical significance and molecular characteristics of MYC associated factor X dimerization protein 1 (MXD1) in ESCC remain unclear. In the present study, bioinformatic analysis of mRNA expression data was used to reveal the relevance of MXD1 activity in ESCC and immunohistochemistry was used to confirm these findings on the protein expression level. We found that MXD1 mRNA expression was significantly decreased in tumor than in normal tissue. Low expression of MXD1 in ESCC was associated with more aggressive tumor stage and worse prognosis on both mRNA and protein level. Moreover, MXD1-low ESCC had upregulation of epithelial-mesenchymal transition and extracellular matrix-related gene sets, and significantly more NFE2L2 and KIAA1324L mutation. Whereas MXD1-high ESCC showed upregulation of tumor differentiation and immune-related gene sets. Furthermore, we applied an established computational approach (CIBERSORT) to infer the proportions of 22 subsets of immune cells. MXD1 high expression seemed to be associated with higher proportion of neutrophils but lower proportion of macrophage M2. On the protein level, MXD1 expression was positively correlated with PDL1 and CD8 expression. In silico analysis predicted that MXD1-high ESCC had more likelihood to benefit from immunotherapy. The findings of current study indicated the essential role of MXD1 in ESCC.

Key words: MXD1; esophageal squamous cell carcinoma; prognosis; mutational profile; tumor microenvironment



135. CPEB4 inhibit cell proliferation via upregulating p21 mRNA stability in Renal cell carcinoma

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Objective: Cytoplasmic polyadenylation element-binding protein 4 (CPEB4) has been reported to be dysregulated in a variety of cancers and seems to play paradoxical roles in different cancers. However, the functional roles of CPEB4 in Renal cell carcinoma (RCC) are still unclear. This study aims to explore the role and underlying mechanism of CPEB4 in RCC.

Methods: Western blot and TCGA database analysis were used to evaluate CPEB4 expression in RCC and adjacent tumor tissues and RCC cell lines. The functional characterization of the role and molecular mechanism of CPEB4 in renal cancer cell growth were examined using a series of biological and cellular approaches in vitro and in vivo.

Results: We found that the relative expression level of CPEB4 is down-regulated in RCC tissues and cell lines, and the low CPEB4 expression is correlated with short overall and disease-free survival of RCC patients. CPEB4 significantly inhibits RCC tumor growth both in vivo and in vitro. CPEB4 exerts an anti-tumor effect by increasing p21 mRNA stability and inducing G1 cell cycle arrest in RCC.

Conclusions : Our data revealed that CPEB4 is a tumor suppressor gene that restrains cell cycle progression upstream of p21 in RCC. These findings revealed that CPEB4 may become a promising predictive biomarker for prognosis in patients with RCC.

Key words: CPEB4; Proliferation; p21; Renal cell carcinoma

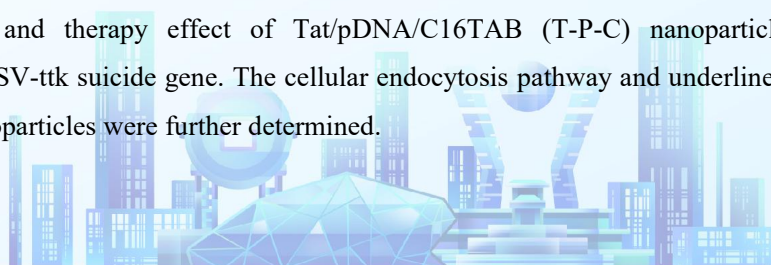
136. Arf6-mediated macropinocytosis enhanced suicide gene therapy of C16TAB-condensed Tat/pDNA nanoparticles in ovarian cancer

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Background: Using cell-penetrating peptides to deliver the therapeutic gene for cancer treatment is hindered by low-efficient delivery and complicated uptake route of nano-complexes. Recent advances in surfactant-modified nano-material and dual molecular imaging technology have offered new opportunities for suicide gene therapy.

Methods: we employed cationic surfactant C16TAB to further condense Tat/pDNA complexes, and tested the delivery and therapy effect of Tat/pDNA/C16TAB (T-P-C) nanoparticles carrying GCV-convertible HSV-ttk suicide gene. The cellular endocytosis pathway and underlined signal mechanism of T-P-C nanoparticles were further determined.



Results: The resulted T-P-C nanoparticles exhibited smaller size, positive charge, irregular granular shape and higher pDNA encapsulation efficiency. In vitro experiments showed that T-P-C nanoparticles mainly used macropinocytosis for uptake in ovarian cancer cells, and their uptake and payload gene-expression were controlled by Arf6 GTPase-dependent, Rab GTPase-activated signal axis. In vivo molecular imaging showed that T-P-C nanoparticles significantly increased the targeted delivery and suicide gene therapy in mice model xenografted with human ovarian cancer. Arf6-mediated macropinocytosis remarkably enhanced the delivery efficiency and suicide gene therapy effect of T-P-C nanoparticles.

Conclusions: Our study provides a new C16TAB-condensed Tat/pDNA nanoparticle combined with dual molecular imaging strategy, highlighting a novel intracellular delivery platform for high-efficient, precise suicide gene therapy of ovarian cancer.

Key words: Arf6 GTPase; Tat/pDNA/C16TAB nanoparticle; suicide gene therapy; molecular imaging

137. 根治术后老年非小细胞肺癌患者的预后影响因素

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目的: 非小细胞肺癌是老年人群常见的恶性肿瘤之一, 且预后不良, 本文探讨影响根治术后老年非小细胞肺癌 (Non-small cell lung cancer, NSCLC) 患者预后的因素, 旨在为其临床诊疗和预后评估等提供依据。

方法: 回顾性分析 2015 年四川省人民医院 80 例首程治疗且接受手术的老年 NSCLC 患者的病历与随访资料。收集其基线临床病理特征, 治疗前的检验结果和随访信息。结合肿瘤标志物 (tumor marker, TM) 和系统性免疫-炎症指数 (systemic immune-inflammation index, SII) 建立 TM-SII 评分。Kaplan-Meier 法和 COX 回归模型分别进行单因素及多因素分析, 用于探索患者的临床病理特征和治疗前的检验结果与预后的关系。

结果: 单因素显示, KPS 评分 ($P < 0.05$), TNM 分期 ($P < 0.05$), 血清白蛋白 (albumin, ALB) ($P < 0.05$), TM-SII ($P < 0.05$), 血清白蛋白 (ALB) ($P < 0.05$) 均与患者生存率有关联。多因素 COX 回归分析显示 KPS 评分 ($P < 0.05$), TNM 分期 ($P < 0.05$), TM-SII ($P < 0.05$) 是根治术后老年 NSCLC 患者生存率的影响因素。

结论: KPS 评分, TNM 分期, TM-SII 与根治术后老年 NSCLC 患者生存率相关的预后因素。

关键词: 老年; 非小细胞肺癌; 根治术后; 预后; 影响因素



138. NIP30 通过 REG γ -蛋白酶体通路调控 p53 基因失活肿瘤发生发展及化疗敏感性

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A major challenge in chemotherapy is anti-cancer drug resistance in cells lacking p53. Here we demonstrate that NIP30, a previously unrecognized inhibitor of the oncogenic REG γ -proteasome, attenuates cancer cell growth and sensitizes p53-compromised cells to chemotherapeutic agents. The tumor suppressive role of NIP30 requires tight binding to REG γ via an evolutionarily-conserved serine-rich domain with 4-serine phosphorylation. We discovered the cyclin-dependent phosphatase, CDC25A, as a key regulator to switch NIP30 phosphorylation and modulate the REG γ activity during the cell cycle or DNA damage. Regulation of p21 in vivo by the CDC25A-NIP30-REG γ pathway was validated in p53^{-/-} and p53/REG γ double-deficient mice. Phosphor-NIP30 mimetics significantly enhanced the growth inhibitory effect of chemotherapeutic agents in vitro and in vivo. Given that NIP30 is frequently mutated in the TCGA cancer database, our results provide insights into the regulatory signal pathway controlling the REG γ -proteasome in carcinogenesis that allows for a promising approach in drug-resistant cancer therapy.

关键词: NIP30; REG γ ; p53-deficient tumor

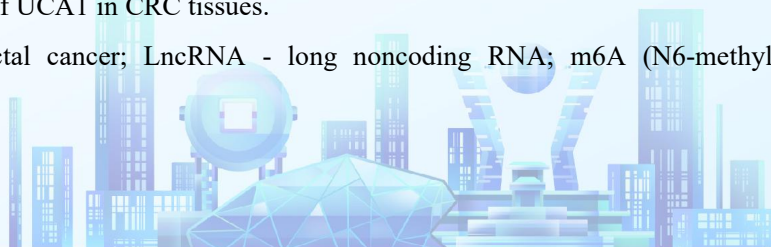
139. UCA1 的 m6A 修饰在结直肠癌中的作用

贺荣章*

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UCA1 is frequently upregulated in a variety of cancers, and it can play an oncogenic role by various mechanisms. However, how UCA1 is regulated in cancer is largely unknown. In this study, we aimed to determine whether RNA methylation at N6-methyladenosine (m6A) can impact UCA1 expression in colorectal cancer (CRC). By immunoprecipitation using m6A antibody we found that UCA1 is subject to m6A modification. In vivo pulldown assays using S1m tagging combined with site-direct mutagenesis revealed that IGF2BP2 serves as a reader for m6A modified UCA1 and that adenosine at 1,038 of UCA1 is critical to the recognition by IGF2BP2. Importantly, we showed that m6A writers, METTL3 and WTAP positively regulate UCA1 expression. Mechanically, IGF2BP2 increases the stability of m6A-modified UCA1. Clinically, IGF2BP2 is upregulated in CRC tissues compared with normal tissues. These results suggest that m6A modification is an important factor contributing to upregulation of UCA1 in CRC tissues.

关键词: colorectal cancer; LncRNA - long noncoding RNA; m6A (N6-methyladenosine); UCA1; IGF2BP2



140. 血清 CA242,CA19-9 及生化指标在结直肠癌检测中的应用价值研究

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目的: 探讨肿瘤标志物 CA242 和 CA19-9 在结肠癌检测中的应用价值。

方法: 收集 2020 年 3 月至 2021 年 5 月 95 例结直肠癌患者为观察组,选取同期收治的良性疾病患者和健康人群各 45 例为对照组和健康组,采用磁微粒化学发光法比较三组血清样本的 CA242 和 CA19-9 水平。

结果: 观察组的血清 CA242 和 CA19-9 水平显著高于对照组和健康组,差异具有统计学意义 ($P < 0.05$); 对照组和健康组的血清 CA242 水平比较,差异不具有统计学意义 ($P > 0.05$); 对照组和健康组的 CA19-9 水平比较,差异具有统计学意义 ($P < 0.05$); 检测观察组,对照组血清生化指标 AST,ALT,TBIL 等指标显著高于健康组; CA242 在结直肠癌患者及良性疾病患者血清中阳性检出率分别为 68.42% (65/98),26.67% (12/45), CA19-9 在结直肠癌患者及良性疾病患者血清中阳性检出率分别为 75.79% (72/95),46.67% (21/45),表明两种标志物对结直肠癌及良性疾病具有一定的鉴别能力,且 CA242 特异性优于 CA19-9。

结论: 血清肿瘤标志物 CA242 和 CA19-9 及生化指标联合检测能够显著提高结直肠癌的检出效果,值得临床推广应用。

关键词: 结直肠癌; CA242; CA19-9

141. Palmitoyltransferase ZNF377 regulates EGFR through lipid metabolism in breast cancer

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Background: Members of the epidermal Growth Factor receptor (EGFR)/ErbB family were the most significant cancer molecular targets identified so far. Aberrant EGFR activation has been confirmed in various subtypes of breast cancers, which may be related to reduced degradation after activation. EGFR is located in lipid rafts on the cell membrane, its binding characteristics and biological functions are profoundly affected by cell membrane lipid metabolism. It has been reported that lipid metabolism is modulated by S-palmitoylation, thus altering EGFR localization, which is the basic prerequisite for EGFR to function correctly and degradation.



Methods: Firstly, the expression of ZNF377 in breast cancer tissues and cells were detected by Real-time PCR and Real-time quantitative PCR, MSP was conducted to test methylation of ZNF377 in BrCa. Secondly, utilizing clone formation, CCK8 assay, transwell assay, xenograft tumor growth in nude mice and flow cytometry to verify functions of ZNF377 as a tumor suppressor in vitro and in vivo. 8-plex isobaric tags for relative and absolute quantitation (iTRAQ) and Quantitative metabolomics were used to detect lipid metabolism around the cell membrane. Indirect immunofluorescence, knockout mice, co-immunoprecipitation and GST-pull down were carried out to study the molecular mechanism of ZNF377 in breast cancer.

Results: We identified palmitoyltransferase ZNF377 inhibited malignant biological phenotype of breast cancer in vitro and in vivo, but frequently downregulated due to promoter methylation. Mechanically, we identify by 8-plex isobaric tags for relative and absolute quantitation (iTRAQ) that ZNF377 downregulated lipid-associated protein PCTP2. Our research indicated ZNF377 S-palmitoylation downregulated PCTP2 thus reducing cell membrane fluidity, which trapped EGFR in lipid rafts to promote its ubiquitination endocytosis degradation, reduce its dimer and autophosphorylation and impeded signaling cascades. Notably, we found in ZNF377 conditional knockout C57BL/6 mice, ZNF377 deleting significantly promoted the spontaneous of breast cancer accompanied by the upregulation of PCTP2 and the increase of EGFR activity. Although EGFR tyrosine kinase inhibitors (TKIs) including gefitinib and lapatinib have been widely used in clinic, the curative effects in breast cancer remain unsatisfied. We confirmed that ZNF377 sensitized TKIs to breast cancer cells.

Conclusion: Our study provided a mechanism that ZNF377 trapping EGFR in lipid rafts and forced it to ubiquitination endocytosis degrade by affecting lipid metabolism. This may provide an insight for solving EGFR resistance in breast cancer.

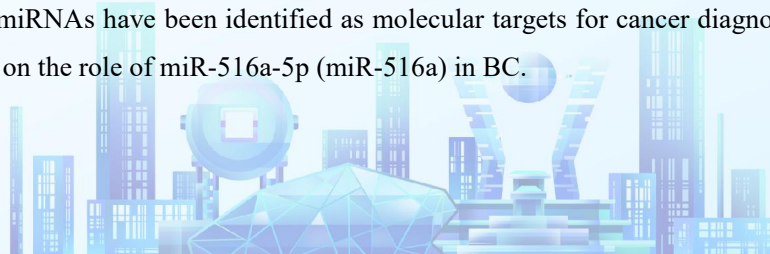
Key words: palmitoyltransferase; EGFR; lipid metabolism

142. MiRNA-516a promotes bladder cancer metastasis by inhibiting MMP9 protein degradation via the AKT/FOXO3A/SMURF1 axis

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Background: Metastasis is the leading cause of death in patients with bladder cancer (BC). However, current available treatments exert little effects on metastatic BC. Moreover, traditional grading and staging have only a limited ability to identify metastatic BC. Accumulating evidence indicates that the aberrant expression of microRNA is intimately associated with tumor progression. So far, many miRNAs have been identified as molecular targets for cancer diagnosis and therapy. This study focused on the role of miR-516a-5p (miR-516a) in BC.



Methods: MiR-516a expression and its downstream signaling pathway were detected using molecular cell biology and biochemistry approaches and techniques. Fresh clinical BC tissue was used to study the clinicopathological characteristics of patients with different miR-516a expression. The biological functions of miR-516a in BC were tested both in vivo and in vitro.

Results: A more invasive BC phenotype was significantly and positively correlated with miR-516a overexpression in BC patients. MiR-516a inhibition significantly decreased BC cell invasion and migration in vitro and in vivo. Furthermore, miR-516a attenuated the expression of PH domain leucine-rich repeat-containing protein phosphatase 2 protein and inhibited SMAD-specific E3 ubiquitin protein ligase 1 transcription by activating the AKT/Forkhead box O3 signaling pathway, which stabilized MMP9 and slowed down its proteasomal degradation, ultimately promoting BC motility and invasiveness.

Conclusions: Our findings reveal the crucial function of miR-516a in promoting BC metastasis, and elucidate the molecular mechanism involved, suggesting that miR-516a may be a promising novel diagnostic and therapeutic target for BC.

Key words: bladder cancer; metastasis; migration and invasion; miR-516a; PHLPP2

143. Zinc Finger Protein 638 Facilitates Aggressive Hepatocellular Carcinoma via motivating canonical MAPK signaling and EMT

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Objectives: Hepatocellular Carcinoma (HCC) is a highly aggressive malignancy causing mass of deaths worldwide with poorly defined molecular mechanisms. Zinc Finger Protein 638 (ZNF638), a member of RNA-binding proteins (RBPs) family, is an essential factor for adipocytes differentiation. However, the specific role of ZNF638 in hepatic tumorigenesis remains poorly understood.

Methods: Real-time PCR screening was performed to determine potential oncogenic RBPs in HCC patients. Among the detected 20 members from three RBP sub-families, ZNF638 was the most significantly up-regulated one both in HCC tissues and cell lines.

Results: The aberrant expression of ZNF638 and its causative effects on worse prognosis of HCC patients were validated through TCGA database, and further confirmed by immunohistochemistry using a panel of HCC tissues. Moreover, we also identified the correlation between ZNF638 expression and tumor differentiation, microvascular invasion and TNM stage. Functional analyzing by genetic silence of ZNF638 in HCC cell lines demonstrated its crucial roles for cell growth, colony or sphere formation,



migration and apoptosis suppression, probably via maintaining oncogenic signaling like MAPK and EMT. Furthermore, ZNF638 was also required for xenografts growth in vivo.

Conclusions: The current study uncovered ZNF638 as a novel oncogene during the pathogenesis of HCC, implying its potentiality as both biomarker and therapeutic target for HCC managements.

Key words: Hepatocellular Carcinoma; ZNF638; RNA-binding proteins; EMT; MAPK signaling

144. 基于 DIA 的蛋白组学技术研究皮肤鳞状细胞癌的发病机制

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目的: 从分子水平研究皮肤鳞状细胞癌 (CSCC) 血清蛋白组学的变化, 为该病的发生、发展机制研究及分子靶向药物的研发提供理论依据。

方法: 基于高分辨质谱的全扫描数据非依赖采集 (Data Independent Acquisition, DIA) 定量蛋白质组学技术, 比较 CSCC 患者与正常人血清中蛋白种类和浓度的差异。而后根据这些差异蛋白进行生物信息分析: GO 功能及富集分析, Pathway 代谢通路富集和蛋白-蛋白相互作用网络 (PPI) 分析。

结果: 在待测血清样品中共检测到 411 个蛋白。通过对比 6 个 CSCC 和 6 个正常人血清样品的蛋白图谱特征, 发现共有 28 个蛋白具有显著性差异。GO 富集分析结果表明 biological process (BP), cellular component (CC) 和 molecular function (MF) 三个本体中分别有 533 个、62 个和 57 个显著性差异的条目 (GO terms)。KEGG pathway 分析提示这些差异蛋白显著地富集在 pantothenate and coA biosynthesis, MAPK signaling pathway, propanoate metabolism, pyruvate metabolism 和 cysteine and methionine metabolism 五条代谢通路上。进一步的 PPI 分析表明 10 条代谢通路和 8 个蛋白相互关联, 具体包括癌症相关的代谢途径 glycolysis/gluconeogenesis, MAPK signaling pathway 等, 以及与癌症发生密切关联的蛋白 CTSB, LDHB 等。

结论: 一些潜在的生物标志物可能用于早期诊断 CSCC, 同时 MAPK 信号通路在该病的发生发展过程中具有十分重要的作用。

关键词: DIA; 蛋白组学; CSCC; MAPK

145. Helicobacter pylori related gastric cancer screening and cost-effectiveness analysis: A hospital-based cross-sectional study (SIGES)

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Objectives: To evaluate the effectiveness of *Helicobacter pylori* (Hp) related gastric cancer screening (Hp-GCS) and cost-effectiveness of protocol candidates in a hospital-based cross-sectional study.

Methods: A total of 163 gastric cancer patients in West China Hospital were retrospectively collected according to ICD-10 code and histologic proof between 2013.4 and 2014.3, and 15,599 cancer-free controls were simultaneously collected from the health check-up registry. Hp infection was examined by urea breath test (UBT). The prevalence of Hp infection was compared between patients and controls. The diagnostic performance of UBT-based predictive index was tested in both training and validation settings. Cost-effectiveness analysis was conducted to assess candidates of Hp-GCS protocols.

Results: The prevalence of Hp infection was 55.8% and 41.2% in gastric cancers and controls, respectively ($p < 0.001$). UBT-based model showed moderate diagnostic strength in Hp-GCS (AUC=0.78, 95% CI 0.74–0.82), better than UBT alone ($p < 0.001$). The sensitivity and specificity of UBT-based index were 80.2% and 61.9% at optimal cutoff in training setting, comparable in validation setting. Number needed to screen was decreased along with older age, as well as stronger positivity of UBT. The optimal cost-effective Hp-GCS protocol with detection rate (DR=77.9%) was endoscopic screening in age 40-59 years and positive UBT, or age ≥ 60 years without UBT. Incremental analysis suggested preferable protocol as endoscopic screening in age ≥ 40 years without UBT (DR=93.3%).

Conclusions: UBT had moderate diagnostic strength in massive gastric cancer screening, and might be cost-effective in middle-aged population (40-59 years). More robust Hp-GCS protocol need further investigate in test methods and individual biologic features.

Key words: *Helicobacter pylori*; urea breath test; gastric cancer; massive screening; cost-effectiveness

146. Nucleolin Malonylation promotes cell proliferation in Hepatocarcinoma cells through hyperactivation of Akt

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Objective: Liver cancer is one of the most common malignant tumors in the world. Metabolic syndrome and obesity together magnify the risk of liver cancer and have become one of the main causes of hepatocarcinoma (HCC). Therefore, it is particularly important to understand the pathological outcomes of the aberrant accumulation of lipid metabolites in liver cancer. Of note, recent studies have characterized malonylation as a novel lysine-specific acylation, which employs malonyl-CoA as the precursor of modifications. In this study, we aim to define the nuclear targets of protein malonylation, and to elucidate the function of malonylation in HCC development.



Methods: Five pairs of normal and cancer tissue specimens from liver cancer patients were collected for lipidomic analysis. The malonylation level of HCC was detected by western blotting and immunohistochemistry. Next, the nuclear fractions of HepG2 cells were applied for Mass spectrometry to identify the targets of malonylation, which was then validated through immunoprecipitation and a malonyl moiety-specific chemical probe. Finally, the function of nucleolin malonylation was investigated in liver cancer cells through the evaluation of cell growth.

Results: We found that the malonylation level in liver cancer tissues was significantly lower than that in normal tissues. Mass spectrometry analysis identified the nucleoprotein NCL as one of the malonylation targets. NCL malonylation significantly promotes HCC growth in vitro. Mechanistic studies demonstrated that the malonylation causes NCL translocation from the nucleolus to nucleoplasm, and promotes Akt expression by facilitating Akt translation.

Conclusion: Malonyl-CoA as well as the global malonylation level in liver cancer tissues is significantly lower than that in normal tissues. Nonetheless, NCL is malonylated and NCL malonylation promotes cell proliferation of liver cancer cells by enhancing Akt translation.

Key words: malonyl-CoA; malonylation; NCL; cell proliferation; Akt; liver cancer

147. Tert-butylhydroquinone attenuates ferroptosis against 5-fluorouracil-induced intestinal mucositis via Nrf2/HO-1 pathway

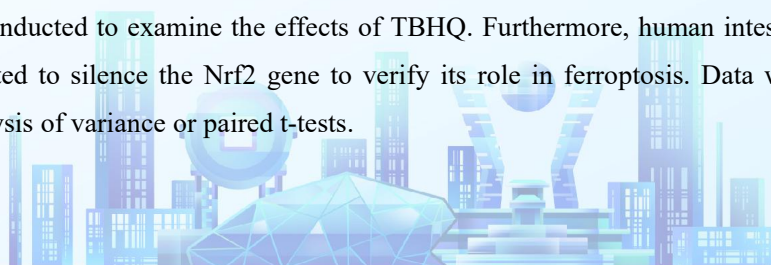
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Background: Intestinal mucositis is a common side effect of chemotherapy and radiotherapy. Nevertheless, there are limited drugs that can efficiently ameliorate it. Tert-butylhydroquinone (TBHQ) is a widely used food preservative with known immunomodulatory activity. However, whether TBHQ has an effect on intestinal mucositis remains unknown. In this study, we investigated the role and mechanism of action of TBHQ on 5-fluorouracil (5-FU)-induced human intestinal epithelial cell (HIEC) injury and intestinal mucositis in mice.

Methods: We established a model of HIEC injury and a mouse model of intestinal mucositis by treating with 5-FU. Samples of in vitro and in vivo models were subjected to cell death assay, Cell Counting Kit-8 assay, and lactate dehydrogenase release assay. Glutathione, reactive oxygen species, and malondialdehyde levels were determined. Additionally, immunohistochemical analysis, immunofluorescence, western blot, quantitative real-time PCR, and enzyme-linked immunosorbent assay were conducted to examine the effects of TBHQ. Furthermore, human intestinal epithelial cells were transfected to silence the Nrf2 gene to verify its role in ferroptosis. Data were analyzed using one-way analysis of variance or paired t-tests.



Results: TBHQ markedly ameliorated 5-FU-induced HIEC damage in vitro and intestinal mucositis in vivo. Moreover, ferroptosis was shown to be involved in 5-FU-induced intestinal mucositis, and TBHQ markedly hampered the activation of ferroptosis. Mechanistically, TBHQ effectively activated the Nrf2/HO-1 pathway in vitro and in vivo, and selective knockdown of Nrf2 significantly abolished the anti-ferroptotic functions of TBHQ in 5-FU-treated HIECs.

Key words: Tert-butylhydroquinone; intestinal mucositis; ferroptosis; 5-fluorouracil

148. Autophagy induced by micheliolide alleviates acute irradiation-induced intestinal injury via inhibition of the NLRP3 inflammasome

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Radiation-induced enteropathy (RIE) is one of the most common and fatal complications of abdominal radiotherapy, with no effective interventions available. Pyroptosis, a form of proinflammatory regulated cell death, was recently found to play a vital role in radiation-induced inflammation and may represent a novel therapeutic target for RIE. To address this, we screened a high throughput pyroptosis drug library with 441 compounds and found that MCL exerted anti-radiation effects in vitro. Therefore, we postulated that MCL may play a promising role in the treatment of RIE and investigated the therapeutic effects of MCL in RIE and evaluated the possible mechanisms by which it may be therapeutic. We developed a mouse model of RIE by exposing C57BL/6J mice to abdominal irradiation. MCL treatment significantly ameliorated radiation-induced intestinal tissue damage, inflammatory cell infiltration, and pro-inflammatory cytokine release. Moreover, MCL markedly inhibited radiation-induced activation of the nucleotide binding domain leucine-rich repeat-containing receptor - pyrin domain containing 3 (NLRP3) and suppressed pyroptosis in vivo and in vivo. Furthermore, we observed that MCL treatment induced autophagy, which inhibited activation of the NLRP3 inflammasome and prevented caspase-1-dependent interleukin (IL)-1 β and IL-18 secretion. In agreement with these observations, the beneficial effects of MCL treatment in RIE were abolished in *Becn1*^{+/-} mice. Furthermore, super-resolution microscopy revealed a close association between NLRP3 and lysosome-associated membrane protein/ light chain 3-positive vesicles following MCL treatment, suggesting that MCL facilitates phagocytosis of the NLRP3 inflammasome. These data support the notion that MCL-mediated induction of autophagy can ameliorate RIE by NLRP3 inflammasome degradation and identify MCL as a novel therapy for RIE.

Key words: Autophagy; micheliolide; NLRP3 inflammasome; Radiation-induced enteropathy



149. Sorafenib-induced autophagy promotes glycolysis by upregulating p62/HDAC6/HSP90 axis in hepatocellular carcinoma cells

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Aims: Sorafenib has attracted much attention as the first drug approved by the FDA for the treatment of advanced hepatocellular carcinoma (HCC). Because of the drug tolerance, the overall outcomes were far from satisfactory. Increasing evidence indicated sorafenib induced autophagy and glycolysis may be contributed to HCC cell survival. In this study, we explored the role of autophagy adaptor p62 in regulating key enzyme of glycolysis, which provided potential targets to increase the sorafenib sensitivity of HCC cells.

Main methods: Immunohistochemistry (IHC) staining was used to detect the expression of autophagy protein p62 and LC3B protein of HCC patients. The relationship between protein expression and prognosis was analysed. The MTT assay was used to detect the cell viability of HCC cells with sorafenib treatment. AnnexinV/PI and Hoechst staining were used to detect apoptosis. We observed the autophagosome by electron microscopy. Glycolysis of HCC was determined through evaluating glucose uptake and lactic acid production. And the OXPHOS was detected by ATP production and OCR probe. PKM2 and HDAC6 enzyme activity was detected by Elisa. The protein co-localization was determined by immunofluorescence and immunoprecipitation.

Key findings: Disturbing autophagy was effective to improve HCC cells sensitivity to sorafenib. We found sorafenib-induced autophagy promoted the deacetylase activity of HDAC6 by degrading the autophagy adaptor p62. Activated HDAC6 enhanced the activity of glycolytic enzyme PKM2 by regulating the acetylation of its critical substrate HSP90, which functioned as the molecular chaperone for protein folding and maturation. p62/HDAC6/HSP90 axis may become promising targets for increasing sensitivity of HCC cells to sorafenib treatment.

Significance: This study further elucidated the possible mechanism of the sorafenib resistance in HCC. We suggested p62/HDAC6/HSP90 axis may play pivotal role in the crosstalk between autophagy and glycolysis with sorafenib treatment, which function as potential therapeutic targets for increasing the sorafenib sensitivity of HCC.

Key words: Autophagy; Glycolysis; p62; HDAC6; HSP90; PKM2



150. miR-338-3p 调控肺癌生长和转移的作用及在宣威肺癌患者血浆中的表达研究

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目的: 课题组前期研究发现 miR-338-3p 在宣威非小细胞肺癌组织中表达显著下调并在人群中做了初步验证, 本研究聚焦 miR-338-3p 影响 A549 细胞和宣威肺癌细胞增殖、凋亡以及迁移侵袭的能力, 探究 miR-338-3p 过表达调控肺癌细胞生长和转移的作用。检测宣威地区非小细胞肺癌患者以及非肿瘤患者血浆标本中 miR-338-3p 的表达情况, 探索 miR-338-3p 作为非小细胞肺癌早期诊断指标的可能性。

方法: 将 miR-338-3p mimics 转染到 A549 细胞和宣威肺癌细胞中, 创建 miR-338-3p 过表达的细胞模型。MTT 检测肺癌细胞的活力; PI 实验检测肺癌细胞的细胞周期; AnnexinV/PI 实验肺癌细胞发生凋亡的情况; Transwell 实验检测肺癌细胞的迁移能力。收集宣威非小细胞肺癌患者血浆标本 30 例, 非肿瘤患者血浆标本 20 例, RT-qPCR 对标本中 miR-338-3p 的相对表达量进行测定, F 检验分析外周血中 miR-338-3p 的表达差异。收集患者的相关临床资料, Mann Whitney 检验分析 miR-338-3p 表达量与相关临床资料的相关性。

结果: miR-338-3p mimics 转染两种肺癌细胞后, 细胞的活力都明显下降, A549 细胞的活力下降为 77.79%, 宣威肺癌细胞下降为 69.24%。A549 细胞周期阻滞在 S 期, 而宣威肺癌细胞周期阻滞在 G2/M 期。都明显诱导了细胞凋亡的发生, A549 细胞早期凋亡细胞的比例是 6.52%, 宣威肺癌细胞早期凋亡细胞的比例是 2.66% ($P < 0.001$)。miR-338-3p 过表达对肺癌细胞迁移有明显的抑制作用, 都可以明显抑制肺癌细胞的迁移能力 ($P < 0.001$ 与 $P < 0.01$)。肺癌患者组血浆标本中 miR-338-3p 的表达量显著降低, 而且 miR-338-3p 的表达量与肺癌分期显著相关, 与 I/II 期肺癌组相比, III/IV 期肺癌组 miR-338-3p 表达量显著降低 ($P < 0.05$)。miR-338-3p 表达量与淋巴结转移显著相关, 淋巴结转移组 miR-338-3p 表达量显著低于无淋巴结转移组 ($P < 0.05$), 但与年龄、性别以及是否吸烟无关。

结论: 1, miR-338-3p 过表达能不同程度的抑制 A549 肺癌细胞与宣威肺癌细胞的增殖、迁移, 且都能促进两种肺癌细胞的凋亡。但也导致 A549 肺癌细胞周期停滞在细胞周期的 S 期, 而宣威肺癌细胞周期停滞在细胞周期的 G2/M 期。2, 相对于非肿瘤患者, 宣威非小细胞肺癌患者血浆中 miR-338-3p 的表达量显著降低, 且相对表达水平与肿瘤分期、是否有淋巴结转移显著相关。

关键词: 非小细胞肺癌; miR-338-3p; 细胞增殖; 迁移; 凋亡



151. 外泌体在肿瘤临床运用中的研究进展

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摘要: 细胞外外泌体 (exosome) 是多种活细胞主动向胞外分泌的囊泡样小体, 富含多种生物活性物质, 主要由蛋白质、核苷酸和脂类等组成, 几乎能被哺乳动物所有细胞分泌, 广泛分布于外周血、尿液、唾液、腹水、羊水多种体液中, 包括等体液, 调控的生理过程包括生殖和器官发育、抗原呈递和免疫反应、神经元通信、控制衰老和细胞增殖等。在肿瘤的发生、发展过程中, 肿瘤细胞分泌的外泌体可以改变肿瘤本身及其微环境, 并且参与到肿瘤转移的过程, 对肿瘤外泌体的分析和检测可以辅助肿瘤的早期诊断、疗效评价和预后分析, 作为非侵袭性血清肿瘤生物标志物用于肿瘤的诊断和预后提供新的思路, 外泌体及其修饰加工产物还可以作为基因或药物的有效载体, 用于肿瘤治疗, 有望成为潜在的转移预测标志物及治疗靶标。肿瘤来源外泌体对肿瘤具有抑制或促进的双重作用, 这是外泌体、细胞和环境因素之间复杂相互作用的结果, 与肿瘤进展程度和机体免疫状态密切相关。基于外泌体建立明确的肿瘤诊断方法, 辅助肿瘤早期检测和诊断, 帮助判断预后和治疗效果, 并开发新的抗肿瘤药物和临床肿瘤干预措施。

关键词: 外泌体; 肿瘤; 生物标志物; microRNA;

152. miRNA-338-3P 检测在肿瘤临床运用中的研究进展

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摘要: 微小 RNA (microRNA) 是一种广泛存在于动植物体内的短链非编码 RNA, 影响许多蛋白编码基因的表达, 通过与靶 mRNA 特异结合可以抑制靶 mRNA 翻译或降解 mRNA, miRNA 是多细胞生物中一类丰富的基因调控分子, 影响许多蛋白编码基因的表达, 参与调控许多基本的细胞行为如细胞分化、增殖、生长、迁移、凋亡, 以及致癌作用或促进癌症发生。随着近年来肿瘤发病率的日益增高, miRNA 与肿瘤的关系成为研究热点, 其可作为肿瘤诊断、治疗及预后的标志物。多项研究发现, miR-338-3p 在多种肿瘤组织及细胞株中表达量显著降低, miR-338-3p 可抑制肿瘤基因, 通过调控肿瘤基因以及相关信号通路等影响肿瘤的进展、侵袭及预后, 有望成为肿瘤早期诊断的指标, 并且有可能成为新的治疗靶点。

关键词: miR-338-3p; 肿瘤; 生物标志物; microRNA;



153. 局部肿瘤为 T1a2-T2a1 FIGO IIIC1r 期宫颈癌患者分层管理模式探索

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目的: 探索局部肿瘤为 T1a2-T2a1 FIGO IIIC1r 期宫颈癌患者分层管理模式, 为其临床治疗决策提供参考。

方法: 回顾性收集 2013 年 1 月至 2018 年 12 月江西省妇幼保健院初治的 85 例 T 分期为 T1a2~T2a1 (除外 T1b2 期) 的 FIGO IIIC1r 期 {经 MRI 和 (或) CT 诊断} 宫颈癌患者, 单因素分析临床病理因素对其预后的影响; 按已接受治疗方案分为手术组和同步放化疗组, 并基于局部肿瘤 T 分期和肿瘤直径进行分层, 对比两组的预后, 放化疗副反应与费用。将 FIGO IIIC1r 期宫颈癌手术组患者按术后病理是否有盆腔淋巴结转移分为 A 组 (26 例无转移) 和 B 组 (30 例有转移), 选择术前影像学无盆腔淋巴结转移的宫颈癌手术患者, 按术后病理是否有盆腔淋巴结转移分为 A 组对照组 (742 例无转移) 和 B 组对照组 (94 例有转移), 比较互为对照的两组及 A 组和 B 组的预后和治疗费用。

结果: ①基线资料比较: 手术组年龄 < 50 岁和局部肿瘤为 T1b1 期的患者比例高于同步放化疗组。②单因素分析: 年龄, 病理类型, 局部肿瘤 T 分期, 肿瘤直径, 影像学盆腔淋巴结转移个数及大小, 治疗方式与 FIGO IIIC1r 期宫颈癌患者的预后无关。③两种治疗方案比较: 分层分析显示两组患者的 3 年 DFS 和 OS 差异均无统计学意义; 手术组 III-IV 级骨髓抑制反应发生率和治疗费用均高于同步放化疗组 ($P < 0.05$)。④手术组间比较: 互为对照的两组患者 3 年 DFS 和 OS 及治疗费用相当; A 组患者 3 年 DFS 高于 B 组, 但治疗费用低于 B 组 ($P < 0.05$)。

结论: 手术组治疗费用和 III-IV 级骨髓抑制发生率高于同步放化疗, 但两者疗效相当; 手术并不影响 FIGO IIIC1r 期宫颈癌患者的预后, 但对于明确盆腔淋巴结状况, 指导后续治疗和避免过度治疗有重要意义; FIGO IIIC1p 期宫颈癌患者, 尽管期别较晚, DFS 低于早期宫颈癌患者, 规范治疗后仍可达到与其相似的 OS。

关键词: IIIC1r 期宫颈癌; TNM 分期; 手术; 放化疗; 分层管理模式

154. TTK1 is related to cisplatin-resistance in ovarian cancer cell line by activating PI3K/AKT signaling pathway

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Cisplatin is a platinum compound widely used in various solid tumors including ovarian cancer. Drug resistance and recurrence are main contributors to the poor prognosis of ovarian cancer.

However, the mechanism of cisplatin resistance in ovarian cancer is not clear. TTK1 (threonine and tyrosine kinase 1), an integral part of the spindle assembly checkpoint, may be a potential new target associated with chemotherapy sensitivity. This study is aimed to explore the relationship between TTK1 and cisplatin-resistance in ovarian cancer cell line. We found that down-regulation of TTK1 could recover the sensitivity of cisplatin-resistant ovarian cancer cells to cisplatin treatment. The signaling pathways activated by TTK1 were further analyzed by RNA-seq and verified by Western blot. It showed that TTK1 was involved in cisplatin-resistance by activating PI3K/AKT pathway. TTK1 in ovarian cancer patients, especially when the patients acquired resistance to cisplatin, was significantly overexpressed, suggesting that TTK1 may be a promising treatment target for cisplatin-resistant ovarian cancer.

关键词: TTK1; cisplatin resistance; ovarian cancer; PI3K; AKT

155. CALD1 Is a Prognostic Biomarker and Correlated with Immune Infiltrates in Gastric Cancers

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Background: Caldesmon gene (CALD1) plays an important role in many cellular functions. Some researchers have found the correlation between CALD1 expression and prognosis of gastrointestinal cancer (GI), but the association with tumor-infiltrating lymphocytes (TILs) still unclear.

Methods: The expression of CALD1 in different human tumor was analyzed by Oncomine and Tumor Immune Estimation Resource (TIMER) databases. The correlations between CALD1 and prognosis in types cancer were explored by Kaplan–Meier plotter and Gene Expression Profiling Interactive Analysis (GEPIA) databases. The association between CALD1 expression and tumor immune cell infiltration was further analyzed via TIMER and GEPIA databases.

Results: The CALD1 expressions in types cancer between tumor tissues and adjacent normal tissues were significantly different. The high expression of CALD1 was related with poor overall survival (OS) of patients with gastric cancer, especially in gastric cancer patients at N1, N2 and N3 stages. The expression of CALD1 was positively associated with immune-infiltrated, such as CD8+T cells, CD4+T cells, macrophages, neutrophils, and dendritic cells (DCs) in gastric cancer.

Conclusions: CALD1 was considerably a key role in prognosis of patients with gastric cancer. The expression level of CALD1 is significantly associated with immune-infiltrated in gastric cancer. Furthermore, CALD1 expression may be involved in regulating tumor-associated macrophages (TAMs), dendritic cells, exhausted T cells and regulatory T cells in gastric cancer. These findings



suggest that CALD1 could be utilized as a marker of prognosis and immune infiltration in gastric cancer.

Key words: CALD1; immune infiltration; gastric cancer; microenvironment

156. 肿瘤免疫微环境特征的性别差异分析

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研究目的: 性别被认为是影响癌症发生、进展、治疗反应和预后的关键变量,然而与癌症免疫治疗相关的肿瘤微环境(TME)特征的性别差异仍不清楚。TME 中除了癌细胞外,还含有许多不同的非癌细胞类型,如成纤维细胞、浸润性免疫细胞等,它们在癌症的进展、转移和免疫治疗效果中起着重要作用。此外,肿瘤突变负荷(TMB)被发现在多种癌症中与 TME 显著相关。因此,亟需进行一项全面的分析,以检查多种癌症类型中存在的性别差异的 TME 及其相关特征,为癌症免疫治疗提供有益的借鉴。

材料与方法: 本研究从 GDC TCGA 数据平台 (<https://portal.gdc.cancer.gov/>) 获取了除性别特异性癌症(如卵巢癌、乳腺癌、前列腺癌等)以外的癌症患者数据,包括分子组学数据和临床特征。我们保留了每种癌症类型的原发癌症样本,并且在分析中排除了年龄小于 18 岁以及年龄大于 85 岁或缺乏性别信息的样本,获得 19 种癌症类型,包括 2908 个癌症样的数据(男性 1771,女性 1137)。根据 TME 细胞的特征基因,我们使用 ESTIMAT 方法推断肿瘤样本的基质评分和免疫评分以及肿瘤纯度,并利用单样本富集分析方法(ssGSEA)计算 TME 细胞的免疫浸润丰度。我们通过使用 Wilcoxon 秩和检验(WRS)比较男女患者在 TMB、基质评分、免疫评分、肿瘤纯度在泛癌和单个癌症中的差异;并利用学生 T-test 检测 TME 细胞浸润丰度以及免疫检测点基因表达的性别差异;同时,使用 GSEA 方法检测免疫功能通路的性别差异;最后,利用 Fisher transformation 方法检测 TMB 与 TME 细胞浸润丰度在男性和女性患者中的关联差异。

结果: 结果显示在泛癌中男性患者具有更高的肿瘤突变负担(TMB)和肿瘤纯度,但免疫评分和基质评分低于女性患者。TMB 与肿瘤纯度、免疫评分及基质评分的相关性也显示出显著的性别差异。我们同时检测了 TME 细胞、免疫检查点基因和免疫功能通路在每种癌症中的性别差异,并揭示了肺腺癌、肺鳞癌、肾乳头状癌和头颈部鳞癌具有明显的性别差异。我们进一步确定了基于免疫细胞的男性和女性患者特异性的预后生物标志物,并在两个独立的数据集中验证了我们的结果。通过以上分析,我们最终将癌症类型分为“弱免疫性别差异组”和“强免疫性别差异组”,其中强免疫性别差异组包括肺腺癌、肺鳞癌、头颈鳞癌、肾乳头状癌、胃癌和恶性胶质瘤,每一种癌症都显示出广泛的性别差异的免疫相关特征。

结论: 本研究在不同癌症中综合分析了 TME 相关特征的性别差异性,揭示了性别可能影响的肿瘤微环境相关特征。因此,在癌症的免疫治疗中应考虑性别因素,从而实现更精准的治疗。



关键词： 性别差异；肿瘤微环境；肿瘤突变负荷；免疫得分

157. 尿液作为肿瘤标志物的潜力

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疾病的早期诊断是医学最重要的问题。早期诊断可以给医生有效治疗的机会。尿液不像血液那样受身体稳态效应的控制，能够汇集大量的疾病相关变化，因此尿液能够更好地反映早期微小的变化，是生物标志物的更好体液来源。本报告将综合现有的研究结果突出展示尿液作为未来肿瘤早期标志物的潜力。也将介绍未来临床应用的思路和初步进展。我们提出，如果能利用同一个人的前后对照，可以解决大量混杂影响因素的对照问题，让尿液标志物更早地用于临床。这个报告还将讨论如何从临床的角度分析当今诊断困难的病例，为医生提供线索。这个应用模式，符合个体化精准医学的未来前景。

关键词： 尿液；蛋白质组；早期；个体化；精准

158. GLI1 和 PD-L1 蛋白在鼻咽癌中表达及其意义

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目的：通过测定鼻咽癌（Nasopharyngeal carcinoma, NPC）组织中 Hedgehog（HH）信号通路转录因子 GLI1 和免疫检测点负调控因子（programmed death-ligand 1, PD-L1）蛋白的表达，分析上述分子表达的关系，并探讨该蛋白表达的临床病理意义，为鼻咽癌的治疗提供新思路。

方法：收集于 2015.1~2019.2 在广西壮族自治区南溪山医院住院治疗,经病理确诊为鼻咽癌的 100 例患者鼻咽活检组织标本（存档石蜡包埋组织块）为研究对象。另，选取同期在该院就诊,并经病理确诊为鼻咽慢性黏膜炎的 20 例患者鼻咽活检组织标本(存档石蜡包埋组织块)为对照组。采用免疫组织化学（immunohistochemistry, IHC)技术检测 PD-L1 和 GLI1 在鼻咽癌及鼻咽慢性黏膜炎组织中的表达，基于免疫反应评分体系（Immune-Response-Scoring, IRS）评估这些蛋白的表达水平。应用 SPSS18.0 软件将有关数据进行分析，计量资料以 $\bar{x} \pm s$ 表示，采用配对 t 检验；计数资料差异比较应用 χ^2 检验；应用 Spearman 等级相关分析两蛋白表达水平的关系。以 $\alpha=0.05$ (双侧)为检验水准， $P<0.05$ 表明差异具有统计学意义。

结果：1.PD-L1 蛋白表达主要定位在胞膜。在 100 例鼻咽癌组织中 PD-L1 呈不同程度表达，其中低表达 47 例(47/100)，高表达 53 例(53/100)；20 例鼻咽慢性黏膜炎组织中,其中 PD-L1 低表达 19 例(19/20)，高表达 1 例(1/20)。上述两组组织标本中，PD-L1 蛋白的表达差异具有统计学意义（ χ^2 为 15.52, $P<0.001$ ）。PD-L1 在鼻咽癌组织中表达与患者性别,年龄,肿瘤分期及淋巴结转移

或远处转移等无统计学意义($P>0.05$)。2.GLI1 蛋白表达主要定位在胞核。GLI1 蛋白在 100 例癌组织中呈不同程度表达,其中低表达 38 例(38/100),高表达 62 例(38/100)。20 例鼻咽慢性黏膜炎组织中,其中 GLI1 低表达 19 例(19/20),高表达 1 例(1/20)。上述两组标本中 GLI1 蛋白表达的差异具有统计学意义(χ^2 值为 21.71, $P<0.05$),但其表达与患者性别、年龄、肿瘤分期及是否存在淋巴结转移或远处转移等均无统计学意义($P>0.05$)。3.经 Spearman 检验, GLI1 和 PD-L1 蛋白在鼻咽癌的表达具有显著正相关性($r=0.06$, $P<0.05$)。

结论: 1.鼻咽癌组织中 PD-L1 和 GLI1 蛋白表达水平升高而且呈显著正相关关系,PD-L1 表达上调可能与 GLI1 转录因子的调控有关。2.联合抑制 PD-1/PD-L1 免疫检测点和 HH/GLI1 信号通路可能是治疗难治性鼻咽癌的新希望。

关键词: 鼻咽癌; PD-L1; GLI1; 免疫组织化学

159. MTA1 调控肿瘤干细胞促进小细胞肺癌转移

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研究目的: 小细胞肺癌 (Small Cell Lung Cancer, SCLC) 占肺癌总数的 10%-15%, 由于其高转移的特点, 且治疗耐药高发, 造成疾病迅速进展, 总体 5 年生存率不足 6%。因此, 高转移和易耐药性是预后不良的直接因素。然而, 解决 SCLC 临床治疗难题的瓶颈在于其发生转移的机制不清, 干预靶点不明。因此, 亟需从更深层次和角度揭示 SCLC 发生、发展的分子机制, 以为 SCLC 治疗提供新的策略。MTA1 (metastasis-associated gene 1) 是一个转移相关蛋白家族基因, 在绝大部分肿瘤中呈高表达状态, 并可促进肿瘤的发生和发展, 导致不良的预后。而 SCLC 是具有高度肿瘤干细胞特征的肺癌亚型, 这种特性是导致 SCLC 转移和治疗耐药的重要根源。通过探讨 MTA1 与 SCLC 肿瘤细胞干性相关性, 明确 MTA1 调控 SCLC 转移的机制。

材料与方法: 通过结合分析 TCGA 和 GEO 数据库现有信息, 通过肺癌组合芯片 (SCLC, LUSC, LUAD), 肺癌细胞系 (NCI-H446, NCI-A549, H1650), 利用免疫组化, 免疫荧光, western-blot, RT-PCR, CO-IP, 干细胞分选培育等技术, 分析 MTA1 与 SCLC 转移的相关性。

结果: 1.MTA1 在肺癌中表达异常增高, 小细胞肺癌最为突出。通过 TCGA 和 GEO 数据表明 MTA1 在肺癌组织较癌旁显著增高 ($P<0.05$), 并且肺癌组织芯片结果同数据库结果一致; 2, 肺癌高表达 MTA1 与患者化疗后临床不良预后密切相关 ($P<0.05$), 13 例 SCLC 患者生存分析得到了与数据库一致的结果 ($P<0.05$); 3, 调控 MTA1 表达后, SCLC 细胞的侵袭转移能力显著改变。上调 SCLC 中 MTA1 表达后, 细胞间变的更疏松, 细胞也变成了更具有运动性的纤维样细胞形态; 下调 MTA1 表达后, 细胞间则变的更紧密, 细胞也变成了更具有粘附性的上皮样细胞形态。调控 MTA1 表达后 ZO1, ZEB1, N-cad, Slug 表达显著改变, 肿瘤细胞的迁移和侵袭

能力显著变化 ($P<0.001$)。4,MTA1 促进 SCLC 细胞干性。连续培养观察 SCLC 干细胞球 8 天, MTA1 过表达组较对照组肿瘤干细胞球变得更大,更圆,细胞结合更紧密,显著形成了更多的单细胞来源的肿瘤干细胞球 ($P=0.0045$)。5,肺癌中 MTA1 调控肿瘤细胞干性。TCGA 数据分析 SCLC 和 NSCLC, 结果表明 MTA1 表达显著增高, 并且 MTA1 同促进肿瘤细胞干细胞特性表达的相关基因相关性高 ($P<0.05$)。

结论: MTA1 可能通过增强 SCLC 肿瘤细胞干性进而促进了肿瘤细胞的转移。

关键词: 小细胞肺癌; 肿瘤转移相关蛋白 1; 肿瘤转移; 肿瘤细胞干性

160. Whole-genome ctDNA methylation landscape and signatures for early detection, therapy prediction, and subtyping of breast cancer

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Abstract: Breast cancer is a leading cause of cancer morbidity in women worldwide. The changes of circulating tumor DNA (ctDNA) methylation are believed to be early events in breast cancer initiation, which makes them suitable as promising biomarkers for early diagnosis. Here, we compared the DNA methylation data of breast cancer patients with normal control to screen candidate methylation CpG sites. Furthermore, potential biomarkers for molecular subtyping and relapse were found. We believe that the obtained breast cancer-specific methylation CpG site biomarkers may be used in early diagnosis, monitoring tumor progression, and molecular subtyping of breast cancer in the clinic.

Key words: breast cancer; early detection; biomarkers; circulating tumor DNA

161. Screening Novel TAAs based on Proteomic Chip and Evaluating the Performance of Them in the Diagnosis of Esophageal Squamous cell carcinoma

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Abstract:

Aim: Esophageal cancer (EC) is one of the common malignant tumors in the world, and its incidence and mortality are relatively high. Global cancer statistics released in 2020 showed that EC has a higher



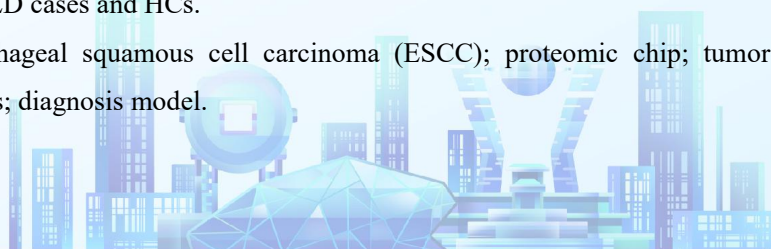
incidence in East Asia, especially in China, and males are significantly higher than females. The number of new cases of EC in China in 2020 was about 324,422, accounting for about 50% of the world; the number of deaths was 301,135, accounting for about 55% of the world. According to the clinical histopathological type, EC was mainly divided into esophageal adenocarcinoma (EAC) and esophageal squamous cell carcinoma (ESCC). Importantly, the incidence of ESCC in China accounts for more than 70% of the world. The onset of ESCC was insidious and there were no obvious clinical symptoms in the early stage. At present, the pathogenesis of ESCC was not clear, and there was lack of effective treatment measures for advanced ESCC patients. Therefore, finding a noninvasive diagnostic method for ESCC of early stage is crucial to improve the 5-year survival rate of patients. Recent years, many studies have found that autoantibodies against tumor-associated antigen (TAAs) can be used as biomarkers in the diagnosis of esophageal squamous cell carcinoma (ESCC). The aim of this study is to screen novel TAAs through proteomic chip and constructing a diagnostic model to discriminate ESCC cases from benign esophageal diseases (BED) cases and healthy controls (HCs).

Methods: HuProt™ human proteomic chip was purchased from BCBIO Biotechnology (Guangzhou, China). The chip is currently the world's largest collection of full-length human proteins available. It contains more than 21,000 recombinant proteins and covers all human recombinant proteins that can be purified, covering 81% of the human proteome. The human proteomic chip was used to screen TAAs. Enzyme-linked immunosorbent assay (ELISA) was used to verify and validate the candidate TAAs screened by the chip in cohort 1 (90 ESCC cases and 90 HCs) and cohort 2 (126 ESCC cases and 126 HCs). Based on the difference of the autoantibody titer between the cases and the controls, the candidate TAAs were further screened, and then the diagnostic model for ESCC was constructed by logistic regression model in the training cohort and validated in the testing cohort.

Results: Firstly, thirteen potential candidate TAAs were identified by proteomic chips, including MAGEA1, VCL, PPP1R15A, PDE4DIP, PRKCZ, TP53, SMARCC1, BASP1, SMARCE1, GABPA, ANKHD1, NFKB1 and MAGEA4. In verification phase, the titer of six TAAs (anti-MAGEA1, anti-VCL, anti-PRKCZ, anti-TP53, anti-NFKB1 and anti-MAGEA4) in ESCC cases were higher than those in HCs while other seven TAAs showed no difference. Subsequently, six candidate TAAs were validated further in validation phase. The six TAAs also showed the trend of high expression in ESCC cases. Finally, the logistic regression model with 3 TAAs (anti-MAGEA1, anti-VCL, anti-TP53) could discriminate ESCC cases from HCs with area under curve (AUC) of 0.80 in the training cohort and 0.73 in the testing cohort, respectively. Meanwhile, the model could discriminate ESCC cases from BED cases with AUC of 0.74.

Conclusion: The study has identified six novel TAAs (anti-MAGEA1, anti-VCL, anti-PRKCZ, anti-TP53, anti-NFKB1 and anti-MAGEA4) through protein chips and constructed a diagnostic model. The panel consisting of anti-MAGEA1, anti-VCL and anti-TP53 showed great performance to distinguish ESCC cases from BED cases and HCs.

Key words: esophageal squamous cell carcinoma (ESCC); proteomic chip; tumor-associated antigen; autoantibodies; diagnosis model.



162. The Relationship of Elevated Preoperative Serum CA19-9 Levels and the Early Recurrence of Single Small Hepatocellular Carcinoma

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Background : Determining the risk factors for the recurrence of single small HCC (≤ 3 cm) may contribute to the implementation of additional treatment strategies in clinical practice.

Methods: A total of 276 patients with single small primary HCC (≤ 3 cm) who received initial treatment from September 2010 to September 2019 were retrospectively enrolled in the primary cohort through random resolution to establish a nomogram. The remaining 137 patients were used to verify the accuracy of the nomogram.

Results: The median RFS for the primary and the validation cohorts were 43.0 and 51.0 months, respectively. The multivariate analysis showed that age, hepatitis, preoperative CA19-9 level, and Child-Pugh score were independent risk factors for recurrence-free survival. On the basis of these four variables, the nomogram was developed. Patients with normal preoperative CA19-9 levels had better RFS than those with abnormal preoperative CA19-9 levels. Especially, among the AFP-negative patients, those with normal preoperative CA19-9 levels had better RFS than those with abnormal preoperative CA19-9 levels.

Conclusions: The preoperative CA19-9 level is an independent risk factor affecting the prognosis of patients with one small HCC, especially among the AFP-negative patients, and should be given full attention in clinical practice.

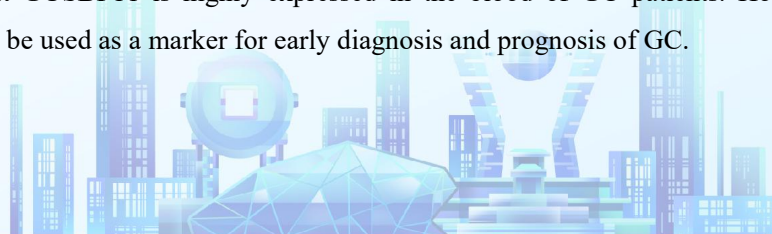
Key words: small hepatocellular carcinoma; early recurrence; nomogram; CA19-9

163. Diagnostic and prognostic value of circulating lncRNA GUSBP11 in gastric cancer

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Background: Gastric cancer (GC) is a common digestive tract tumor. GC progresses rapidly with a poor prognosis. Circulating long non-coding RNA (lncRNAs) has been reported as a marker for early diagnosis and screening in many cancers. The genome-wide lncRNA microarray assay results have confirmed that GUSBP11 is highly expressed in the blood of GC patients. However, it is unclear whether it can be used as a marker for early diagnosis and prognosis of GC.



Methods: We collected the peripheral blood of patients with GC (n = 227) and healthy donor individuals (n = 210) in Shaanxi Provincial People Hospital from June 2019 to October 2020. The serum GUSBP11 expression level was detected by quantitative real-time polymerase chain reaction (qRT-PCR). Receiver operating characteristic curve analysis was applied to assess the diagnostic value of serum GUSBP11 and 3 traditional biomarkers (carcinoembryonic antigen [CEA], cancer antigen 72-4 [CA72-4], and CA19-9) in GC.

Result: The results demonstrated that GUSBP11 expression level was significantly elevated in GC patients compared with that in healthy donor individuals ($P < 0.001$). Serum GUSBP11 could be used as a molecular marker for distinguishing GC patients from healthy people with an area under the curve of 0.768 (95% confidence interval=0.675-0.874; $P < 0.001$). Intriguingly, the ROC showed serum GUSBP11 was a better diagnostic potential compared to the traditional biomarkers (CEA, CA72-4, and CA19-9). Further analysis found that high serum GUSBP11 expression levels correlated with lymph node metastasis ($P = 0.022$), distant metastasis ($P = 0.018$), TNM stage ($P = 0.01$). The Kaplan-Meier analysis showed a correlation between increased serum GUSBP11 levels and poor overall survival (OS) (logrank $P < 0.001$). And univariate and multivariate COX analysis revealed serum GUSBP11 was an independent prognostic factor in GC patients ($P < 0.001$).

Conclusion: Serum GUSBP11 could serve as an ideal serum biomarker for GC diagnosis and for monitoring disease progression.

Key words: GUSBP11; Diagnostic biomarker; Gastric cancer; Circulating RNA; Long non-coding RNA.

164. Comparative Analysis and in vitro Experiments of Signatures and Prognostic Value of Immune Checkpoint Genes in Colorectal Cancer

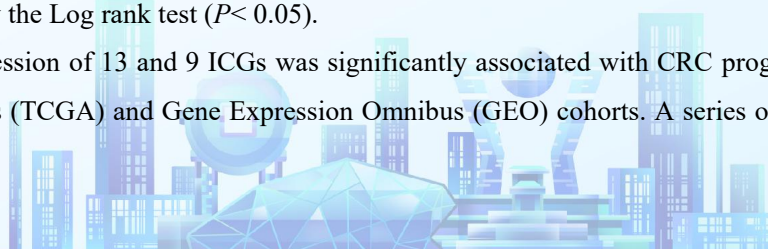
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The first affiliated hospital of China medical university

Purpose: Immune checkpoints, as pivotal regulators of immune escape in cancer, can motivate the emergence of immune checkpoint inhibitors (ICIs). The aim of this study is to identify the expression of the immune checkpoint genes (ICGs) in colorectal cancer (CRC) and to relate their individual as well as combined expression to prognosis and therapeutic effectiveness in CRC.

Methods: RNA expression of 47 ICGs and clinical information of CRC patients were collected from two public databases to elucidate the expression levels and prognostic values of these ICGs in CRC. Then, the Shapiro–Wilk normality test was used to determine the normality of variables. Overall survival (OS) rates of each subset were found by Kaplan–Meier method, and the statistical significance was determined by the Log rank test ($P < 0.05$).

Results: The expression of 13 and 9 ICGs was significantly associated with CRC prognosis in The Cancer Genome Atlas (TCGA) and Gene Expression Omnibus (GEO) cohorts. A series of ICGs was found to



be significantly associated with TMB, neoantigens and MMR in CRC indicating that the combination of immunotherapy treatment biomarkers and ICGs may achieve accurate prognostic stratification of CRC, and potentially identify CRC cases that might respond to checkpoint inhibitors (CPIs). The subsets of high or low PD1/PD-L1/IDO1 expression stratified by CD48 were accurately associated with prognosis in CRC. In addition, in vitro experiments confirmed that VTCN1(B7-H4)-KD increases anti- PD-L1-mediated NK cell cytotoxicity on CRC tumor cells.

Conclusion: Although the expression of a single immune-checkpoint molecule does not predict the efficacy of immunotherapy in CRC, our findings infer that subsets defined by ICGs are associated with prognosis and imply the possibility that VTCN1 and CD48 serve as new immunotherapeutic targets.

Key words: immune checkpoint genes; colorectal cancer; prognosis; immunotherapy

165. High-grade neuroepithelial tumor with BCOR exon 15 internal tandem duplication

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Aims: Central nervous system high-grade neuroepithelial tumor with BCOR alteration (CNS HGNET-BOCR) represents a distinct molecular entity. The genetic characteristic is the internal tandem duplication within exon 15 of the BCOR transcriptional co-repressor gene (BCOR-ITD), which has also been reported in clear cell sarcomas of the kidney (CCSK), primitive myxoid mesenchymal tumors of infancy (PMMTI), and undifferentiated round cell sarcomas (URCS).

Methods and results: The clinical, pathological, and molecular characteristics of four cases of HGNET-BOCR were presented in this study. Three cases occurred in infants (23 months to 4 years old) and one case was 13 years old teenager. The tumors were located in the cerebellum (two cases), frontal lobe (one case) and parietal lobe (one case). On magnetic resonance imaging, a large and well-circumscribed mass with inconspicuous enhancement was revealed in each case. Histologically, the tumors were composed of spindle to ovoid cells, prone to forming perivascular pseudorosettes and palisading necrosis, but absence of microvascular proliferation. Immunohistochemistry showed that the tumor cells were diffusely positive for BCOR, SOX2, CD133, Nestin, CD56, CD99, Vimentin, and focally positive for Olig-2, S100, SOX10, Syn. GFAP was negative and Ki-67 index was about 20% to 40%. BCOR-ITD was found in all 4 cases with the duplicated sequences between 87 bp and 119 bp.

Conclusion: As a new entity of central nervous system tumors, CNS HGNET-BCOR has unique clinical, pathological and molecular characteristics, which can be detected by BCOR immunohistochemistry and confirmed by BCOR molecular testing. This study discovered that these tumors express stem cell markers, suggesting that it may be derived from tumor stem cells.

Key words: BCOR; HGNET-BOCR; BCOR-ITD; HGNET

166. 基于 HNF4A 变异位点所表现的特殊临床表现分析

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目的: 探讨 HNF4A 基因 Exon7 位点变异所致新生儿低血糖,高乳酸,高血氨血症的临床特征。

方法: 整理分析新生儿女童的临床表现,HNF4A 基因分析和随访资料, 并进行相关文献复习。以“HNF4A”“chr20:43048381”“neonatal hypoglycemia”为检索词分别查阅在线人类孟德尔遗传数据库,PubMed 数据库,中国知网数据库及万方数据库建库至 2021 年 6 月相关文献, 总结 HNF4A 基因 Exon7 位点变异患儿临床表现,实验室及影像学检查,治疗及预后特点。

结论: 新生儿低血糖的表现大多会影响大脑皮层的发育, 严重者会影响机体代谢及危及生命等。但反复出现低血糖伴高乳酸血症,血氨升高等临床表现较为罕见。本例患儿通过基因分析确诊。目前尚无明确的治疗方法, 大多数通过低血糖的紧急处理,抗感染,提高患儿营养等方式进行处理。本例患儿以提高患儿营养热卡为主要方式控制低血糖后, 患儿未再出现低血糖, 通过短暂周期性抗生素满疗程后, 患儿血氨值下降, 临床症状改善后出院。鉴于目前患儿仍处于新生儿期, 暂未进行其他特殊处置, 定期随访仍在继续进行中。

关键词: 新生儿低血糖; 高血氨血症; 基因诊断;

167. Primary erythromelalgia mainly manifested by hypertensive crisis: A case report and literature review

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Objective: Primary erythromelalgia (PEM) is a rare autosomal dominant single-gene disease commonly presenting during hypertensive crisis. Herein, we describe the main clinical features, diagnosis and treatment of a typical PEM case.

Methods: Medical records of an 8-year-old boy with PEM were analyzed retrospectively, which included clinical characteristics, follow-up information, and SCN9A (Sodium Voltage-Gated Channel Alpha Subunit 9) gene analysis.

Results: The 8-year-old boy had complained of abnormal paresthesia in his feet and ankles with burning sensation and pain for 2 years. The skin of both lower legs was red and underwent ichthyosis and lichenification. Genetic analysis confirmed the existence of a SCN9A gene mutation. The symptoms



were gradually improved by treating with intravenous drip and oral administration of nitroglycerin to slow his heart rhythm.

Conclusion: PEM is characterized by skin ulceration, redness, elevated temperature, and severe burning pain primarily in both lower extremities. PEM can be diagnosed by genetic analysis. As this case demonstrates, treating with nitroglycerin as the drug of choice to control the hypertensive crisis significantly improved the symptoms of PEM and hypertension in this patient.

Key words: Erythromelalgia; Pain; Nitroglycerin; Slow heart rhythm; Genetic diagnosis

168. CEA,NSE 在非小细胞肺癌中的临床意义

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目的: 探索与分析 CEA,NSE 在非小细胞肺癌中的临床意义。

方法: 2019 年 9 月至 2020 年 8 月在云南省肿瘤医院收治的患者共 196 例, 其中实验组为非小细胞肺癌患者 106 例, 对照组为肺良性肿瘤患者 90 例。采用电化学发光法检测两组血清 CEA,NSE 浓度并进行比较分析。考察不同临床病理特征 NSCLC 患者的 CEA,NSE 浓度水平。

结果: 1.实验组中血清 CEA,,NSE 含量比对照组明显升高, 差异具有统计学意义 ($P<0.05$); 2.CEA,,NSE 含量在鳞癌组中比在腺癌组中升高明显, 但差异无统计学意义 ($P>0.05$); 3.NSE 在有淋巴结转移时含量升高, 但差异无统计学意义 ($P>0.05$), 而 CEA 在有淋巴结转移时含量也升高, 但差异有统计学意义 ($P<0.05$); 4.NSE 在发生远处转移时含量升高, 但差异无统计学意义 ($P>0.05$), 而 CEA 在发生远处转移时含量也升高, 差异有统计学意义 ($P<0.05$); 4.CEA,,NSE 含量在肿瘤直径中无统计学意义; 5.CEA 在晚期患者中含量升高, 差异有统计学意义 ($P<0.05$), NSE 虽然在晚期患者中含量也升高, 但差异无统计学意义 ($P>0.05$)。

结论: 通过检测 CEA,,NSE, 对辅助鉴别良恶性,判断患者病理分期,评估疾病进展程度,淋巴结的转移情况以及用于临床指导手术具有重要临床意义,

关键词: 非小细胞肺癌; CEA; NSE; 临床病理特征

169. 肺上皮-肌上皮癌

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肺上皮-肌上皮癌 (Pulmonary Epithelial myoepithelial Carcinoma, PMEC) 是一种起源于气管/支气管腺体的罕见唾液腺类型的肺肿瘤, 具有双向分化, 由管状结构的内层上皮细胞和外层的梭形, 透明细胞样肌上皮组成。其没有特异性的临床症状, 主要表现为支气管阻塞症状。由于其临床表现,影像学特征与其他类型非小细胞肺癌无太大差异,因此,容易造成漏诊和误诊。诊断主要基

于病理学和免疫组化, 一般来说, 内层上皮细胞对细胞角蛋白免疫反应阳性, 外层肌上皮细胞对 S-100 和平滑肌肌动蛋白免疫反应阳性。因此, 细胞角蛋白, S-100 和平滑肌肌动蛋白都阳性可以协助诊断。虽然 PMEC 通常被认为是一种低度恶性肿瘤, 但其也具有复发和转移的能力, 目前尚无标准治疗方案。治疗上多以手术为主, 对放、化疗并不十分敏感。除此之外, 靶向治疗及免疫治疗相关疗效有待进一步研究。本文就 PMEC 的病理特点、分子特征、诊断、治疗及预后作阐述。

关键词: 肺上皮-肌上皮癌; 病理特征; 诊断; 治疗; 预后

170. 肺黏液表皮样癌

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肺黏液表皮样癌 (Pulmonary mucoepidermoid carcinoma, PMEC) 是最常见的恶性涎腺型肿瘤, 在肺部的发病率极低, 在成人中的发病率只有 0.1-0.2%。PMEC 没有特定的流行病学特点和临床特征, 因此容易与良性疾病混淆。对 PMEC 正确的诊断需要结合影像学、实验室检查、病理学和免疫组化结果以及分子检查。PMEC 由三种细胞组成: 鳞状细胞、中间细胞和黏液分泌细胞, 并根据这三种细胞的分布比例和细胞的分化程度、异型性被区分为高级别和低级别的肿瘤。在 PMEC 中最常见的基因改变是 $t(11;19)(q21;p13)$, 由此产生的 MECT1-MAML2 融合基因被认为是 PMEC 的基因驱动事件。PMEC 的治疗方式在现有的文献上还没有被充分的了解, 但是手术完整切除是主要的治疗手段, 辅助放化疗的疗效还存有争议, 针对 EGFR 突变的 TKI 治疗取得了一定的疗效, 免疫和靶向治疗还处于探索的阶段。本文就 PMEC 的流行病学特点、临床表现、影像学特征、病理检查和免疫组化结果、分子检查、诊断和鉴别诊断以及治疗方法和预后因素进行综述。

关键词: 肺黏液表皮样癌; 免疫组织化学; 诊断; 治疗; 预后

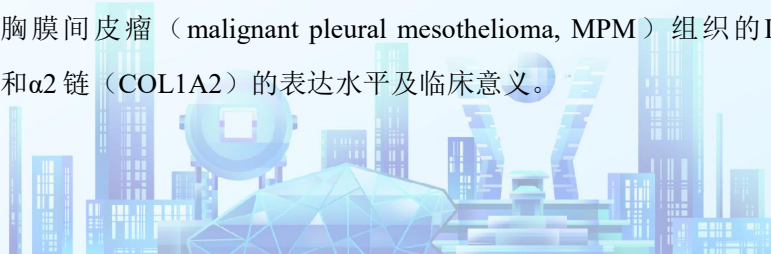
171. 恶性胸膜间皮瘤组织中 COL1A1 和 COL1A2 的表达及临床意义研究

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目的: 探讨恶性胸膜间皮瘤 (malignant pleural mesothelioma, MPM) 组织的 I 型胶原蛋白 $\alpha 1$ 链 (COL1A1) 和 $\alpha 2$ 链 (COL1A2) 的表达水平及临床意义。



方法: 通过 Oncomine 数据库对非瘤组织与 MPM 组织中 COL1A1 和 COL1A2 基因的表达差异进行分析。采用实时定量 PCR 检测手术切除的 26 例 MPM 组织及配对正常胸膜组织中 COL1A1 和 COL1A2 基因 mRNA 表达量。采用受试者工作特征 (ROC) 曲线评估组织两者水平诊断 MPM 的效能。通过 TCGA 数据集分析 MPM 组织 COL1A1 和 COL1A2 基因表达水平与 MPM 临床病理特征的关系。采用基因表达谱动态分析 (GEPIA) 两者表达水平与 MPM 患者总生存期 (OS) 和无疾病进展生存期 (DFS) 的关系。通过 Cox 风险比例模型探讨影响 MPM 患者预后的因素。采用 TIMER 平台探讨 COL1A1 和 COL1A2 在 MPM 中的表达与肿瘤免疫浸润性细胞的关系。

结果: Oncomine 数据库分析和 RT-qPCR 检测发现, 与配对正常胸膜组织相比, MPM 组织中 COL1A1 和 COL1A2 基因 mRNA 的表达量显著增加 ($P<0.01$), 且两者表达正相关。ROC 曲线显示组织 COL1A1 和 COL1A2 水平诊断 MPM 的曲线下面积分别为 0.900 和 0.897。COL1A1 基因表达量与 MPM 患者肿瘤类型相关 ($P<0.05$), COL1A2 基因表达量与 MPM 患者 T 分期相关 ($P<0.05$)。COL1A1 和 COL1A2 基因表达量与 MPM 患者总生存率 (OS) 负相关 (logrank $P<0.05$), 与无疾病进展生存率 (DFS) 无关 (logrank $P>0.05$)。TCGA 数据集 Cox 多因素分析结果显示, COL1A1 和 COL1A2 基因高表达及双相混合型 MPM 患者的死亡风险较高 ($P<0.05$)。TIMER 平台分析结果表明, COL1A1 基因在 MPM 中的表达与巨噬细胞成正相关。COL1A2 基因在 MPM 中的表达与巨噬细胞成正相关, 与中性粒细胞成负相关。

结论: COL1A1 和 COL1A2 在 MPM 中高表达, 在其疾病诊断、病情预测和预后评估上有一定价值, 两者可能共同促进了 MPM 的发生发展。

关键词: I型胶原蛋白 $\alpha 1$ 链; I型胶原蛋白 $\alpha 2$ 链; 胸膜间皮瘤; TCGA 数据库; 临床意义

172. 肺腺样囊性癌

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肺腺样囊性癌 (Pulmonary adenoid cystic carcinoma, PACC) 是一种非常罕见的唾液腺型恶性肿瘤。由于其临床表现、影像学特征与其他类型非小细胞肺癌无太大差异, 因此, 容易造成漏诊和误诊。CD117, SMA, P63, Vim, S-100 等共同阳性表达在协助 PACC 诊断中具有一定价值。肺腺样囊性癌的治疗手段多以手术治疗为主, 对放、化疗并不十分敏感。对于晚期无法行手术及放化疗的患者, 有关分子靶向药物的临床试验也在进行。目前, PACC 靶向治疗的研究主要集中在禽成髓细胞瘤病毒致癌基因同源物类 (v-myb avian myeloblastosis viral oncogene homolog, MYB) 及其下游靶点的探索上。此外, PACC 的中位肿瘤突变负担 (median tumor mutation burden, mTMB) 及程序性细胞死亡蛋白-1 (programmed death-1, PD-1) 及其配体 (PD-L1) 低于其他实体肿瘤, 这可能提示免疫治疗在 PACC 中疗效较差。本文就 PACC 的病理特点、分子特征、诊断、治疗及预后作一综述。

关键词：肺腺样囊性癌；免疫组化；分子特征；诊断；治疗；预后

173. Expression and clinical significance of LOXL1 and LOXL2 genes in malignant pleural mesothelioma

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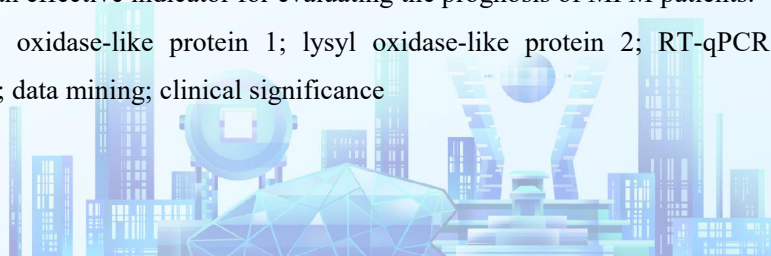
Objective: The differences in the expression of lysyl oxidase-like protein 1 (LOXL1) and lysyl oxidase-like protein 2 (LOXL2) in malignant pleural mesothelioma (MPM) and its prognostic value are still unclear. This article aims to explore the mRNA expression of LOXL1 and LOXL2 genes in MPM tissues and their prognostic significance.

Methods: RT-qPCR was used to detect the mRNA expression of LOXL1 and LOXL2 genes in 12 cases of MPM tissues and matched normal pleural tissues. The differences in the expression of LOXL1 and LOXL2 genes in non-tumor tissues and MPM tissues were analyzed through the Oncomine database. The correlation between the mRNA expression of LOXL1 and LOXL2 genes in the TCGA database and the clinicopathological characteristics of MPM was analyzed by R software. A Kaplan-Meier model was constructed to investigate the effects of LOXL1 and LOXL2 mRNA expression on the prognosis of MPM patients. Gene expression profiling interactive analysis (GEPIA) was used to analyze the correlation between LOXL1 and LOXL2 and the expression of MPM tumor marker genes and other members of the LOX family.

Results: RT-qPCR detection showed that the expression of LOXL1 and LOXL2 mRNA in MPM tissue was significantly increased compared with matched normal pleural tissue. The expression of LOXL2 gene is correlated with the cancer types of MPM patients. The high expression of LOXL1 and LOXL2 genes and tumor types are independent factors leading to poor prognosis of MPM patients. LOXL1 gene expression has a significant correlation with EFEMP1, MSLN, CALB2, THBS2 and CDH11 gene expression; LOXL2 gene expression has a significant correlation with MSLN, CALB2, THBS2 and CDH11 gene expression. In addition, LOXL1 gene and LOXL2, LOXL4 gene expression are significantly positively correlated. LOXL2 gene expression was significantly positively correlated with LOX, LOXL1 and LOXL4 gene expression.

Conclusion: LOXL1 and LOXL2 genes are significantly high expression in MPM tissues, and their gene expression is an effective indicator for evaluating the prognosis of MPM patients.

Key words: lysyl oxidase-like protein 1; lysyl oxidase-like protein 2; RT-qPCR; malignant pleural mesothelioma; data mining; clinical significance



174. 肝细胞性肝癌中线粒体转录延伸因子的表达及其临床病理学意义

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目的: 探讨线粒体转录延伸因子 (mitochondrial transcription elongation factor, TEFM) 在肝细胞性肝癌 (hepatocellular carcinoma, HCC) 中的表达和临床意义。

方法: 采用 Western blotting 检测人正常肝细胞 (THLE-2) 和 6 种 HCC 细胞中 TEFM 蛋白的表达差异。对 HCC 组织芯片进行免疫组化检测, 在 70 例 HCC 组织和对应的癌旁组织中检测 TEFM 表达量和细胞阳性率的差异, 分析 TEFM 表达量与临床病理学特征的相关性, 分析 TEFM 蛋白表达量与 HCC 患者预后的关联。

结果: 与人正常肝细胞 (THLE-2) 相比, TEFM 蛋白在 6 种 HCC 细胞中均显著上调 1.803 ± 0.275 倍 ($P < 0.05$); 与对应的癌旁组织相比, HCC 的 TEFM 蛋白表达量增高, 其细胞阳性率也增高 ($P < 0.05$)。TEFM 蛋白在 HCC 组织的表达量与患者 AFP 含量具有相关性 ($P = 0.002$), 而与患者年龄、性别、肿瘤分期、淋巴结转移、分化程度、HBV 病毒感染、肝硬化、血管侵犯、肿瘤数量、肿瘤大小、肿瘤包膜完整性和肿瘤复发无相关性 (均 $P > 0.05$)。TEFM 蛋白表达量与 HCC 患者总生存期 (overall survival, OS) 和无瘤生存期 (disease-free survival, DFS) 无相关性。

结论: TEFM 蛋白在 HCC 细胞和组织中的表达增高, 且与 HCC 患者的血清 AFP 含量呈正相关。TEFM 蛋白表达量与 HCC 患者预后之间无关联。

关键词: 肝细胞性肝癌; 线粒体转录延伸因子; 组织芯片; 临床病理学意义

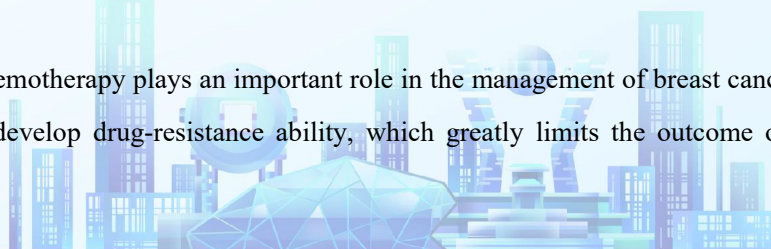
175. Mitochondrial BCRP sustains the proliferation and survival of drug-resistant breast-cancer cells by regulating intracellular ROS

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Background: Chemotherapy plays an important role in the management of breast cancer; however, cancer cells always develop drug-resistance ability, which greatly limits the outcome of chemotherapeutic



treatment. ATP-binding cassette (ABC) transporter family are major contributors to the drug-resistance establishment of breast cancer cells. Breast cancer resistant protein (BCRP), one of the ABC transporters, has long been recognized as a pump that effluxes the therapeutic drugs against the concentration gradient. Recent studies found that ABC transporters are involved in a broad range of physiological processes that do not completely depend on its transport activity, but the related studies are still limited.

BCRP is a well-characterized drug pump generally believed to be localized in the cell membrane to mediate the efflux of chemotherapeutic drugs. Recent studies have suggested that BCRP can also be located in the mitochondria, nucleus and cytoplasm of cells. These findings suggest that BCRP may play important functional roles in cancer cells independently of its drug-pump activity; however, the detailed mechanism that is responsible for these drug-pump-independent roles of BCRP in various malignancies is poorly investigated.

Results: *BCRP is not the dominant efflux pump in drug-resistant cells with multiple activated ABC transporters and confers survival advantages in drug-resistant breast cancer cells.*

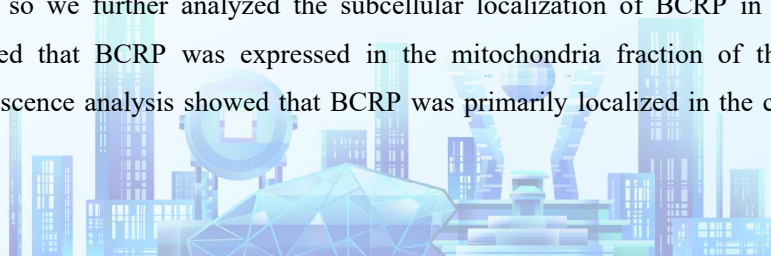
In the present study, we took advantage of a previously established drug-resistant breast cancer cell line and investigated the biological function of mitochondrial BCRP in drug-resistant breast cancer cells. This study suggested that BCRP was not the dominant drug pump that contributed to the exclusion of drugs in the two specific drug-resistant cell models which expressed multiple ABC transporters. BCRP conferred proliferation advantage on drug-resistant cells independent of its drug-efflux activity. Moreover, BCRP was vital for the drug-resistant cells to sustain their proliferation and evade programmed cell death.

BCRP inhibits oxidative phosphorylation (OXPHOS) in drug-resistant breast cancer cells

We further examined the transcriptome-wide alteration of SK/EPI cells upon BCRP silencing. Bioinformatics analysis suggested that 2492 genes were downregulated and 2837 genes were upregulated in SK/EPI cells versus SK-BR-3 cells. Notably, a large number of metabolic-related signaling pathways were upregulated in BCRP-silenced SK/EPI cells compared with that in control cells, as suggested by Gene Set Enrichment Analysis (GSEA). GSEA also suggested that OXPHOS- and citric acid cycle-related signaling pathways were activated upon BCRP silencing in SK/EPI cells. Collectively, these *in silico* data was consistent with the extensively accepted perspective that drug-resistant cells rely more on anaerobic than on aerobic respiration to sustain their energy need. Notably, BCRP silencing reactivated the suppressed OXPHOS in drug-resistant cells, suggesting that BCRP was involved in regulating the OXPHOS-related signaling pathway in drug-resistant breast cancer cells.

BCRP is localized in mitochondria of drug-resistant breast cancer cells

Bioinformatics analyses indicated that BCRP was linked with OXPHOS, which primarily occurred inside mitochondria, so we further analyzed the subcellular localization of BCRP in drug-resistant cells. Results showed that BCRP was expressed in the mitochondria fraction of these cells. Notably, immunofluorescence analysis showed that BCRP was primarily localized in the cytoplasm instead of



the cell membrane in drug-resistant cells, whereas P-gp was dominantly expressed in the cell membrane, further supporting the notion that BCRP was not the major drug-efflux pump that excluded the chemotherapy drugs in these two specific drug-resistant cell models.

BCRP inhibits ROS production in drug-resistant breast cancer cells

Mitochondria is the major source of intercellular ROS. We have demonstrated that BCRP was localized in mitochondria and potentially linked with mitochondrial activity. Results showed that intercellular ROS level was significantly elevated in BCRP-silenced SK/EPI and 468/EPI cells compared with that in control cells. Furthermore, BCRP was silenced in the Dox-inducible shBCRP cell line (468/EPI-tet) by treating the cells with 100 ng/mL Dox. Consistently, ROS level was profoundly elevated in Dox-treated cells compared with that in control cells. In summary, these results indicated that BCRP was an essential factor that maintained the homeostasis of intercellular ROS in drug-resistant cells. The elevated ROS in BCRP-silenced cells may exceed the safety threshold and induce the cells to undergo apoptosis.

Conclusion: In conclusion, we identified a novel, drug-efflux independent function of BCRP in drug-resistant breast cancer cells. The elevated BCRP, instead of pumping the drug out of the cells, may act as a modulator to inhibit mitochondrion-originating ROS, thereby preventing cells from drug-induced oxidative toxicity and apoptosis (Figure 7H). This work demonstrated that BCRP is essential in the proliferation and survival of drug-resistant breast cancer cells.

Key words: Mitochondria; BCRP; Survival; Breast cancer; Drug-resistance

176. 全长转录组测序技术解析不同转移性能肝癌细胞系的转录本表达谱与结构变异

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赣南医学院

为了更好地研究肝细胞癌的转移机制, 并筛选出与肝癌预后密切相关的潜在靶点, 本研究利用纳米孔长读长测序技术对两株不同转移潜能的肝癌细胞 (MHCC97H 与 MHCC97L) 进行全长转录组比较分析。通过生物信息学分析发现 643 个新基因 (novel gene) 和 2471 个新转录本 (new transcripts)。在这两株细胞中有 293 个差异表达基因及 74 个差异表达转录本。在结构变异分析中鉴定出 1008 个可变剪切事件, 其中外显子跳跃占比最多。本研究通过全长转录组分析进一步完善了肝癌细胞的基因注释, 并筛选到与肝癌转移相关的潜在靶点。

关键词: 肝细胞癌; 转录本表达谱; mRNA 可变剪切; 全长转录组测序; 纳米孔测序



177. Comprehensive analysis of splicing factor and alternative splicing event to construct subtype-specific prognosis-predicting models for breast cancer

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天津医科大学肿瘤医院公共实验室

Background: Alternative splicing (AS) is a post-transcriptional process, in which the precursor mRNA is processed to different mature mRNAs from one protein-coding gene. The AS is a highly regulated process and nearly all multiexon genes are involved in AS and most cellular processes may be regulated by AS. In this process, genes can produce many different mature mRNAs to produce different proteins. AS includes seven types of alternative splicing, namely, alternate acceptor site (AA), alternate donor site (AD), alternate promoter (AP), alternate terminator (AT), exon skip (ES), mutually exclusive exons (ME), and retained intron (RI).

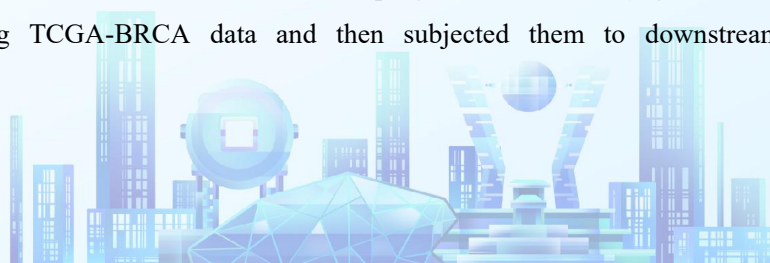
In the present study, we comprehensively analyzed the expression patterns of SFs and ASs in BRCA with different molecular subtypes. Furthermore, four subtype-specific SF risk models were constructed using the survival-related SFs. The potential mechanistic connections in the risk models were described using a series of bioinformatics approaches. Lastly, we identified key AS events and constructed four subtype-specific AS risk models by using a combination of SF risk models and survival-related AS events. The constructed AS/SF risk models may provide new multidimensional biomarkers for the prognosis and diagnosis of BRCA with different molecular subtypes.

Results: *Landscape of SFs and alternate splicing events in BRCA*

We perform the principal component analysis (PCA) to characterize the expression pattern of SFs and ASs in the four molecular subtypes. Notably, AS-events were clustered into distinct groups in the PCA plots, especially for the Basal-like subtype. This finding indicated that the expression patterns of SFs and ASs were different across the four BRCA molecular subtypes. Then, the survival-related SFs and ASs were determined by univariate Cox analysis in each molecular subtype. However, the identified survival-related SFs and ASs showed little overlapping among the four subtypes. This finding may indicate that the contribution of SFs and ASs in the progression of BRCA is distinct in the different molecular subtypes. Collectively, these results suggested that ASs may play important roles in BRCA, especially, each molecular subtype may be regulated by unique groups of SFs and ASs. Thus, the connections among SF, AS, and BRCA are subtype specifically.

Construction and validation of subtype-specific prognostic risk models using survival-related SFs

We constructed risk models in the four BRCA subtypes using Lasso-Cox regression to address the connection between survival-related SFs and prognosis. We initially generated training and testing datasets using TCGA-BRCA data and then subjected them to downstream prognosis model construction.



In Luminal A BRCA, a three-gene (PAXBP1, NKAP, and NCBP2) SF-risk-model was obtained with the area under curve (AUC) = 0.752 in the training set and AUC = 0.705 in the testing set. We identified a four-gene SF-risk-model (RBM15B, PNN, ACIN1, and SRSF8) in Luminal-B BRCA with an AUC = 0.953 in the training set and AUC = 0.706 in the testing set. We also constructed a three-gene SF-risk-model (LSM3, SNRNP200, and SNU13) in patients with Her-2 BRCA with AUC = 0.953 in the training and AUC = 0.794 in the testing set. Finally, we constructed a three-gene risk model (SRPK3, PUF60, and PNN) in Basal-like subtype with AUC = 0.838 in the training set and AUC = 0.713 in the testing dataset.

Mechanistic exploration of model-predicted high-risk patients by gene set enrichment analysis

We subsequently used gene set enrichment analysis (GSEA) to explore the possible mechanisms that linked the RiskScore and prognosis. The GSEAs were performed using model predicted low- and high-risk samples to calculate the fold change of gene expression, and the analysis was conducted using Hallmark 50 and KEGG pathway datasets.

In the Luminal A subtype, the GSEA revealed that high-risk samples were enriched in genes related to cell cycle progressions, such as G2M checkpoint and mitotic spindle. In Luminal B BRCA, we found that the top enriched Hallmark gene sets were not closely related to cancer progression. Interestingly, cytochrome p450 related genes, which were enriched in the low-risk Luminal A BRCA, were enriched in the high-risk Luminal B BRCA, suggesting that this set of genes may play a different role in the two Luminal BRCA subtypes. In Her-2 BRCA, as expected, estrogen response-related genes were enriched in high-risk patients. Similar to the Luminal A BRCA, the E2F target genes and G2M checkpoint-related genes were also enriched in the high-risk patients. In Basal-like BRCA, we found that interferon-gamma-related genes, inflammatory response-related genes, and IL-2 STAT5 signaling related genes were enriched in low-risk patients.

Comprehensive analysis of genes in subtype-specific SF-risk-models

Then, we analyzed the genes expressed in the four subtype-specific risk-models using different approaches.

We found that PAXBP1 and NCBP were differentially expressed in Luminal A BRCA compared with normal samples. In Luminal B BRCA, PNN was the only gene that passed the significant threshold ($\log FC > 0.5$, $P < 0.01$) and was downregulated in tumor samples. In Her-2 BRCA, LSM3 and SNU13 were significantly upregulated in tumor samples and both genes were negatively correlated with prognosis. In Basal-like BRCA, PUF60 was upregulated and PNN was downregulated in tumor samples. Notably, PUF60 showed a high frequency of mRNA hyperexpression among BRCA samples. However, only a small fraction of samples was involved in gene amplification, deletion, and mutation. The PPI network indicated that LSM3, SNRNP200, PUF60, NHP2L1, and NCBP2 were closely interconnected, suggesting a potential regulatory cascade among these proteins. In summary, these results suggested that the 12 genes selected for risk prediction have strong connections to the tumor-related pathways. In addition, genes that are differentially expressed between the tumor and normal tissue indicated that they may serve as reliable markers to predict a patient's disease outcome.



Conclusions: To sum up, our study shows that the SFs and ASs have promising potential as biomarkers and therapeutic targets for diagnosis and prognosis in BRCA. The constructed risk-predicting models have good performance in predicting the prognosis of BRCA patients.

Key words: splicing factor; alternative splicing; prognosis; breast cancer; TCGA database

178. Cancer biomarkers discovery of methylation modification with direct high-throughput nanopore sequencing

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Cancer is a complex disease, driven by a combination of genetic and epigenetic alterations. DNA and RNA methylation modifications are the most common epigenetic events that play critical roles in cancer development and progression. Bisulfite converted sequencing is a widely used technique to detect base modifications in DNA methylation, but its main drawbacks lie in DNA degradation, lack of specificity, or short reads with low sequence diversity. The nanopore sequencing technology can directly detect base modifications in native DNA as well as RNA without harsh chemical treatment, compared to bisulfite sequencing. Furthermore, CRISPR/Cas9-targeted enrichment nanopore sequencing techniques are straightforward and cost-effective when targeting genomic regions are of interest. In this review, we mainly focus on DNA and RNA methylation modifications detection in cancer with the current nanopore sequencing approaches. We also present the respective strengths, weaknesses of nanopore sequencing techniques and their future translational applications in identification of epigenetic biomarkers for cancer detection and prognosis.

Key words: Nanopore sequencing; Cancer biomarker; Cas9 enrichment; DNA methylation; RNA methylation

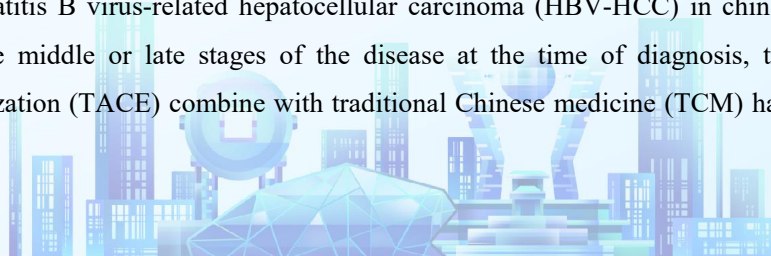
179. Circulating cell-free mtDNA content as non-invasive biomarker for outcome prediction in HCC patients receiving TACE and traditional Chinese medicine treatments

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Objectives: Hepatocellular carcinoma (HCC) accounts for 70%-85% of liver cancer, and about 85% of HCC are hepatitis B virus-related hepatocellular carcinoma (HBV-HCC) in china. Most patients are already in the middle or late stages of the disease at the time of diagnosis, trans-hepatic arterial chemoembolization (TACE) combine with traditional Chinese medicine (TCM) have been reported as



an effective treatment, and effective predictive molecular markers are helpful to predict therapeutic efficacy. In this study, we aim to explore whether circulating cell-free mitochondrial DNA (ccf-mtDNA) content is associated with the outcome for HCC patients receiving TACE combine with TCM treatment.

Method: Retrospective analysis was conducted in a cohort with 141 HBV-HCC patients. Univariate and multivariate analysis was conducted with Cox proportional risk regression model to explore the correlation between ccf-mtDNA content and patient outcome. Kaplan-Meier method was used to draw the curve of ccf-mtDNA content and the survival of patients.

Results: (1) high content of serum ccf-mtDNA is an independent risk factor for the outcome of HBV-HCC patients treated with TACE combined with TCM adjuvant therapy (HR=4.010, 95%IC=1.252-12.844, $P = 0.019$). (2) K-M survival analysis showed that patients with high ccf-mtDNA content had poor survival rate (Log Rank $P=0.027$).

Conclusions: Our findings suggest that ccf-mtDNA is a potential novel non-invasive cancer biomarker for clinical outcome prediction of HCC patients receiving TACE combine with TCM treatment.

Key words: Hepatocellular carcinoma; mitochondrial DNA; TACE; non-invasive biomarker; clinical outcome

180. CD147 supports paclitaxel resistance via interacting with RanBP1

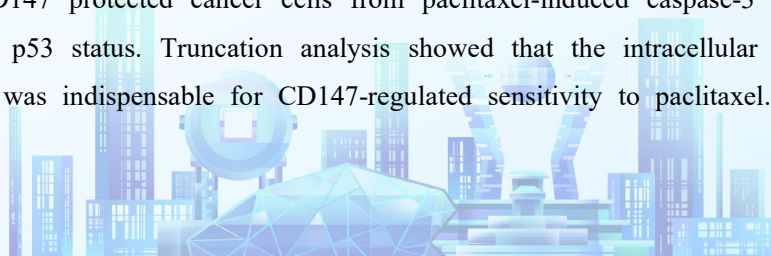
Gang Nan*, Hongyong Cui

空军军医大学

Objectives: Though the great success of paclitaxel, the variable response activity of patients to the drug limits its clinical utility and the precise mechanisms underlying the variable response to paclitaxel remain largely unknown. This study aims to verify the role and the underlying mechanisms of CD147 in paclitaxel resistance. Immunostaining was used to analyze human ovarian cancer tissues. RNA-sequencing was used to identify downstream effectors.

Method: Annexin V-FITC/propidium iodide and terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL) staining were used to detect apoptosis. Co-immunoprecipitation (Co-IP), fluorescence resonance energy transfer (FRET) and surface plasmon resonance (SPR) were performed to determine protein interactions. Fluorescence recovery after photobleaching (FRAP) was performed to measure the speed of microtubule turnover. Xenograft tumor model was established to evaluate sensitivity of cancer cells to paclitaxel in vivo.

Results: In vitro and in vivo assays showed that silencing CD147 sensitized the cancer cells to paclitaxel treatment. CD147 protected cancer cells from paclitaxel-induced caspase-3 mediated apoptosis regardless of p53 status. Truncation analysis showed that the intracellular domain of CD147 (CD147ICD) was indispensable for CD147-regulated sensitivity to paclitaxel. Via screening the



interacting proteins of CD147/ICD, Ran binding protein 1 (RanBP1) was identified to interact with CD147/ICD via its C-terminal tail. Furthermore, we showed that RanBP1 mediated CD147-regulated microtubule stability and dynamics as well as response to paclitaxel treatment.

Conclusions: These results demonstrated that CD147 regulated paclitaxel response by interacting with the C-terminal tail of RanBP1 and targeting CD147 may be a promising strategy for preventing paclitaxel resistant.

Key words: Ovarian cancer; non-small-cell lung cancer; paclitaxel; CD147; RanBP1; microtubule stability

181. 纳米孔基因测序技术在 DNA 甲基化修饰检测中的应用研究进展

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赣南医学院

DNA 甲基化是最常见的表观遗传修饰类型之一, 其中哺乳动物基因组中最常见的 5mC 甲基化修饰参与了许多重要的生命活动, 其含量的异常与疾病, 尤其是癌症的发生发展密切相关。当前检测 5mC 最常用的方法是基于亚硫酸氢盐转化的 PCR 扩增或第二代基因测序技术, 该方法虽然转化效率高且测定准确, 但仍然存在不足之处, 包括 DNA 分子降解, 处理过程繁杂, 测序读长较短, 检测特异性不高等。近年来发展起来的纳米孔基因测序技术凭借其能对 DNA 修饰直接进行检测, 且具有读长长, 通量高, 速度快等优势, 在 DNA 表观遗传修饰检测方面展现了良好优势。本文对 DNA 的 5mC 甲基化修饰的形成与去除和其经典的检测方法进行了简要介绍, 并重点介绍了纳米孔基因测序技术在 DNA 的 5mC 甲基化修饰检测中的应用研究进展。

关键词: 纳米孔基因测序技术; DNA 甲基化; 5-甲基胞嘧啶

182. Targeted proteomics-derived biomarker profile develops a multi-protein classifier in liquid biopsies for early detection of esophageal squamous cell carcinoma from a population-based case-control study

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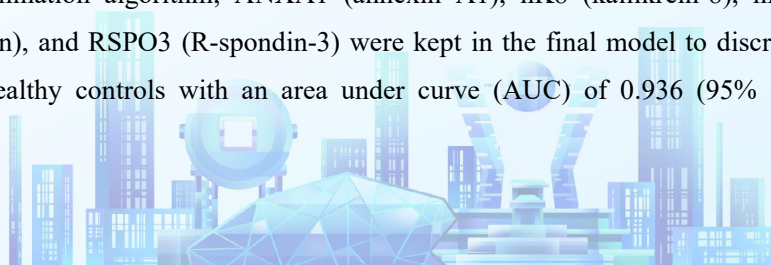
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Background: Early diagnosis of esophageal squamous cell carcinoma (ESCC) remains a challenge due to the lack of specific blood biomarkers. We aimed to develop a serum multi-protein signature for the early detection of ESCC.

Methods: We selected 70 healthy controls, 30 precancerous patients, 60 stage I patients, 70 stage II patients and 70 stage III/IV ESCC patients from a completed ESCC population-based case-control study in a high-risk area of China. Olink Multiplex Oncology II targeted proteomics panel was used to simultaneously detect the levels of 92 cancer-related proteins in serum using proximity extension assay. Blood samples have been stored in the -80 °C refrigerator before shipment. The serum samples were shipped to Olink Proteomics AB (Uppsala, Sweden) using cold chains and the samples were randomly placed in four 96-well plates. The early-stage ESCC was defined as precancerous lesions and stage I cancer in our study because of mini-invasive treatment, better prognosis and small sample size, and early screening requirement in community-based practice. An exploratory multivariate analysis (principal component analysis, PCA) was applied to test for potential clustering of study groups. The association between each protein NPX value and early ESCC was investigated using unconditional logistic regression, and the *P* value was adjusted by the Benjamini-Hochberg method for controlling the false discovery rate ($FDR < 0.01$). For the potential protein biomarkers, we further applied Spearman correlation to assess the dose-response relationship between protein levels and stages of ESCC, and the *P* value was also adjusted by the Benjamini-Hochberg method. For all preliminarily verified proteins, unsupervised clustering methods were applied to the data to identify clusters of proteins and visually evaluate their association with disease status. For developing a multi-biomarker classifier to discriminate early ESCC cases from healthy controls, we used the least absolute shrinkage and selection operator (LASSO) regression to select optimal proteins. Moreover, we further used the backward elimination logistic regression model to build a more concise and efficient classification model. The specificity and sensitivity of the classifier were evaluated using the receiver operating characteristic (ROC) curve and the optimal cutoff points were selected using Youden's index, which maximizes the sum of sensitivity and specificity. The AUC was applied to summarize the classification accuracy of diagnostic models and 95% confidence intervals (CI) were estimated by the non-parametric bootstrap. Five-fold cross-validation was used to estimate the validity of our multiple-protein model on the same data that was used to build the classifier.

Results: We found that 10 upregulated and 13 downregulated protein biomarkers in serum could distinguish the early-stage ESCC from healthy controls, which were validated by the significant dose-response relationships with ESCC pathological progression. Applying LASSO regression and backward elimination algorithm, ANXA1 (annexin A1), hK8 (kallikrein-8), hK14 (kallikrein-14), VIM (vimentin), and RSPO3 (R-spondin-3) were kept in the final model to discriminate early ESCC cases from healthy controls with an area under curve (AUC) of 0.936 (95% confidence interval:



0.899~0.973). The average accuracy rates of the five-protein classifier were 0.861 and 0.825 in training and test data by five-fold cross-validation.

Conclusions: Our study suggested that a combination of ANXA1, hK8, hK14, VIM and RSPO3 serum proteins could be considered as a potential tool for screening and early diagnosis of ESCC, especially with the establishment of a three-level hierarchical screening strategy for ESCC control. This study was conducted in an ESCC high-risk area of China, which might weaken the generalization of our five-protein prediction classifier to other relatively normal-risk areas. Hence, the results need to be further validated in prospective cohort studies.

Key words: Esophageal squamous cell carcinoma; early detection; diagnostic biomarkers; affinity proteomics; proximity extension assay; screening

183. 染色体碎裂化在肿瘤中的作用及长读长高通量基因测序检测技术的应用进展

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染色体碎裂化 (Chromothripsis) 是指细胞内的染色体上发生大量基因重排现象, 存活下来的细胞会获得强大的选择优势。在染色体碎裂化的过程中, 会出现肿瘤抑制基因的丢失, 碎裂片段在染色体外形成环状 DNA——双微染色体 (double-minute chromosome, DM), 借助 DM 来实现癌基因的扩增以及致癌融合基因的构建, 从而促进肿瘤的发生发展。此外, DM 的形成还有助于细胞对外界环境改变的耐受, 帮助细胞增加对药物的抗性。染色体碎裂化与许多肿瘤类型有关, 尤其与癌症患者侵袭性肿瘤行为和不良预后有关。当前染色体碎裂化检测技术可分为常规检测技术与高通量检测技术。常规检测技术有荧光原位杂交 (FISH), 通过外周淋巴细胞的核型分析和染色体微阵列技术 (CMA)。高通量测序检测技术有下一代测序技术 (NGS) 以及长读长测序技术。在检测染色体碎裂化技术上, 长读长测序技术具有更大的优势。它不仅识别染色体碎裂化上的复杂重排, 准确检测出断点, 对破碎的碎片进行排序和定向, 还能检测平衡染色体重排, 弥补了短读长测序和常规检测技术上的缺陷。

关键词: 染色体碎裂化; 结构变异; 肿瘤耐药; 长读长测序; 纳米孔基因测序

184. Therapeutic Targeting of CDK12/CDK13 in Epithelial Ovarian Cancer

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Novel treatment options for epithelial ovarian cancer are urgently needed to improve patient outcome.

Cyclin-dependent kinases 12 and 13 (CDK12 and CDK13) play critical roles in the regulation of gene transcription. However, the absence of oral CDK12 and CDK13 inhibitors has hindered the ability to investigate the consequences of their inhibition in healthy cells and cancer cells. Here, we report an oral CDK12 and CDK13 covalent inhibitor, ZSQ836. Coincident with transcriptional perturbation, ZSQ836 dramatically induced apoptotic cell death. Knockout of CCNK or both CDK12 and CDK13 decreases proliferation of ovarian cancer cells in vitro and tumor growth in vivo. Mechanistically, inhibition or loss of CDK12/CDK13 suppresses the expression of core DNA damage response proteins. This provokes a phenotype that results in deficiencies in DNA damage repair, promoting synergy with DNA-damaging chemotherapy and PARP inhibitors. We also find single inhibition of CDK12 or CDK13 induced transcriptional responses associated with cellular growth signaling pathways and/or DNA damage, with minimal effects on cell viability. In contrast, dual kinase inhibition potently induced cell death, which was associated with extensive genome-wide transcriptional changes. At the molecular level, dual kinase inhibition resulted in the loss of POLII CTD phosphorylation and greatly reduced POLII elongation rates and processivity. These data define substantial redundancy between CDK12 and CDK13 and identify both as fundamental regulators of global POLII processivity and transcription elongation.

Key words: ovarian cancer; target therapy; CDK12

185. miR-525-5p regulates radio sensitivity of gastric cancer by targeting RECQL5

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Objective: To investigate the effect and mechanism of miR-525-5p on the sensitivity of gastric cancer cells to radiation exposure.

Methods: qRT-PCR was used to detect the expression of miR-525-5p mRNA in human gastric cancer cell line MKN45, MGC803, SGC7901 and non-malignant gastric epithelial GES1; miR-NC group, the miR-525-5p group, si-NC group, si-RECQL5 group, miR-525-5p+pcDNA group, miR-525-5p+pcDNA-RECQL5 group were all transfected into MKN45 cells by liposome; the protein expression of RECQ protein-like 5 in cells was detected by Western blot; the apoptosis was detected by flow cytometry; the fluorescence activity of cells was detected by double luciferase reporter gene assay; the colony formation assay detects the survival fraction of the cells.

Results: Compared with non-malignant gastric epithelial cells GES1, the expression of miR-525-5p was significantly decreased and the expression of RECQL5 was significantly increased in human gastric



cancer cells MKN45 , MGC803, and SGC7901($P<0.05$). Overexpression of miR-525-5p or knockdown of RECQL5 can promote the apoptosis of gastric cancer cells MKN45 and enhance the sensitivity to radiation exposure. miR-525-5p inhibits the fluorescence activity of wild-type RECQL5 cells and negatively regulates the expression of RECQL5. Overexpression of RECQL5 reversed the apoptosis promotion and irradiation sensitization of gastric cancer cells by miR-525-5p.

Conclusion: miR-525-5p can promote the apoptosis of gastric cancer cells and enhance the sensitivity to radiation exposure. The mechanism is related to the targeting of RECQL5, which will provide a new direction for radiation therapy of gastric cancer.

Key words: miR-525-5p; RECQL5; gastric cancer; radiosensitivity

186. Clinical observation on the treatment of platinum resistant recurrent ovarian cancer with Thalidomide combined with etoposide

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Objectives: To observe the curative effect and toxic side effects of the combination Oral Thalidomide and etoposide in the treatment of platinum resistant recurrent ovarian cancer.

Methods: 29 patients with platinum resistant recurrent ovarian cancer, treated with Thalidomide 100mg, d1-7 per night before bed, d8-14 to 200mg, d15 to 300mg, Etoposide capsule 50 mg/d, d1-14 oral, repeated every 21 days, until the disease progresses or there is an intolerable adverse reaction, every two cycles, the efficacy of the treatment was evaluated and the side effects were recorded by physical examination, imaging examination, and detection of the CA125 level.

Results: The median age of 29 patients with recurrent platinum resistant ovarian cancer was 49 years (28-72 years), and FIGO was divided into stages III-IV, with partial remission (PR) in 7 cases (8.0 %) and disease stabilization (SD) in 50 cases (56.8 %). In 31 cases (35.2 %) of patients with progressive disease (PD) and incomplete remission (CR), the total effective rate was 53.1 %. Midpoint follow-up time 18. In June, the median disease had no progress in survival time (PFS) of 6. In August (0-36 months), the median total survival time was 22. May (9-36 months). Common toxic reactions included nausea and vomiting in 3 cases, leucocyte reduction in 2 cases, rash in 2 cases, drowsiness in 2 cases, and dizziness in 1 case, all of which were I-II degrees.

Conclusion: oral etoposide and Thalidomide are effective in the treatment of platinum resistant recurrent ovarian cancer. The side effects are relatively small, and the patient is well tolerated, which is worthy of clinical application.

Key words: Recurrent epithelial ovarian cancer; Thalidomide; Etoposide; Chemotherapy



187. 不同癌症患者血清的傅里叶变换中红外光谱研究

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目的: 癌症的危害对人们生命健康的影响已广泛引起人们的重视。现阶段癌症诊断所用的取材方法使患者承受的痛苦较大,因此需要建立一种快速,经济,可靠,痛苦小的辅助诊断癌症新方法。

方法: 基于傅里叶变换中红外光谱技术,区分不同癌症人群(乳腺癌,肺癌)的血清光谱。

结果: 不同癌症人群的光谱特征峰在 3357 cm⁻¹,3271 cm⁻¹,2363 cm⁻¹,2343 cm⁻¹,1636 cm⁻¹,655 cm⁻¹,597 cm⁻¹ 波峰处具有显著差异;建立的中红外判别分析模型可将不同癌症人群血清光谱有效区分,所建模型性能评分为 91.3 分,验证集正判率 96.6%,校正集正判率为 100%。

结论: 傅里叶变换中红外光谱技术法具有快速诊断癌症的潜力,值得进一步研究。

关键词: 傅里叶变换中红外光谱; 乳腺癌; 肺癌; 血清; 判别分析

188. 蒿甲醚逆转结直肠癌放化疗抗性的作用及作用机制

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目的: 探讨蒿甲醚逆转结直肠癌放化疗抗性的作用及作用机制。

方法: 1. 体外细胞实验: 将结直肠癌放化疗抵抗(chemoradiotherapy resistance, CRR)细胞 HCT116CRR 和 HT29CRR 分 4 组处理: a. 对照组; b. 蒿甲醚组; c. 放化疗组; d. 蒿甲醚联合放化疗组。CCK8 和克隆形成实验检测各组增殖能力,流式细胞术检测各组的细胞凋亡和周期阻滞情况,Western Bolt 检测各组 EMT 相关蛋白 E-cadherin, N-cadherin, Vimentin, Snail, 凋亡相关蛋白 Bax, Bcl-2 和 Wnt/ β -catenin 信号通路关键因子 β -catenin 及下游靶标 c-Myc, cyclinD1 的表达情况。2. 体内动物实验: 于裸鼠右侧背部皮下注射 HCT116CRR/HT29CRR 细胞构建皮下移植瘤模型,待移植瘤体积长至 100mm³ 左右,将裸鼠随机分 4 组处理: a. 对照组; b. 蒿甲醚组; c. 放化疗组; d. 蒿甲醚联合放化疗组。分组处理后每 3 天测量裸鼠体重,瘤体积,绘制体重,瘤体积增长曲线。治疗结束后(21 天后),脱颈处死裸鼠,取出肿瘤组织,称瘤重,计算各组抑瘤率,流式检测各组肿瘤组织的凋亡情况,Western Bolt 和免疫组化检测各组肿瘤组织 EMT 相关蛋白 E-cadherin, N-cadherin, Vimentin, Snail, 凋亡相关蛋白 Bax, Bcl-2, Wnt/ β -catenin 信号通路关键因子 β -catenin 和下游靶标 c-Myc, cyclinD1 的表达情况。



结果: 在体外细胞实验中, CCK8 和克隆形成结果显示, 蒿甲醚能抑制结直肠癌放化疗抵抗细胞增殖, 蒿甲醚与放化疗联合, 能明显增强放化疗对抗性细胞的增殖抑制 ($P<0.05$)。流式检测细胞凋亡结果显示, 相较对照组, 蒿甲醚组, 放化疗组和蒿甲醚联合放化疗组均增加了 HCT116CRR 和 HT29CRR 细胞的凋亡率, 其中蒿甲醚联合放化疗组的凋亡率最高 ($P<0.05$)。流式检测细胞周期结果显示, 对照组和放化疗组的细胞表现出较高的 G2/M 期阻滞, 蒿甲醚组较对照组, 蒿甲醚联合放化疗组较放化疗组使细胞 G2/M 期比例下降, 逆转了 G2/M 期阻滞 ($P<0.05$)。Western Bolt 检测各组 EMT 相关蛋白结果显示, 相比对照组, 放化疗组间质相关蛋白 N-cadherin, Vimentin 和 Snail 表达升高; 蒿甲醚组和蒿甲醚联合放化疗组上皮标志物 E-cadherin 表达升高, 间质相关蛋白 N-cadherin, Vimentin 和 Snail 表达降低 ($P<0.05$)。Western Bolt 检测凋亡相关蛋白结果显示, 相比对照组, 蒿甲醚组, 单纯放化疗组和蒿甲醚联合放化疗组的促凋亡蛋白 Bax 的表达升高, 抗凋亡蛋白 Bcl-2 的表达降低, 其中蒿甲醚联合放化疗组的作用最明显 ($P<0.05$)。Western Bolt 检测 Wnt/ β -catenin 通路相关蛋白结果显示, 相比对照组, 蒿甲醚组显著降低 β -catenin, c-Myc 和 cyclinD1 的表达 ($P<0.05$); 相比放化疗组, 蒿甲醚联合放化疗组同样显著抑制 β -catenin, c-Myc 和 cyclinD1 的表达 ($P<0.05$)。

在体内动物实验中, 治疗期间各组裸鼠体重无明显差异。HCT116CRR 细胞移植瘤中, 各组抑瘤率分别为: 蒿甲醚组: 29.82%, 放化疗组: 52.73%, 蒿甲醚联合放化疗组: 76.73%; HT29CRR 细胞移植瘤中, 各组抑瘤率分别为: 蒿甲醚组: 29.92%, 放化疗组: 47.94%, 蒿甲醚联合放化疗组: 66.72%。流式检测各组肿瘤组织凋亡结果与体外一致, 相比于对照组, 蒿甲醚组, 放化疗组和蒿甲醚联合放化疗组均增加了肿瘤组织的凋亡率, 其中蒿甲醚联合放化疗组的凋亡率最高 ($P<0.05$)。Western Bolt 和免疫组化检测各组肿瘤组织 EMT, 凋亡, Wnt/ β -catenin 通路相关蛋白表达结果与体外一致。蒿甲醚能促进 E-cadherin 表达, 抑制 N-cadherin, Vimentin 和 Snail 表达, 抑制 EMT; 促进 Bax 表达, 抑制 Bcl-2 表达, 促进凋亡; 抑制 β -catenin, c-Myc 和 cyclinD1 的表达, 失活 Wnt/ β -catenin 通路 ($P<0.05$)。

结论: 蒿甲醚能抑制增殖, 促进凋亡, 逆转 G2/M 期阻滞, 抑制 EMT, 逆转结直肠癌放化疗抗性, 这种作用可能是通过失活 Wnt/ β -catenin 信号通路实现。

关键词: 结直肠癌; 蒿甲醚; 放化疗抵抗; Wnt/ β -catenin 信号通路;

189. 超级增强子调控的转录因子簇通过促进 ADAM10 转录活性 促进鼻咽癌血管拟态和转移的机制

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目的：鼻咽癌是头颈部最常见的恶性肿瘤，极易转移，转移是致使鼻咽癌患者预后不良的主要原因。

尼妥珠单抗是我国第一个用于治疗恶性肿瘤的功能性单抗药物，靶向 EGFR，抑制肿瘤血管的生成，临床上主要用于 III/IV 期鼻咽癌。我们发现，使用尼妥珠单抗的患者在短期内肿瘤可以得到缓解，控制，可往往会发生耐药，缓解期过后肿瘤快速增长，发生远处转移。血管拟态作为一种新型肿瘤血管灌注系统受到我们的关注。本研究探究了血管拟态在尼妥珠单抗耐药及鼻咽癌的转移中的作用，深入探究外泌体对血管拟态形成的影响及具体机制，为指导鼻咽癌临床精准治疗提供理论基础。

方法：使用组织芯片探究了鼻咽癌的分期、转移及预后与肿瘤血管、拟态数量的关系；使用 3D 细胞培养、类器官模型、拟态形成等探究外泌体对拟态形成的影响；通过 DIA 外泌体蛋白定量分析探究不同分期病人血清外泌体中的蛋白含量差异；通过裸鼠鼻咽癌原位转移模型、裸鼠尾静脉转移模型、类器官模型等探究拟态形成与尼妥珠单抗耐药，外泌体中的差异蛋白 ADAM10 与拟态形成、转移间的关系；通过 HIC、H3K27AC CHIP-seq、ATAC-seq、cas9、超级增强子组分分析探究 ADAM10 上游转录因子簇的表观调控关系及绘制染色质三维图谱。

结果：拟态形成促进鼻咽癌的转移，与鼻咽癌的预后相关；有转移的鼻咽癌患者来源外泌体可促进鼻咽癌中拟态的形成；鼻咽癌转移患者来源的外泌体中富含 ADAM10；转录因子 DDX5、E2F1、NR4A1 促进 ADAM10 的转录；鼻咽癌细胞中 DDX5、E2F1 形成染色质环并受超级增强子调控，NR4A1 受超级增强子调控；抑制超级增强子对 DDX5、E2F1、NR4A1 的调控可显著抑制拟态的形成；抑制超级增强子驱动 DDX5、E2F1、NR4A1 同时联合使用尼妥珠单抗显著抑制鼻咽癌的转移。

结论：超级增强子驱动的转录因子 DDX5、E2F1、NR4A1 通过促进 ADAM10 转录活性继而促进血管拟态形成及鼻咽癌转移；抑制超级增强子驱动 DDX5、E2F1、NR4A1 同时联合使用尼妥珠单抗可显著抑制鼻咽癌的转移。

关键词：鼻咽癌；转移；血管拟态；尼妥珠单抗

190. ANKDD1A 在肿瘤中的研究

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ANKDD1A 在神经胶质瘤中被实验证明是一种功能性肿瘤抑制基因，ANKDD1A 在神经胶质瘤中发生特异性甲基化，可以用作潜在的表观遗传生物标志物和可能的治疗靶标。基因组 DNA 甲基化是表观遗传修饰的主要形式，表观遗传和遗传事件都调节着癌症的发生和扩散，而表观遗传修饰被越来越多地确定为癌症研究的重要目标。与此同时，甲基化过高可能会影响转录因子与 DNA 的结合并改变染色质的结构，从而导致抑癌基因沉默，这在癌症的发生和发展中起着重要的作用。本文就 ANKDD1A 在肿瘤中的表达与生物学效应及 DNA 甲基化进行综述。

关键词：ANKDD1A; 表观遗传修饰; DNA 甲基化; 肿瘤

191. Genomic analysis uncovers prognostic biomarkers and immunogenic therapy profiles of neutrophil extracellular traps in glioblastoma

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Background: Neutrophil extracellular traps (NETs) have critical impacts on cell inflammation, growth, invasion, metastasis and therapy resistance. However, the roles of NETs in glioblastoma (GBM) remain largely unknown. This study aimed to explore the NETs expression profiles, relations with tumor microenvironment (TME) and their values in the survival and therapeutic response in patients with GBM.

Methods: Prognostic signature of NETs was constructed according to the NETs-related genes expression. Cox regression was used to identify the risk factors for overall survival (OS). Tumor-infiltrating immune cells (TIICs) in the TME were investigated through single sample gene set enrichment analysis (ssGSEA). Tumor mutation burden (TMB), drug sensitivity and immune checkpoint blockade (ICB) therapy were also analyzed. Finally, the results were validated using external cohort.

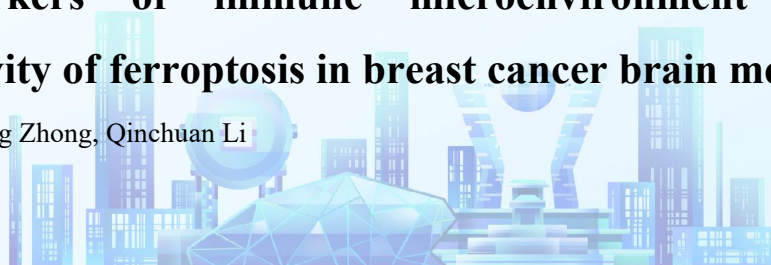
Results: A total of 160 eligible patients with complete information were recruited. Survival analysis showed patients with high-NETs score had poorer OS than those with low-NETs score ($P < 0.001$). Multivariate cox regression demonstrated NETs score was an independent risk factor for OS ($P < 0.05$). High-NETs score was associated with increased infiltrating immune cells, higher immunological activities, distinct TMB and neutrophil-related pathways. Patients with high-NETs score were more sensitive to some targeted and chemotherapeutic drugs, as well as enhanced response to ICB therapy. In addition, potential small molecular drugs that target NETs were identified between the high- and low-NETs score groups. Following an external validation, the NETs score was strongly correlated with OS and TIICs.

Conclusion: NETs may be diversely involved in the biology of GBM, and could serve as a prognostic biomarker for OS. Evaluation of the NETs could help to identify individualized therapeutic agents. New efforts targeting GBM should incorporate the idea that NETs could reshape the TME.

Key words: glioblastoma; neutrophil extracellular traps; tumor microenvironment; immunotherapy; prognosis

192. Biomarkers of immune microenvironment and drug sensitivity of ferroptosis in breast cancer brain metastasis

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Background: The role of ferroptosis in breast cancer brain metastasis (BCBM) is unclear. This study aimed to explore the ferroptosis-related genes (FRG) relations with tumor microenvironment, as well as evaluate their values in predicting survival and drug sensitivity in patients with BCBM.

Methods: Univariate and multivariate cox regression analysis were performed to explore the independent prognostic factors. Consensus cluster principal component analysis (PCA) were used to establish the ferroptosis score. Immunological signatures were analyzed by the single-sample gene set enrichment analysis (ssGSEA). Drug sensitivity was evaluated through the estimated half maximal inhibitory concentration (IC50). Finally, results were validated in external cohorts.

Results: Fourteen significantly different FRG were identified between breast cancer (BC) and BCBM tissues. Survival analysis demonstrated HMOX1, PEBP1, KEAP1 and LPCAT3 were significantly associated with overall survival (OS) and relapse-free survival (RFS) ($P < 0.05$). High ferroptosis was correlated with iron ion homeostasis, iron metabolism, higher stromal cells and immune cells scores. Patients with high- and low-ferroptosis scores were characterized by different drug sensitivities. Following external validation, the ferroptosis had distinct expression profiles between the BC and BCBM, and could serve as biomarkers for OS and drug response.

Conclusions: Our findings suggested that ferroptosis may be involved in the process of BCBM, and ferroptosis could serve as prognostic biomarkers. Evaluation of ferroptosis may deepen our understanding about the tumor microenvironment, and could help clinicians to make individualized therapy.

Key words: ferroptosis; breast cancer; brain metastasis; prognosis; drug sensitivity

193. IRX5 在原发性肝癌患者血清中的表达研究

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目的: 探讨肝细胞肝癌 (HCC) 患者血清中易洛魁家族同源盒基因(Iroquois homeobox Gene ,IRX5) 的表达与临床病理的关系。

方法: 收集 117 例 HCC 患者,12 例 HCC 术后复发患者,11 例转移性肝癌患者,20 例胆管癌患者,52 例肝脏良性疾病患者和 46 例健康体检者 (对照组) 的血清及相应病例,用酶联免疫吸附试验 (ELISA) 测定血清中 IRX5 的表达水平,结合临床资料,对 IRX5 的表达与 HCC 患者临床病理信息的相关性进行分析。

结果: IRX5 在 HCC 组血清中表达量明显高于转移性肝癌组,胆管癌组,肝脏良性疾病组及对照组 ($P < 0.05$), 而 IRX5 在转移性肝癌组,胆管癌组,肝脏良性疾病组及对照组之间的表达水平无统计



学意义 ($P>0.05$)。HCC 组血清中 IRX5 表达量与甲胎蛋白 (AFP) 表达量显著相关 ($P<0.05$)，而与 ALT 表达量无相关 ($P>0.05$)，且 IRX5 的表达量与 AFP 表达量成正相关 (r 值为 0.27, $P<0.05$)。受试者工作特征 (ROC) 曲线显示，IRX5 和 AFP 诊断 HCC 的曲线下面积 (AUC) 分别为 0.738 (95%CI: 0.667~0.808), 0.838 (95%CI: 0.781~0.895)，最佳临界值分别为 27.41ng/ml, 7.55ng/ml，敏感性分别为 73%, 77.4%，特异性分别为 72.7%, 79.5%。

结论：IRX5 在 HCC 组血清中表达显著升高，其表达量与 HCC 肿瘤标志物 AFP 表达量呈正相关，且两者具有相似的诊断效能，提示 IRX5 可能作为 HCC 诊断的候选标志物。

关键词：原发性肝癌；易洛魁族同源盒基因 5；甲胎蛋白

194. 循环肿瘤细胞可作为神经胶质瘤手术预后生物标志物的研究

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研究目的：神经胶质瘤是中枢神经系统最常见的恶性肿瘤，占成人原发性颅内肿瘤的 75%。研究表明，手术联合放化疗后，胶质瘤仍有颅内复发的侵袭性倾向，且复发后的生长速度加快。因此，考虑到胶质瘤预后较差以及进展监测的困难性，有必要建立一种评估胶质瘤患者预后的方法。因此，基于本团队建立的基于肿瘤端粒酶活性的循环肿瘤细胞 (CTCs) 检测方法，本研究探讨其在胶质瘤手术预后评估中的应用价值。

材料与方法：本研究纳入了 106 名神经胶质瘤患者。我们采用基于端粒酶逆转录酶的循环肿瘤细胞检测方法 (TBCD) 捕获胶质瘤患者的循环肿瘤细胞。通过 FlowSigh 和 FISH 验证捕获的循环肿瘤细胞的真实性。并通过患者的随访，将循环肿瘤细胞与预后的相关性进行分析。

结果：结果显示，在检测阈值选取为 1 个 CTC/4 ml 外周血的条件下，神经胶质瘤患者的 CTCs 检测灵敏度为 83%，特异性为 86.5%。通过对入组患者的病理类型进行分组分析，发现 CTCs 普遍存在于胶质瘤患者外周血中，与患者的病理分型或分级无关。随后，我们比较了胶质瘤患者手术前后 CTCs 的变化。值得注意的是，患者术前和术后 CTCs 计数有显著差异 ($P<0.0001$)。进一步，根据 CTCs 检测结果将患者分为 CTC 阳性组 (CTCs >1) 和 CTC 阴性组 (CTCs ≤ 1)，并对术前/术后不同 CTCs 分组患者进行生存分析。术前 CTC 阳性组与 CTC 阴性组织间之间没有明显差异，然而，术后 CTCs 与患者的 DFS 和 OS 显著恶化相关。结果提示，术后 CTCs 可能是一个独立的、显著的预测 DFS 和 OS 的指标。

结论：综上所述，我们提出了一种更易于临床检测和监测胶质瘤患者治疗的 TBCD 方法。该方法能够稳定、简便地检测出广泛病理类型的胶质瘤 CTCs，具有监测胶质瘤患者病情进展、预测预后和评价个体化治疗效果的临床应用潜力。

关键词：循环肿瘤细胞；神经胶质瘤；端粒酶逆转录酶；预后



195. 血清 fPSA 与 PSA 的比值在诊断良恶性前列腺疾病的应用价值研究

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研究目的: 前列腺癌是老年男性的常见疾病,在世界范围内,前列腺癌发病率在男性所有恶性肿瘤中位居第二。人前列腺特异性抗原(PSA)是一种分子量约为 34kD 的丝氨酸蛋白酶。它在人血清中,主要与 α 1-抗胰凝乳蛋白酶(ACT)和 α 2-巨球蛋白(AMG)结合。也可找到痕量的 α 1-抗胰蛋白酶和 α 胰蛋白酶抑制剂与 PSA 结合,其它 PSA 则是以游离形式存在的。PSA 水平是检测前列腺癌发生和转移的重要指标,但血清 PSA 水平升高,也可能是良性前列腺增生或前列腺炎等。基础研究表明,前列腺癌患者的 fPSA 所占 PSA 的百分含量低于良性前列腺增生患者,PSA 为 4-10ng/mL 时, fPSA 与 PSA 的比值在诊断良恶性前列腺疾病中具有重要的价值。本文通过研究良恶性患者血清中 f/t 的值,以期前列腺良恶性疾病的诊断提供一定的依据。

材料与方法: 收集医院正常男性血清 95 例,前列腺增生患者血清 57 例,前列腺炎患者血清 55 例,前列腺癌患者血清 48 例,采用试剂:郑州安图生物工程股份有限公司的前列腺特异性抗原检测试剂盒(磁微粒化学发光法),游离前列腺特异性抗原检测试剂盒(磁微粒化学发光法);仪器:全自动磁微粒化学发光仪 AutoLumo A2000 Plus。

结果: 正常男性血清 PSA 浓度值约为 1.03 ± 0.05 ng/mL;对 PSA 为 4-10ng/mL 的样本进行统计:前列腺增生患者血清 PSA 浓度值约为 8.65 ± 0.51 ng/mL,血清 fPSA 浓度值约为 1.61 ± 0.07 ng/mL, f/t 约为 18.6%;前列腺炎患者血清 PSA 浓度值约为 5.33 ± 0.35 ng/mL,血清 fPSA 浓度值约为 1.42 ± 0.06 ng/mL, f/t 约为 26.6%;前列腺癌患者血清 PSA 浓度值约为 9.17 ± 0.64 ng/mL,血清 fPSA 浓度值约为 0.74 ± 0.03 ng/mL, f/t 约为 8.1%。

结论: 前列腺良恶性疾病均会引起 PSA 升高;PSA 为 4-10ng/mL 时,前列腺癌的 fPSA 与 PSA 的比值水平明显低于良性前列腺增生或前列腺炎,为前列腺良恶性疾病的诊断提供一定的依据。

关键词: PSA; fPSA; f/t; 前列腺良恶性疾病

196. 前列腺癌相关标志物研究进展

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研究目的: 前列腺癌是指源于前列腺上皮的恶性肿瘤。在欧美国家,其发病率已连续多年居男性恶性肿瘤发病率首位,死亡率居第二位,仅次于肺癌。随着我国人口老龄化及饮食结构的改变,



前列腺癌发病率也呈逐年上升趋势，已成为我国男性发病率增长速度最快的恶性肿瘤。为了对前列腺癌进行更精准的早期诊断，很有必要探寻敏感度更高,特异性更好的标志物。本文将汇总近几年发表的前列腺癌早期诊断相关标志物文献，为前列腺癌筛查工作提供参考。

材料与方法：汇总近几年发表的前列腺癌早期诊断相关标志物文献，为前列腺癌早期诊断和筛查工作提供参考。

结果：PSA：第一个被 FDA 批准的用于早期诊断肿瘤的标志物，目前已广泛用于前列腺癌的筛查，早期诊断及肿瘤监测；fPSA：PSA 水平在 4~10ng/mL 时，fPSA/tPSA 比值来辅助鉴别前列腺癌和良性增生，fPSA 的百分比低，提示患前列腺癌的可能性较高；PCA3：目前最具特异性的前列腺癌标志物，不受年龄,前列腺体积以及其他前列腺疾病如前列腺炎的影响，可通过检测尿液 PCA3 水平来预测前列腺癌；p2PSA 与前列腺健康指数（PHI）：p2PSA 在外周前列腺癌组织中显著升高，且对于前列腺癌患者，血清 p2PSA 也会出现特异性升高。 $PHI=(p2PSA/fPSA) \times tPSA$ ，直观地说，有更高总 PSA 和 p2PSA 而有较低游离 PSA 的男性更可能患临床意义上的前列腺癌；早期 PSA(early PSA, EPCA)：本质是核基质蛋白，其决定了细胞核的形态和 DNA 的高级结构。前列腺穿刺活检为阴性而 EPCA 表达为阳性的 PSA 低水平异常者可能会在 5~10 年被最终诊断为 PCa，尤其是病理诊断为高级别上皮内瘤的患者，故其有望成为一种真正能够早期诊断 PCa 的肿瘤标志物；甲酰基辅酶 A 消旋酶(AMACR)：一种细胞质内蛋白，是当前仅有的确认支持 PCa 病理解释的组织学标志物，可辅助用于 PCa 的筛查，提高 PCa 的早期诊断率；前列腺特异膜抗原(PSMA)：在 PCa 淋巴结转移灶,骨转移灶中亦呈阳性表达，其表达与肿瘤恶性程度呈正相关，在 PCa 诊断,分期,预后以及将 PSMA 作为靶向角蛋白进行免疫导向治疗中具有广阔前景；TMPRSS2-ERG 融合基因：50%的前列腺癌切除标本中被检测到，在尿液中亦可检测到，因此可将其作为前列腺癌早期诊断的特异性分子标志物。

结论：前列腺癌相关标志物具有早期诊断和预测 PCa 的作用，但也各有缺点，所以联合检测是今后 PCa 早期诊断的一个必然发展方向，不仅可以辅助解决对 PSA 低水平异常患者临床处理的困扰，更重要的是可以明显提高诊断准确率，可逐步获得临床推广。

关键词：前列腺癌；前列腺癌标志物

197. CYS1 Promotes Peritoneal Metastasis via Inhibiting the Formation of E-cadherin/ β -catenin Complex by Binding PHB2 in Gastric Cancer

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Background: Peritoneum is the most common metastatic site in advanced gastric cancer (GC), which shortens the survival of GC patients and lacks effective treatment. It is of great significance for early diagnosis of peritoneal metastasis and looking for new treatment strategies that screening the key oncogenes in gastric cancer peritoneal metastasis and clarifying their novel mechanisms.

Purpose: This study aims to explore the ability of prognostic prediction of CYS1 in GC and clarify the underlying mechanisms of CYS1 in facilitating peritoneal metastasis (PM) in GC.

Methods: The Cancer Genome Atlas (TCGA) and Gene Expression Omnibus (GEO) databases were used to analyze PM-related genes and the association between CYS1 expression and prognosis in GC. Immunohistochemistry was performed to detect the expression of CYS1 in tumor and normal tissues of GC patients. Quantitative real-time polymerase chain reaction and western blots were applied to examine the expression of CYS1 in GC cell lines and expression of genes in downstream pathways. The role of CYS1 on the adhesion between GC cells was explored with the hanging drop assay. The effect of CYS1 on the adhesion between GC cells and peritoneal mesothelial cells (PMC) was performed by the adhesion assay. The role of CYS1 on the migration and invasion of GC cell lines was investigated with the transwell assay. Mass spectrometry (MS) was used to detect the proteins binding with CYS1 in GC cells. GST-pull down assay was carried out to verify the binding motifs in vitro. Nuclear and cytosol fractionation assay and immunofluorescence assay exhibited the distribution of β -catenin. Orthotopic mouse model of GC demonstrated the effect of CYS1 on peritoneal metastasis of GC.

Results: 1. CYS1 is associated with peritoneal metastasis of GC. By using TCGA and GSE62254 datasets, we screened 804 genes related to poor prognosis in GC. Among them, by comparing genes in different metastatic sites, we finally found 59 genes whose expression was higher only in patients with PM. CYS1 ranked third. Correlation analysis showed that high expression of CYS1 was significantly associated with tumor stage and peritoneal dissemination in GSE62254 dataset. IHC assay demonstrated that the expression of CYS1 in tumor tissues of 100 GC patients was dramatically higher than in normal tissues.

2. CYS1 promotes peritoneal metastasis by inhibiting the formation of E-ca/ β -catenin complex. Hanging drop assay showed that CYS1 suppressed the adhesive ability of homogeneous cells. Transwell assay and PMC adhesion assay revealed that CYS1 facilitated the ability of migration, invasion and adhesion in GC cells, suggesting that CYS1 promoted the process of PM in GC. Besides, intraperitoneal metastatic xenograft mouse model verified that CYS1 promoted PM in vivo. For in-depth mechanism, we found that CYS1 accelerated the degradation of E-ca by inhibiting the formation of E-ca/ β -catenin complex which is an important compound in the formation of adherent junction.

3. CYS1 inhibits adherent junction through competitively combining β -catenin with E-cadherin via PHB2. Results of mass spectrometry demonstrated that PHB2 had the highest affinity with CYS1. Co-immunoprecipitation (Co-IP) assay verified PHB2 could simultaneously interact with CYS1 and β -

catenin. In addition, Co-IP assay further demonstrated that knockdown of CYS1 increased the interaction between E-ca and β -catenin but decreased the interaction of β -catenin and PHB2, β -catenin and CYS1. Further experiments in vivo and in vitro (hanging drop assay, transwell assay) all showed that knockdown of PHB2 could reverse the phenomenon resulting from over-expression CYS1. Moreover, GST-pull down assay indicated that CYS1 and PHB2 bound β -catenin at the same domains as E-ca.

4. CYS1-PHB2 complex promotes nuclear accumulation of β -catenin and the expression of target genes. By performing nuclear and cytosol fractionation and immunofluorescence assays, we found knockdown of CYS1 increased the accumulation of β -catenin in the cytoplasm and reduced the amount of β -catenin in the nucleus meanwhile. The expression of metastasis-related target genes of β -catenin, such as MMP2, MMP7, MMP9 and CD44 all decreased along with downregulation of CYS1. Further, we constructed two plasmids carrying mutant sites at nuclear localization sequence (NLS) of CYS1 and PHB2, respectively. Consistently, the accumulation of β -catenin in the nucleus was significantly reduced both in cells carrying mutant CYS1 and PHB2 comparing cells carrying wild plasmid.

Conclusion: The expression of CYS1 is higher in tumor tissues and associated with peritoneal metastasis in GC. CYS1 binds β -catenin competing against E-ca via capturing PHB2 in cytoplasm, leading to the depolymerization of E-ca/ β -catenin consequently. CYS1-PHB2 facilitates nuclear translocation of β -catenin to activate the target genes, MMP2, MMP7, MMP9 and CD44 to promote PM in GC.

Key words: CYS1; gastric cancer; E-ca/ β -catenin; PHB2; peritoneal metastasis

198. 单一蛋白糖组变化与肺癌预后

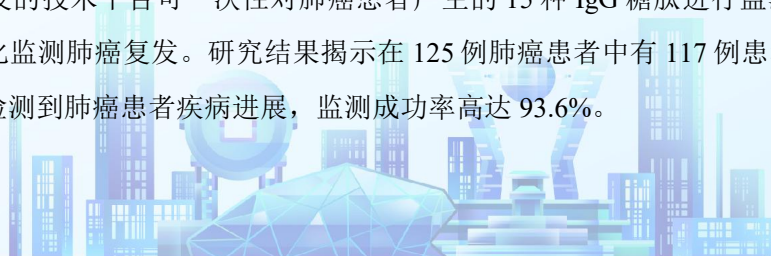
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目的: 肺癌是世界范围内死亡率最高的恶性肿瘤, 预后不良, 严重危害患者生命健康, 尽早监测到肺癌患者的疾病进展至关重要。在肺癌患者疾病进展过程中, 伴随着肿瘤细胞和免疫系统的博弈。其中, 免疫球蛋白 G (IgG) 是免疫系统的关键糖蛋白, 其糖基化修饰变化反映患者抗炎活性、免疫能力和生理病理状态。本研究旨在探究肺癌患者 IgG 糖肽变化与疾病进展的关系, 为肺癌预后评估提供一新型的策略。

方法: 本研究从肺癌患者随访血清中分离出 IgG, 采用高分辨基质辅助激光解吸电离-傅里叶变换离子回旋共振质谱技术对 IgG 的糖基化修饰进行定性和定量分析, 绘制糖肽-时间变化曲线, 建立个体化的 IgG 糖肽变化与肺癌进展的模型。

结果: 本研究研发的技术平台可一次性对肺癌患者产生的 15 种 IgG 糖肽进行监测, 实现一种技术平台可个体化监测肺癌复发。研究结果揭示在 125 例肺癌患者中有 117 例患者可在临床影像学发现复发前检测到肺癌患者疾病进展, 监测成功率高达 93.6%。



结论： IgG 糖基化修饰是肺癌患者疾病进展早期监测的潜在个体化生物标志物， 为可为患者分层，精准医疗,治疗方案选择,预后评估提供新的判别依据。

关键词： 蛋白质糖基化修饰；肺癌预后

199. 免疫炎症相关蛋白复合物谱与肺癌预后

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目的： 血液中免疫炎症相关蛋白复合物 (immunoinflammation-related protein complexes, IIRPCs) 与疾病状态密切相关，本研究旨在通过血液中 IIRPCs 表达水平的变化建立一种监测肺癌疾病进展的新方法。

方法： 本研究对 113 例肺癌患者血液样本中的 IIRPCs 进行凝胶分离，并对其进行相对定量分析。通过对不同病理状态下患者的复合物表达水平差异进行统计分析，探究复合物表达水平变化与肺癌患者疾病进展之间的相关性，建立基于 IIRPCs 的监测肺癌疾病进展的新方法。

结果： 在 113 例肺癌患者中，根据各随访时间点 IIRPCs 表达水平相对于基线表达水平变化的情况，可对 108 例肺癌患者的疾病进展作出预警，其成功率为 95.6%。

结论： IIRPCs 可作为肺癌患者疾病进展早期预警的个体化标志物。

关键词： 免疫炎症相关蛋白复合物；肺癌；预后

200. Heat Shock Protein 90 Triggers Multi-Drug Resistance of Ovarian Cancer via AKT/GSK3 β / β -Catenin Signaling

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Ovarian cancer is the most lethal gynaecologic tumor, with which multi-drug resistance as the major therapeutic hindrance. Heat shock protein 90 (Hsp90) has been involved in cancer malignant behaviors. However, its role and mechanism in multi-drug resistance of ovarian cancer remains poorly understood. Our results demonstrated that Hsp90 was overexpressed in multi-drug resistant ovarian cancer cells. Hsp90 downregulation by shHsp90 or inhibitor BIIB021 increased the sensitivity of multi-drug resistant ovarian cancer cells to paclitaxel and cisplatin, and augmented the drugs-induced apoptosis. Hsp90 positively regulated the expressions of multi-drug resistance protein 1 (P-gp/MDR1), breast cancer resistance protein (BCRP), Survivin and Bcl-2 expressions closely associated with multi-drug resistance. Moreover, overexpression of Hsp90 promoted β -catenin accumulation, while Hsp90 downregulation decreased the accumulation, nuclear translocation and transcriptional activity of β -

catenin. We also identified that β -catenin was responsible for Hsp90-mediated expressions of P-gp, BCRP, Survivin, and Bcl-2. Furthermore, Hsp90 enhanced the AKT/GSK3 β signaling, and AKT signaling played a critical role in Hsp90-induced accumulation and transcriptional activity of β -catenin, as well as multi-drug resistance to paclitaxel and cisplatin. In conclusion, Hsp90 enhanced the AKT/GSK3 β / β -catenin signaling to induce multi-drug resistance of ovarian cancer. Suppressing Hsp90 chemosensitized multi-drug resistant ovarian cancer cells via impairing the AKT/GSK3 β / β -catenin signaling, providing a promising therapeutic strategy for a successful treatment of ovarian cancer.

Key words: multi-drug resistance; heat shock protein 90; ovarian cancer; β -catenin; chemotherapy

201. FAP α 酶激活式前药 Z-GP-DAVLBH 通过调控 Axl 信号通路抑制骨肉瘤细胞的生长和肺转移

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研究目的: 骨肉瘤是一种具有高度增殖性和侵袭性,肺转移发生率高,预后差的骨肿瘤。化疗是骨肉瘤的主要治疗方法之一。目前,尚无批准用于骨肉瘤治疗的分子靶向药物,尤其是对肺转移骨肉瘤有效的药物。据报道,成纤维细胞活化蛋白 α (FAP α)在骨肉瘤中表达上调,并且与骨肉瘤的进展和转移密切相关,表明 FAP α 靶向药物可能是一种有前景的骨肉瘤治疗策略。前期研究表明, FAP α 酶激活的长春碱前药 Z-GP-DAVLBH 在多种异种移植模型中显示出有效的抗肿瘤作用。然而, Z-GP-DAVLBH 对骨肉瘤的作用及其机制尚不清楚。因此,我们进一步研究了 Z-GP-DAVLBH 对 FAP α 阳性骨肉瘤细胞恶性行为的影响及机制,为开发治疗骨肉瘤的新药提供理论依据。

材料与方法: 1. 研究骨肉瘤细胞 FAP α 的表达情况及 Z-GP-DAVLBH 在骨肉瘤细胞中的水解效率:

Western blotting 检测骨肉瘤细胞 FAP α 的蛋白表达水平。使用 UPLC-MS 检测 Z-GP-DAVLBH 处理后细胞上清中母药 DAVLBH 的浓度。2. 研究 Z-GP-DAVLBH 对骨肉瘤细胞生长的影响: 采用 MTT 实验与克隆形成实验检测 Z-GP-DAVLBH 对骨肉瘤细胞存活和增殖的影响。流式检测 Z-GP-DAVLBH 对细胞周期,细胞凋亡以及细胞线粒体膜电位的影响。3. 研究 Z-GP-DAVLBH 对骨肉瘤细胞粘附和运动的影响: 采用纤维蛋白粘附实验,Transwell 迁移及侵袭性实验来检测 Z-GP-DAVLBH 对骨肉瘤细胞粘附与运动能力的影响。4. 研究 Z-GP-DAVLBH 对骨肉瘤细胞 EMT 过程的影响: 采用 Western blotting 实验,RT-PCR 实验及免疫荧光实验检测 Z-GP-DAVLBH 对骨肉瘤细胞上皮细胞标志物 (E-cadherin,ZO-1) 和间质细胞标志物 (N-cadherin,Vimentin) 的影响。5. 研究 Z-GP-DAVLBH 对 Axl/Akt/GSK-3 β / β -catenin 信号通路的影响: Western blotting 实验检测 Z-GP-DAVLBH 处理对骨肉瘤细胞 Axl 信号通路相关蛋白表达水

平的影响。6. 研究 Axl 在 Z-GP-DAVLBH 抑制骨肉瘤的生长和转移中发挥的作用：敲除和过表达 Axl 后，Western blotting 实验检测 Axl/Akt/GSK-3 β / β -catenin 通路及 EMT 相关蛋白变化的情况，Transwell 迁移和侵袭实验检测骨肉瘤细胞的运动能力的变化，而 MTT 实验和流式检测骨肉瘤细胞存活和凋亡的变化。7. 体内研究 Z-GP-DAVLBH 对骨肉瘤生长和转移的影响：构建人骨肉瘤 SJSA-1 和 143B 原位模型，使用 Z-GP-DAVLBH 治疗后，记录裸鼠体重及肿瘤径径的变化情况。采用 H&E 染色检测 143B 肿瘤肺转移灶数量和面积，IF 和 IHC 实验检测肿瘤组织中 Ki67, Cleaved caspase 3, p-Histone H3, Axl 信号通路和 EMT 相关蛋白的变化情况。

研究结果：1. Z-GP-DAVLBH 能被 FAP α 阳性的骨肉瘤细胞水解，并呈时间、剂量依赖性地抑制 SJSA-1 和 143B 细胞的存活和增殖，诱导骨肉瘤细胞周期阻滞于 G2/M 期。2. Z-GP-DAVLBH 能降低骨肉瘤细胞的线粒体膜电位和诱导细胞凋亡。3. Z-GP-DAVLBH 能明显减少粘附到纤维蛋白的细胞数量，也能显著抑制细胞的迁移和侵袭能力。4. Z-GP-DAVLBH 能抑制骨肉瘤细胞的 EMT 过程。

5. Z-GP-DAVLBH 抑制骨肉瘤细胞的 Axl/Akt/GSK-3 β / β -catenin 信号通路。敲除 Axl 能增强 Z-GP-DAVLBH 抑制骨肉瘤细胞存活、迁移、侵袭能力、EMT 和 Axl/Akt/GSK-3 β / β -catenin 通路的作用。而过表达 Axl 则能降低 Z-GP-DAVLBH 对骨肉瘤细胞存活、迁移、侵袭能力、EMT 和 Axl/Akt/GSK-3 β / β -catenin 通路的抑制作用。6. Z-GP-DAVLBH 在体内能显著抑制 SJSA-1 和 143B 原位瘤的生长，抑制 Ki67 和 p-Histone H3 的表达，增加 Cleaved caspase 3 的阳性率。同时，Z-GP-DAVLBH 还能减少 143B 肺转移灶的数量和面积，增加 E-cadherin 和 ZO-1 的表达而减少 Vimentin 和 ZEB1 的表达。

结论：总之，我们的研究表明，Z-GP-DAVLBH 在体外和体内对骨肉瘤细胞具有显著的抗增殖和抗转移作用。Z-GP-DAVLBH 通过抑制 Axl/Akt/GSK-3 β / β -catenin 通路来抑制骨肉瘤细胞的生长、EMT 和肺转移。我们的研究结果揭示了 Z-GP-DAVLBH 抗肿瘤活性的潜在机制，并证明 Z-GP-DAVLBH 用于治疗肺转移性骨肉瘤患者的临床试验是可行的。

关键词：Osteosarcoma; Fibroblast activation protein alpha; Growth; Pulmonary metastasis; Vinblastine prodrug; Axl; β -catenin.

202. 血清转铁蛋白复合物与肝病之间关系研究

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目的：转铁蛋白主要由肝脏合成，其在血清中的水平可以反映肝脏的受损程度和炎症程度。本研究旨在比较不同肝病患者血清转铁蛋白水平的差异，评估血清转铁蛋白作为肝癌临床诊断标志物的应用潜力。



方法：本研究对 501 例肝病患者（分为肝炎组、肝硬化组和肝癌组）和 240 例健康者（对照组）的血清样本中的转铁蛋白进行分离和定量。采用统计学方法对各组血清转铁蛋白水平进行显著性差异分析和 ROC 曲线分析。

结果：与健康者相比，肝病患者的血清转铁蛋白水平均显著下降。在三组肝病患者中，肝炎组、肝硬化组和肝癌组的血清转铁蛋白水平依次降低。ROC 曲线分析结果表明，血清转铁蛋白不仅可以区分健康者和肝病患者，而且可以区分良性肝病患者和肝癌患者。

结论：血清转铁蛋白可作为肝癌诊断的潜在标志物。

关键词：转铁蛋白；肝部疾病；蛋白质复合物

203. 蛋白糖基化修饰与肺癌预后

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目的：肺癌是世界范围内死亡率最高的恶性肿瘤，预后不良，严重危害患者生命健康，尽早监测到肺癌患者的疾病进展至关重要。在肺癌患者疾病进展过程中，伴随着肿瘤细胞和免疫系统的博弈。其中，免疫球蛋白 G (IgG) 是免疫系统的关键糖蛋白，其糖基化修饰变化反映患者抗炎活性、免疫能力和生理病理状态。本研究旨在探究肺癌患者 IgG 糖肽变化与疾病进展的关系，为肺癌预后评估提供一新型的策略。

方法：本研究从 125 例肺癌患者随访血清中分离出 IgG，采用高分辨基质辅助激光解吸电离-傅里叶变换离子回旋共振质谱技术对 IgG 的糖基化修饰进行定性和定量分析，绘制糖肽-时间变化曲线，建立个体化的 IgG 糖肽变化与肺癌进展的模型。

结果：本研究研发的技术平台可一次性对肺癌患者产生的 15 种 IgG 糖肽进行监测，实现一种技术平台可个体化监测肺癌复发。研究结果揭示在 125 例肺癌患者中有 117 例患者可在临床影像学发现复发前检测到肺癌患者疾病进展，监测成功率高达 93.6%。

结论：IgG 糖基化修饰是肺癌患者疾病进展早期监测的潜在个体化生物标志物，可为患者分层、精准医疗、治疗方案选择、预后评估提供新的判别依据。

关键词：蛋白质糖基化修饰；肺癌预后

204. JMJD 家族成员在胃腺癌中表达和预后的综合分析

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目的：JMJD 家族是一组表观遗传调控基因，参与多种癌症的发生发展。然而，JMJD1B、JMJD1C、JMJD2D、JMJD4、JMJD5、JARID2、HSPBAP1 和 TYW5 在胃腺癌中的作用尚未有

人研究。在这项研究中，我们调查了 JMJD1B, JMJD1C, JMJD2D, JMJD4, JMJD5, JARID2, HSPBAP1 和 TYW5 在胃腺癌患者中的表达和对预后的影响。

方法：使用免疫组织化学染色和 UALCAN, GEPIA, Kaplan-Meier Plotter 在线工具检测 JMJD1B, JMJD1C, JMJD2D, JMJD4, JMJD5, JARID2, HSPBAP1 和 TYW5 在胃腺癌中的表达，对病理特征的影响和对预后的影响。

结果：我们发现 JMJD1B, JMJD1C, JMJD2D, JMJD4, JARID2, HSPBAP1 和 TYW5 在胃腺癌中高表达，JMJD5 在胃腺癌中低表达。此外，这些基因的表达与肿瘤分期和分级具有相关性。生存分析表明，JMJD1C, JMJD2D, JMJD4, JARID2, HSPBAP1 和 TYW5 基因的高表达与胃腺癌患者低生存率相关，JMJD1B 和 JMJD5 基因的高表达与高生存率相关。

结论：这些发现表明 JMJD1B, JMJD1C, JMJD2D, JMJD4, JMJD5, JARID2, HSPBAP1 和 TYW5 可以作为胃腺癌患者的潜在治疗靶点和新型生物标志物。

关键词：JMJD 家族；胃腺癌；预后

205. 应用生物信息学技术预测三阴乳腺癌特异表达基因通过影响 CD8⁺T 细胞对肿瘤免疫微环境免疫状态的影响

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目的：乳腺癌具有多种生物学行为,临床病理特点和分子特征各不相同的差异。根据临床诊断标记的差异将乳腺癌分为不同的分子亚型，包括管腔 A 型(luminal subtype A),管腔 B / C 型(luminal subtype B / C),正常乳腺样型(normal breast— like subtype),HER-2 过表达型(HER-2 over— expression subtype)以及基底细胞样型(basal—like subtype)，不同亚型乳腺癌的临床特点,治疗反应性和预后均存在明显差异。且 CD8⁺T 细胞是免疫微环境中主要的杀伤性免疫细胞，同时也是 ICB 治疗的主要靶点。本课题旨在研究三阴乳腺癌特异表达基因通过影响 CD8⁺T 细胞对乳腺癌肿瘤免疫微环境免疫状态的影响。

方法：选取 TCGA 数据库中 BRCA 患者 mRNA 表达数据并汇总，以 CD8⁺T 细胞表面特异标志物（CD8A, CD8B, GZMA, GZMB, PRF1），获得可能影响 CD8⁺T 细胞浸润程度的差异基因。根据临床数据将病理分为三阴组和非三阴组，筛选差异基因，将两组差异基因取交集做 Venn 图，获得 168 个共同差异基因。通过 STRING 蛋白互作网络探索共同差异基因中的核心基因，而后进行单因素 COX 分析，获得 8 个预后核心基因（ART3, PSAT1, BPI, IL12RB2, HAPLN3, STAC, BCL11A, GABRP），推测可能这些基因在三阴乳腺癌免疫微环境中特异性影响 CD8⁺T 细胞的状态，继而造成了三阴乳腺癌治疗困难的情况。



结论：我们推测三阴乳腺癌通过此类基因对 CD8+T 细胞产生影响使肿瘤免疫微环境的免疫状态向免疫抑制方向转变，同时提出了三阴乳腺癌可能通过此类因子影响 ICBs 治疗效果的一些猜想。

关键词：三阴乳腺癌；生信分析；CD8+T 细胞；肿瘤免疫微环境

206. 影响胃癌患者预后和耐药过程的免疫相关基因分析

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背景：肿瘤微环境是由细胞外基质，细胞因子，趋化因子和一些非肿瘤细胞构成的复杂系统。而肿瘤浸润免疫细胞是肿瘤微环境中的重要组成部分，与促进或抑制肿瘤的生长关系密切。然而，由免疫相关基因（IRGs）所介导的肿瘤免疫微环境的变化与胃癌的发生发展之间关系尚不清楚。

方法：我们从癌症基因组图谱（TCGA）数据库中共获取了 368 例胃癌样本的 mRNA 表达数据。我们首先筛选在胃癌组织和正常组织中表达具有差异的免疫相关基因。使用 COX 回归和随机生存森林 (RSF) 算法筛选出预后相关的免疫基因并构建胃癌的生存风险模型。此外，我们还使用 GEO 数据库获取了与胃癌耐药相关的转录组数据集（GSE58118 和 GSE77346），筛选出与耐药相关的差异表达基因。然后，我们通过 TIMER 网站分析了差异基因表达与胃癌免疫细胞浸润之间的相关性。最后，使用 cBioportal 数据库分析耐药基因突变状态和存活率之间的相关性。

结果：通过对胃癌样本和正常样本的比较，我们共筛选出 155 个差异表达的免疫相关基因。在这些差异基因中，我们发现 4 个免疫基因（NRP1,PPP3R1,IL17RA 和 FGF16）与胃癌的生存密切相关。我们利用筛选的预后基因构建了胃癌的风险模型，根据风险评分的最佳截断值，将患者分为高危组和低危组。在训练集（ $P < 0.0001$ ）和测试集（ $P = 0.0021$ ）中，高风险组患者的 OS 明显低于低风险组患者。此外，我们筛选出 5 个可能参与胃癌耐药过程的免疫基因（LGR6,DKK1,TNFRSF1B,NRP1 和 CXCR4）。生存分析显示，耐药基因突变患者的 OS（ $P = 0.0459$ ）和 DFS（ $P < 0.001$ ）明显短于野生型的患者。

结论：在本研究中，我们通过生物信息学的方法筛选出了 4 个与胃癌预后相关的免疫基因，并构建了胃癌风险模型。我们还同时筛选出 5 个与胃癌耐药相关的免疫基因。本研究为更好的理解胃癌肿瘤免疫微环境的机制和做够提供了新的理念和思路，对于未来的肿瘤免疫相关的研究和免疫治疗的发展也具有一定的参考价值。

关键词：胃癌；免疫相关基因；预后；耐药

207. RNA 结合蛋白 TTP 在肿瘤中相关研究的进展

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RNA 结合蛋白三四脯氨酸（TTP）是具有串联锌指结构域的功能蛋白，在其结构域内存在磷酸化位点可以进行磷酸化反应。TTP 可以直接结合到富含腺嘌呤（A）和尿嘧啶（U）核苷酸的短区域，然后促进其衰变或是抑制其翻译，TTP 的缺失会导致严重的炎症综合征。TTP 在细胞的生理和病理中都起到重要的作用，参与调节了细胞的分化、编程、周期、增殖、代谢、肿瘤发生等多种生理病理过程，TTP 在肿瘤和免疫细胞中的紊乱受到越来越多的关注。据报道，TTP 在多种人类癌症中如乳腺癌、膀胱癌等中的缺失与患者的预后不良和生存率低有很密切的关系。TTP 与大量的细胞因子表达有关，通过影响因子的表达起到调控的作用，TTP 可以通过影响细胞周期中的蛋白和结合与破坏关键细胞周期调节剂等途径来影响和控制细胞周期，还可以通过负向调控 PD-L1 mRNA 来调节非小细胞肺癌的细胞自噬，使其出现下调作用。本文阐述 TTP 在人类肿瘤中的各种作用，简单总结 TTP 在几种常见肿瘤中的表达情况，并进一步讨论了 TTP 的缺乏对肿瘤发生以及发展的影响，如促进肿瘤细胞增殖；加速细胞周期；提高细胞抗死亡能力，诱导肿瘤中血管的生成；激活肿瘤细胞的侵袭转移；诱导上皮-间充质转化；解除对细胞能量学的调控。最后，由于 TTP 在肿瘤中的重要作用，本文亦阐述了当前诸多报道关于 TTP 自身表达与肿瘤相关的调控机制，这一认识可能有助于 TTP 成为肿瘤或免疫相关疾病的诊断标志物和可能的治疗靶点。

关键词: TTP；肿瘤代谢；免疫细胞

208. 肿瘤浸润淋巴细胞在非小细胞肺癌中的功能及预后作用

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摘要: 肿瘤浸润淋巴细胞(Tumor-infiltrating lymphocytes, TIL)是位于癌组织和癌间质内以 T 细胞为主的淋巴细胞群，在癌组织和癌间质内形成抗肿瘤的免疫微环境。研究表明肿瘤浸润淋巴细胞在恶性黑色素瘤、乳腺癌等肿瘤的治疗中获得了令人振奋的效果，同时其逐渐作为生物标志物用于预测肿瘤的预后。虽然肿瘤浸润淋巴细胞在多种肿瘤中具有满意的治疗效果及预测预后作用，但肿瘤浸润淋巴细胞在非小细胞肺癌（non-small cell lung cancer, NSCLC）中的治疗效果仍然未获得较大进展，同时其各亚群在非小细胞肺癌中的预后作用仍然存在争议。

关键词: 肿瘤浸润淋巴细胞；非小细胞肺癌；功能；预后

209. UBE3A Promotes Invasion and Metastasis of the Triple Negative Breast Cancer through Regulating Expression and Localization of ANXA2



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Objective: To investigate the mechanism of BUEA3A affects the biological behavior of breast cancer cells through ANXA2.

Methods: Breast cancer tissues and adjacent tissues of 172 patients were collected to investigate relationship between UBE3A and clinicopathological features of breast cancer patients. Biological behavior of MDA-MB-231 cells were detected in vivo and in vitro experiments after knock-down UBE3A expression. Changed genes and proteins were detected by transcriptome sequencing and 2-Directional electrophoresis (2-DE) experiments and protein tandem mass spectrometry before and after UBE3A knock down. ANXA2 expression were detected by WB and ICH after knocking-down UBE3A expression. Subcellular location of ANXA2 were observed by LSCM.

Results: UBE3A was upregulated in breast cancer tissues, as well as in particular pathological tissues, including large-sized tumor, invasive, lymph node metastasis, high clinical stage, HER2-, Ki-67+ and triple negative breast cancer. UBE3A knockdown caused cells S phase arrest, apoptosis and decrease of cell proliferation, invasion and metastasis; In vivo, breast cancer cells' metastasis decreased significantly with UBE3A knock-down. Interestingly, ANXA2 consistently appeared in transcriptome sequencing, gene expression profiling and tandem mass spectrometry by observing 44 genes and 24 proteins. We also identified that UBE3A knockdown in breast cancer induced ANXA2 migration from membrane to cytoplasm, which may benefit for further clarify the mechanism of breast cancer.

Conclusion: In conclusion, our results indicate that UBE3A expression is closely correlated with clinicopathological characteristics of breast cancer and MDA-MB-231 cells' proliferation, invasion and metastasis. UBE3A also regulates expression and subcellular location of ANXA2.

Key words: Breast Cancer; UBE3A; ANXA2; Subcellular location

210. NCAPG is a prognostic biomarker and correlated with immune infiltrates in glioma: A study based on TCGA, GEO and CGGA data

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Background: This study aims to provide a new prognostic biomarker of glioma, and to investigate the molecular mechanisms induced by NCAPG.

Methods: A cohort of 1,131 glioma patients with RNA-seq data from The Cancer Genome Atlas (TCGA project) and Gene Expression Omnibus (GSE4290 and GSE16011 datasets) were analyzed, and the results were well validated in Chinese Glioma Genome Atlas (CGGA project) RNA-seq data of 1,018 gliomas. R language was used as the main tool for statistical analysis and graphical work. The glioma cell lines T98G and LN-229 were selected. Western blotting and qRT-PCR were used to detect the protein and mRNA expression levels, respectively. An CCK-8 assay was applied for the detection of cell proliferation, while cell scratch test was used to detect the healing rates.

Results: NCAPG was highly expressed in glioma tissues with RNA-seq data from TCGA, GEO and CGGA database. Furthermore, the expression of NCAPG could be the independent prognostic factors. With the growth of tumor grade, NCAPG expression increases significantly, and high NCAPG expression was the predictor of poor overall survival in glioma patients ($P < 0.001$). Importantly, when the expression of NCAPG was knockdown, the CCK-8 assay revealed the proliferation of glioma cells (LN-229 and T98G) decreased significantly in contrast to the vector group. In addition, the healing rates of glioma cells (LN-229 and T98G) detected by cell scratch test in RNA-si group was significantly lower than the vector group ($P < 0.001$). Moreover, the expression of NCAPG has a significantly negative relation in NK cells activated from 22 subpopulations of immune cells by using the CIBERSORT algorithm. Specially, the expression of NCAPG have a positive correlation with MHC-I molecules and ADAM17.

Conclusion: The expression of NCAPG is high in glioma, and it can facilitate the proliferation, migration and differentiation of glioma. Meanwhile, NCAPG may inhibit the activation of NK cells by regulating the expression of MHC-I class molecules and ADAM17 in glioma cells, thus forming immune escape.

Key words: NCAPG; glioma; immune infiltrates; NK cells

211. ALDH2 在微管蛋白抑制剂耐药过程中的作用,分子调控机制及化学干预研究

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目的: 紫杉醇 (Paclitaxel, PTX) 作为一种微管蛋白抑制剂, 广泛应用于非小细胞肺癌 (non-small cell lung cancer, NSCLC) 临床治疗, 然而治疗过程中产生的耐药性减弱了其治疗效果。课题组前期发现乙醛脱氢酶 2 (Acetaldehyde dehydrogenase, ALDH2) 表达失调与 PTX 耐药有关, 但



其在 PTX 耐药中的具体角色和表达失调机制还不是很清楚，以及是否通过药理性抑制 ALDH2 或表观调控的方式下调 ALDH2 来逆转 PTX 耐药也亟待阐明。

方法：首先，通过基因微阵列分析，克隆形成实验，Transwell 迁移实验，蛋白免疫印迹实验以及数据库资源等证明 ALDH2 与 PTX 耐药相关，进一步通过基因和药物干预确证 ALDH2 与 PTX 耐药之间的相关性。其次，通过双荧光素酶报告实验，ChIP-sequence 和 ChIP-qPCR 实验揭示 PTX 耐药细胞中 ALDH2 上调受核转录因子 Y 亚基 α (Nuclear transcription factor Y subunit alpha, NFYA) 和常染色质组蛋白赖氨酸甲基转移酶 2 (Euchromatic histone lysine methyltransferase 2, EHMT2) 协同调控。最后，在体内外通过药理性抑制 ALDH2 或表观调控的方式下调 ALDH2，增加 NSCLC/PTX 对 PTX 的敏感性，抑制 PTX 耐药细胞异位荷瘤小鼠肿瘤生长，逆转 PTX 耐药。

结果：1. ALDH2 在肺癌 PTX 耐药过程中的作用及表观调控机制：基因微阵列分析揭示，与亲本细胞相比，PTX 耐药细胞的干性相关通路发生改变。进一步研究发现 PTX 耐药细胞干细胞转录因子表达增强，干性生物学特征显著增强，ALDH 活性显著增高，且发现在 ALDH 亚型中以 ALDH2 表达变化最为明显。进一步研究发现基因或药物干预 ALDH2，PTX 敏感性和肿瘤恶性生物学特性改变。表达调控机制研究发现 EHMT2 和 NFYA 对 ALDH2 的调控具有协同作用。综上所述，ALDH2 与肺癌 PTX 耐药相关，ALDH2 表达水平受到转录因子 NFYA 和表观调控酶 EHMT2 的协同调控。

2. ALDH2 通过激活 RAS/RAF 通路介导紫杉醇耐药：在耐药细胞中稳定敲低 ALDH2，RAS/RAF 通路被抑制，过表达 KRAS 和 RAF1，与重输 ALDH2 作用类似，耐药细胞对 PTX 的敏感性减弱。进一步研究显示，ALDH2 可能通过影响 RAF1 的 E3 泛素连接酶从而稳定 RAF1。

3. 药理性抑制 ALDH2 或通过表观调控的方式下调 ALDH2 逆转肺癌 PTX 耐药：给予 ALDH2 抑制剂异黄酮苷 (Daidzin, DZN) 或双硫仑 (Disulfiram, DSF)，或者给予表观遗传酶 EHMT2 的反向调控酶 JMJD2 的抑制剂 JIB04 下调 ALDH2，同时联用 PTX 增加耐药细胞对 PTX 的敏感性，抑制 NCI-H460/PTX 异位荷瘤小鼠肿瘤生长，逆转 PTX 耐药。

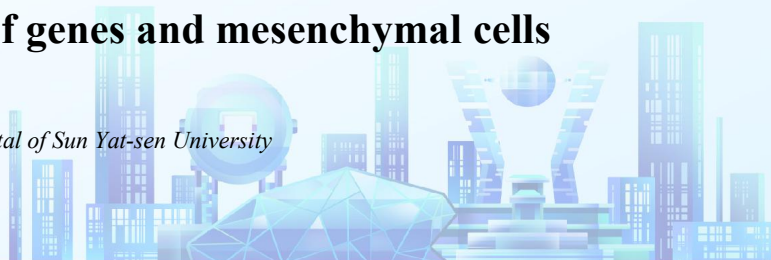
结论：本研究发现 ALDH2 在肺癌耐药细胞中表达失调并参与肺癌耐药进程，并首次揭示表观调控酶/转录因子的协同调控机制对 ALDH2 表达调控的影响。此外，我们还发现小分子化合物可通过多种方式实现对 ALDH2 表达的调控，逆转肺癌耐药。ALDH2 可以作为逆转紫杉醇耐药的一个潜在治疗靶点。

关键词：非小细胞肺癌；紫杉醇耐药；乙醛脱氢酶 2

212. Clinically relevant colorectal cancer subtypes based on the levels of genes and mesenchymal cells

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Aim: Most previous studies focused on subtype identification of colorectal cancer (CRC) based on expressions of genes or immune cells. We aimed to combine gene expression and the composition of immune and stroma cells for subtype identification.

Methods: We estimated composition and density of 64 cell types by xCell, including immune and stroma cell types, and then combined expressions of the top 3000 most variable genes from a total of 20174 genes for CRC subtype identification.

Results: In the training group, we identified 3 clinically relevant subtypes by an ensemble method of similarity network fusion and consensus clustering and their representative genes, immune and stroma cells. Moreover, subtype with poor prognosis had high recurrence rate, higher proportion of stage 3 or 4 patients according to the AJCC system compared with other subtypes. We also confirmed these subtypes and their correlation with clinical characteristics in the validation group. Pathway enrichment analysis revealed that the representative genes of subtype with poor prognosis correlated with extracellular matrix structural constituent, while subtype with good prognosis correlated with Toll-like receptor signaling pathway or chemokine signaling pathway. Moreover, subtype with poor prognosis had high abundance of fibroblasts and endothelial cells; subtype with median prognosis had higher abundance of immune cells, such as CD4⁺ T-cell, Th2 cells and aDC; subtype with good prognosis had higher abundance of NKT.

Conclusion: Our results highlight that combination of the levels of gene, immune and stroma cells could provide more prognostic information for patients with CRC, and different subtype may need targeted treatment approach.

Key words: colorectal cancer; subtype; immune and stroma cells

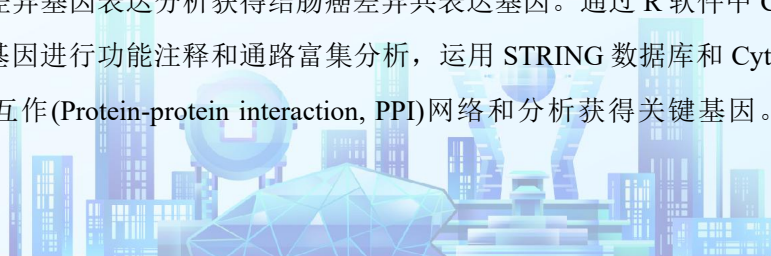
213. 基于 WGCNA 和差异表达分析挖掘结肠癌诊断和预后的关键基因

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目的: 结肠癌是常见的消化系统恶性肿瘤，提高对结肠癌分子机制的认识是提高结肠癌诊断率，预测患者预后和开发新的治疗靶点的关键。本研究旨在基于生物信息学技术分析并结肠癌发生相关的关键基因，并进一步分析其预后意义。

方法: 分别从 TCGA 数据库和 GEO 数据库中的 GSE44076 数据集下载结肠癌及癌旁正常组织的基因表达谱数据。通过加权基因共表达网络分析(Weighted gene co-expression network analysis, WGCNA)和差异基因表达分析获得结肠癌差异共表达基因。通过 R 软件中 Cluster Profiler 包对差异共表达基因进行功能注释和通路富集分析，运用 STRING 数据库和 Cytoscape 软件构建及可视化蛋白互作(Protein-protein interaction, PPI)网络和分析获得关键基因。对关键基因进行



mRNA 水平表达验证, 并分析其生存预后, 筛选出与预后相关的基因。利用 HPA 数据库对预后相关的基因进行蛋白水平表达验证。

结果: 共获得 360 个结肠癌差异共表达基因。功能注释分析显示, 它们主要富集在脂肪分解过程, 离子跨膜运输等生物学过程, 细胞顶端, 刷状缘等细胞组分, 阴离子跨膜转运活性, 脂肪酶活性等分子功能; 通路富集分析显示, 其主要富集在矿物质吸收, 胆汁分泌等通路。在 355 个节点和 561 条边组成的 PPI 网络中, 鉴定出 10 个关键基因(CPT2, ACOX1, CPT1A, HMGCS2, FABP1, PCK1, PPARGC1A, MT1H, MT1G, MT1E)。与正常组织相比, 10 个关键基因在结肠癌组织中的 mRNA 表达水平均下调。生存分析显示, CPT2, HMGCS2 和 PPARGC1A 的低表达与结肠癌患者较差的总生存期相关。HPA 数据库验证显示 CPT2, HMGCS2 和 PPARGC1A 的蛋白表达水平在结肠癌样本中均下调, 与 mRNA 水平一致。

结论: CPT2, HMGCS2 和 PPARGC1A 作为结肠癌发生的关键基因, 与结肠癌患者预后密切相关, 其未来有望成为结肠癌诊断和治疗的潜在生物标志物。

关键词: 结肠癌; WGCNA; 差异表达基因; 生物信息学

214. TFRC 在胶质瘤免疫和临床预后意义的综合分析

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目的: 胶质瘤(glioma)是世界范围内常见的恶性肿瘤之一。铁死亡是一种依赖铁的程序性细胞死亡形式, 具有广泛的化疗潜力。转铁蛋白受体 (TFRC), 也称为 CD71, 是一个重要的膜蛋白调节细胞内铁的转运介导其细胞死亡过程, 并且在许多肿瘤中与生存预后显著相关, 但目前 TFRC 在胶质瘤中的相关文献很少报道, 本研究主要分析 TFRC 在胶质瘤的临床预后和免疫浸润相关情况分析。

方法: 通过使用 GEPIA 数据库分析了 TRRC 的 mRNA 在胶质瘤中的表达情况。使用癌症基因组图谱(TCGA)数据集进行 TFRC 表达与临床病理特征的关联, 并分析了 TFRC 表达对预后的影响。并且通过基因集富集分析(GSEA) TFRC 表达相关通路。用 ssGSEA 进行 TFRC 基因表达与免疫浸润的相关性分析。

结果: 胶质母细胞瘤组织中 mRNA 的表达高于正常组织($P < 0.05$)。TFRC 在胶质瘤中 mRNA 的表达增高与 IDH 突变, 1p/19q 缺失和 WHO 分级显著相关($P < 0.001$)。与 TFRC 低表达的胶质瘤相比, TFRC 高表达的胶质瘤的总生存期(OS), 无进展生存期(PFS)和疾病特异性生存期(DSS)均较差($P < 0.001$)。单因素分析显示, TFRC 表达, WHO 分级, 1p/19q 缺失, IDH 突变和年龄与 OS 显著相关($P < 0.001$)。多因素 Cox 回归分析显示: TFRC 表达($P = 0.011$), WHO 分级($P < 0.001$), IDH 突变

($P < 0.001$), 性别($P = 0.047$)和年龄($P < 0.001$)是影响 OS 的独立预后因素。GSEA 分析表明, TFRC 在 PD1 信号通路, P53 信号通路, JAK-STAT 信号通路, IL17, IL18, NF- κ B 炎症信号通路, FOXM1, FOCAL, DNA 甲基化信号, DNA 损伤通路, G2/M 检查点及细胞周期检查点均有富集($P < 0.05$)。TFRC 与巨噬细胞, 嗜酸性粒细胞, Th2 细胞, 中性粒细胞, T 细胞, CD8 T 细胞, 活化树突状细胞和浆细胞样树突状细胞的浸润程度显著相关($P < 0.001$)。

结论: TFRC 可能是胶质瘤的潜在预后标志物。TFRC 通过炎症反应, 细胞周期, DNA 损失及 DNA 甲基化等机制参与胶质瘤的发生发展。此外, PD1 信号, IL17, IL18, NF- κ B, FOXM1, FOCAL 及 JAK-STAT 信号可能是 TFRC 调控的关键信号通路。TFRC 在胶质瘤中的表达与免疫浸润程度有关。

关键词: 胶质瘤; TFRC; 铁死亡; 免疫浸润; 炎症反应; 临床预后

215. CBLN3 对胶质母细胞瘤细胞增殖, 克隆和迁移的初步研究

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背景: 胶质母细胞瘤 (glioblastoma multidimensional, GBM) 是目前最常见的高侵袭性恶性中枢神经肿瘤。CBLN3 作为 C1q / TNF 超家族的成员之一, 与 TNF 具有结构同源性。在 CGGA 数据库和 R2 数据库发现 CBLN3 在 GBM 中表达较高, 但其作用机制尚未报道。这项研究目的是探索 CBLN3 在 GBM 中的作用。

方法: Western Blot 和 qRT-PCR 检测 CBLN3 在 GBM 细胞中的表达水平; 构建 CBLN3 干扰载体 (shCBLN3#1, shCBLN3#2, shCBLN3#3), 以及阴性对照 shGFP, 使用慢病毒感染细胞, 用 RT-PCR 和 WB 进行干扰验证; 采用细胞计数, MTT, BrdU 以及平板克隆实验, 多角度检测 CBLN3 对 GBM 细胞增值的影响; 使用 Soft Agar 检测 CBLN3 对 GBM 细胞体外成球能力的影响, Transwell 检测 CBLN3 对 GBM 细胞迁移的影响。

结果: Western Blot 和 qRT-PCR 实验结果表明 CBLN3 在正常星形胶质细胞 (SVGP12) 和 4 种 GBM 细胞系 (LN-229, U87-MG, A172, U251-MG) 中普遍表达, 并在 LN-229 和 U87-MG 中表达量相对较高。shCBLN3#2 和 shCBLN3#3 显著降低 GBM 细胞中 CBLN3 的表达水平; MTT, BrdU 及平板克隆实验表明 CBLN3 干扰后 GBM 细胞的生长及增殖受到明显的抑制; Soft Agar 表明在干扰 CBLN3 后 GBM 细胞的体外成球能力得到明显抑制; Transwell 表明 shCBLN3 抑制了 GBM 细胞的迁移能力。

结论: CBLN3 的表达与胶质母细胞瘤患者的预后不良密切相关, 并且 CBLN3 显著促进 GBM 细胞的增殖, 迁移, 侵袭和体外克隆能力。因此, CBLN3 对临床判断以及预后有重要意义, 有望成为肿瘤治疗靶点, 并为后续开发 GBM 靶向药物提供了新的思路。

关键词: CBLN3; GBM; 增殖; 迁移



216. GRTP1 对胃癌细胞增殖,克隆和迁移的初步研究

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背景: 胃癌的有效治疗主要依靠手术切除和化疗, 辅以一定的生物药物治疗, 但其治疗效果并不理想。因此, 探索胃癌的潜在分子机制和制定新的治疗策略显得尤为迫切。GRTP1 (Growth Hormone Regulated TBC protein-1, 生长激素调节 TBC 蛋白 1) 具有 TBC 1 结构域, 是 GTPase 激活蛋白中的一个明显保守的区域, 与胞内转运相关, 在细胞周期和有丝分裂过程中起着重要的作用。R2 数据库显示 GRTP1 与胃癌病人预后显著相关。因此 在这项研究中, 我们将探讨 GRTP1 对人胃癌细胞株 HGC-27 和 MKN-45 增殖能力的影响, 期望为胃癌患者的临床治疗提供新的靶点。

方法: 使用 Western Blot 检测 GRTP1 在胃癌细胞中的表达水平; 构建 GRTP1 干扰载体 (shGRTP1#1, shGRTP1#2, shGRTP1#3), 以及阴性对照 shGFP, 使用慢病毒感染细胞, 用 RT-PCR 和 WB 进行干扰验证; 采用细胞计数, MTT, BrdU 以及平板克隆实验, 多角度检测 GRTP1 对胃癌细胞增值的影响; 使用 Soft Agar 实验检测 GRTP1 对胃癌细胞体外成球能力的影响。

结果: Western Blot 实验结果表明 GRTP1 在胃癌细胞系 HGC-27 和 MKN-45 中高表达; shGRTP1#2 和 shGRTP1#3 显著降低 HGC-27 MKN-45 细胞的增殖能力; MTT, BrdU 及平板克隆实验表明 GRTP1 干扰后 HGC-27 和 MKN-45 细胞的生长及增殖受到明显的抑制; Soft Agar 实验表明在干扰 GRTP1 后 HGC-27 和 MKN-45 的体外成球能力得到明显抑制。

结论: GRTP1 在胃癌细胞中高表达, 具有促癌基因的功能, 干扰 GRTP1 后胃癌细胞的增殖能力和体外成球能力得到明显抑制, 后续研究将会围绕 GRTP1 对胃癌细胞生长的信号调控网络开展, 验证其对整个胃癌致病网络调控作用的分子机制。这对胃癌临床判断以及预后有重要意义, 并为后续开发胃癌靶向药物提供了新的思路。

关键词: GRTP1; 胃癌; 迁移; 增殖

217. Role of exosomal FZD10 in angiogenesis of non-small cell lung cancer

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Guangdong Medical University



Objective: To investigate the expression of FZD10 in non-small cell lung cancer cells (NSCLC) and the effects of FZD10 on the proliferation, migration and invasion of NSCLC cells, and to further explore the role of exosome-derived FZD10 in angiogenesis of NSCLC and the underlying molecular mechanisms.

Methods: Western blot assay and RT-qPCR were performed to analyze the expression of FZD10 in NSCLC cells (95D and H1299) and normal human bronchial epithelial cells (BEAS-2B). FZD10 knockdown later, cell counting kit-8 (CCK8) assay and Transwell migration and invasion assays were used to analyze the roles of FZD10 in proliferation, migration and invasion of NSCLC cells. Exosomes derived from NSCLC cells and FZD10-siRNA transfected NSCLC cells were isolated and identified, and the expression of FZD10 in exosomes were determined by Western blot assay and RT-qPCR. HUVECs were respectively treated with exosomes derived from NSCLC cells or FZD10-siRNA transfected NSCLC cells, then the ability of HUVEC tube formation was analyzed by Angiogenesis Assay in Vitro, and ELISA was performed to determine the concentration of VEGFA and Ang-1 in the conditioned media of HUVECs, and RT-qPCR was used to analyze the mRNA levels of VEGFA and Ang-1 in HUVECs. Moreover, the effects of exosome-derived FZD10 on the activation of PI3K, Erk1/2 and YAP/TAZ signaling pathways in angiogenesis of NSCLC were analyzed by Western blot.

Results: FZD10 was up-regulated in NSCLC cells and FZD10 promoted the proliferation, migration and invasion of NSCLC cells. The isolated exosomes exhibited typical cup-shaped morphology with double-layer membrane under the transmission electron microscope, and the exosome-related markers including CD9, CD81 and TSG101 were enriched in exosomes but no Grp94, indicating that the exosomes were successfully isolated. Moreover, the exosomes derived from NSCLC cells enhanced HUVEC tube formation and the expression of angiogenic factors (VEGFA and Ang-1), but FZD10 knockdown inhibited these effects. Furthermore, exosomal FZD10 knockdown suppressed the activation of PI3K and Erk1/2 signaling pathways, while the YAP/TAZ signaling pathway had no significant change.

Conclusion: FZD10 expression is up-regulated in NSCLC cells, which not only enhances proliferation, migration and invasion of NSCLC cells, but also promotes angiogenesis in vitro through exosome uptake by HUVEC cells. The mechanism may be related to the activation of PI3K and Erk1/2 signaling pathways.

This work was supported by the grants from Guangdong Basic and Applied Basic Research Foundation (Natural Science Foundation of Guangdong Province) (2019A1515011081); “Sail plan” in Guangdong Province to cultivate high-level talents (201635011); Competitive Allocation of Special Funds for Science and Technology Development in Zhanjiang (2018A01041).

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Key words: Exosomes; FZD10; Angiogenesis; NSCLC



218. 5'-tRF-GlyGCC: a tRNA-derived small RNA as a novel biomarker for colorectal cancer diagnosis

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Background: tRNA-derived small RNAs (tDRs), which are widely distributed in human tissues including blood and urine, play an important role in the progression of cancer. However, the expression of tDRs in colorectal cancer (CRC) plasma and their potential diagnostic values have not been systematically explored.

Methods: The expression profiles of tDRs in plasma of CRC and health controls (HCs) are investigated by small RNA sequencing. The level and diagnostic value of 5'-tRF-GlyGCC are evaluated by quantitative PCR in plasma samples from 105 CRC patients and 90 HCs. The mechanisms responsible for biogenesis of 5'-tRF-GlyGCC are checked by in vitro and in vivo models.

Results: 5'-tRF-GlyGCC is dramatically increased in plasma of CRC patients compared to that of HCs. The area under curve (AUC) for 5'-tRF-GlyGCC in CRC group is 0.882. The combination of carcinoembryonic antigen (CEA) and carbohydrate antigen 199 (CA199) with 5'-tRF-GlyGCC improves the AUC to 0.926. Consistently, the expression levels of 5'-tRF-GlyGCC in CRC cells and xenograft tissues are significantly greater than that in their corresponding controls. Blood cells co-cultured with CRC cells or mice xenografted with CRC tumors show increased levels of 5'-tRF-GlyGCC. In addition, we find that the increased expression of 5'-tRF-GlyGCC is dependent on the upregulation of AlkB homolog 3 (ALKBH3), a tRNA demethylase which can promote tRNA cleaving to generate tDRs.

Conclusions: The level of 5'-tRF-GlyGCC in plasma is a promising diagnostic biomarker for CRC diagnosis.

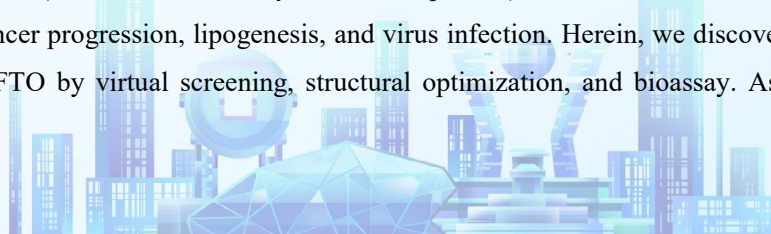
Key words : 5'-tRF-GlyGCC; CRC; ALKBH3; Plasma; tRNA-derived small RNAs

219. A novel inhibitor of N6-methyladenosine demethylase FTO induces mRNA methylation and suppresses cancer cell malignancy

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Sun Yat-sen University

N6-methyladenosine (m6A) modification is critical for RNA splicing, nuclear export, stability and translation. FTO (fat mass and obesity-associated protein), the first identified m6A demethylase, is critical for cancer progression, lipogenesis, and virus infection. Herein, we discovered small-molecule inhibitors of FTO by virtual screening, structural optimization, and bioassay. As a result, two FTO



inhibitors namely 18077 and 18097 were identified, which can selectively inhibit demethylase activity of FTO. 18097 can competitively bind to the active site of FTO to further inhibit the malignancy of cancer cells, including blocking the cell cycle and inhibiting migration and invasion. In addition, 18097 reprogrammed the epi-transcriptome of cancer cells, especially genes related to the P53 pathway. Among them, 18097 can increase the binding of suppressor of cytokine signaling 1 (SOCS1) mRNA to IGF2BP1 by increasing the abundance of m6A modification of SOCS1 mRNA, leading to the stability of SOCS1 mRNA and the activation of the P53 pathway. Further, 18097 can suppress cellular lipogenesis via suppression of PPAR γ , C/EBP α , and C/EBP β . Animal and clinical studies confirmed that the inhibition of FTO can significantly suppress in vivo lung colonization of breast cancer cells and we have also confirmed that 18091 has this effect in animal. Collectively, we identified that FTO can work as a potential drug target and small-molecule inhibitor 18097 of FTO can serve as a potential agent against cancer.

Key words: m6A; FTO inhibitors; cancer cell; lipogenesis; SOCS1

220. Combined inhibition of MET and VEGF enhances therapeutic efficacy of EGFR TKIs in EGFR-mutant NSCLC with concomitant aberrant MET activation

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Aberrant activation of mesenchymal epithelial transition (MET) has been considered to mediate primary and acquired resistance to epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) in EGFR-mutant non-small-cell lung cancer (NSCLC). However, mechanisms underlying this process are not wholly clear and the effective therapeutic strategy remains to be determined. Here, we substantiated previous findings that MET plays an oncogenic role in NSCLC by promoting cell proliferation, migration, and invasion. Ectopic overexpression of MET in EGFR-mutant NSCLC cells is sufficient to confer gefitinib resistance. We further observed that MET formed a positive feedback loop with the vascular endothelial growth factor (VEGF)/ VEGF receptor 2 (VEGFR2) signaling pathway, leading to persistent downstream signaling activation. Specifically, MET up-regulated VEGFR2 expression in a MAPK/ERK-dependent manner, while VEGF promoted physical interaction between VEGFR2 and MET, thereby facilitating MET phosphorylation. A MET inhibitor, crizotinib, combined with an anti-VEGF antibody, bevacizumab, enhanced the sensitivity of NSCLC cells to gefitinib and synergistically inhibited the activation of downstream signaling in vitro. Dual inhibition of MET and VEGF combined with EGFR TKIs markedly regressed tumor growth in both human NSCLC xenograft models and in an EGFR/MET co-altered case. Thus, this three-drug regimen shows clinical potential as a treatment for EGFR-mutant NSCLC with concomitant aberrant MET activation.



Key words: mesenchymal epithelial transition factor; vascular endothelial growth factor; epidermal growth factor receptor; non-small-cell lung cancer

221. Chemically synthesized cinobufagin suppresses nasopharyngeal carcinoma metastasis by inducing ENKUR to stabilize p53 expression

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Clinically, the metastasis of tumor cells is the key factor of death in patients with cancer. In this study, we used a model of metastatic nasopharyngeal carcinoma (NPC) to explore the effects of a new chemical, cinobufagin (CB), combined with cisplatin (DDP). We observed that chemically synthesized CB strongly decreased the metastasis of NPC. Furthermore, a better therapeutic effect was shown when CB was combined with DDP. Molecular analysis revealed that CB induced ENKUR expression by deregulating the PI3K/AKT pathway and suppressing c-Jun, an oncogenic transcriptional factor that binds to the ENKUR promoter. ENKUR as a tumor suppressor binds to MYH9 and decreases its expression by recruiting β -catenin via its enkurin domain to prevent its nuclear accumulation, which therefore suppresses c-Jun-induced MYH9 expression. Subsequently, downregulated MYH9 reduces the enlistment of E3 ligase UBE3A and thus decreases the UBE3A-mediated ubiquitination degradation of p53, a key tumor suppressor that decreases epithelial-mesenchymal transition (EMT). Clinical sample analysis demonstrated that the ENKUR expression level was significantly reduced in NPC tissues. Its decreased expression substantially promoted clinical progression and reflected poor prognosis for patients with NPC. This study demonstrated that CB induced ENKUR to repress the β -catenin/c-Jun/MYH9 signal and thus decreased UBE3A-mediated p53 ubiquitination degradation. As a result, the EMT signal was inactivated to suppress NPC metastasis.

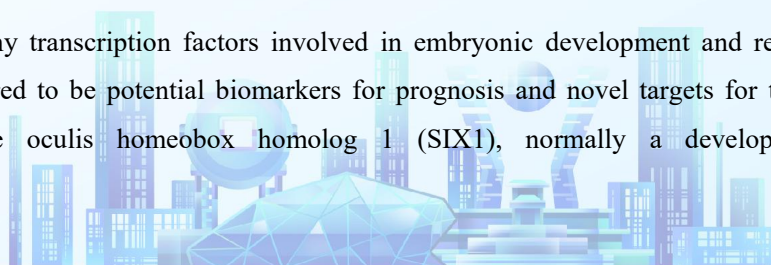
Key words: Cancer cell metastasis; cinobufagin; ENKUR; P53; Nasopharyngeal carcinoma

222. SIX1 predicts poor prognosis and facilitates the progression of non-small lung cancer via activating the Notch signaling pathway

Shanshan Huang*, Wanling Lin, Lei Wang, Yuan Gao, Xun Yuan, Yuan Chen, Peng Zhang, Qian Chu

Tongji Hospital of Tongji Medical College, Huazhong University of Science and Technology

Background: Many transcription factors involved in embryonic development and reactivated in tumors were considered to be potential biomarkers for prognosis and novel targets for treatment in various cancers. *Sine oculis homeobox homolog 1* (SIX1), normally a developmentally restricted



transcriptional regulator, was reported to play a critical role during tumor initiation and development. However, the prognostic value and biological function of SIX1 in non-small cell lung cancer (NSCLC) are not wholly clear.

Methods: Bioinformatic analyses were performed to investigate the SIX1 expression in cancer and adjacent normal tissues of NSCLC and further explore the correlation between SIX1 expression and clinical outcomes. Western blotting and RT-PCR analysis were conducted to detect the expression level of SIX1 in NSCLC cell lines and a normal bronchial epithelial cell. EdU, CCK-8, clonal formation assay, transwell, and wound healing assay were performed to investigate the effects of gain- or loss-of-function of SIX1 on cellular proliferation, migration and invasion in vitro. Gene set enrichment analysis (GSEA) was used to identify the potential signaling pathways involved in SIX1 mediated biological function, and the correlation was confirmed by western blotting and RT-PCR analysis. In vivo experiment was conducted to further validate the tumor-promoting effects of SIX1.

Results: Bioinformatic analysis indicated that SIX1 was markedly upregulated in cancer tissues of NSCLC, and positively correlated with poor prognosis of NSCLC patients. Ectopic expression of SIX1 facilitated proliferation, migration, invasion, and epithelial-mesenchymal transition (EMT) of NSCLC cells. On the contrary, knocking down SIX1 exhibited the opposite effects. Mechanistic studies suggested that SIX1 activated the Notch pathway to promote the malignant biological behaviors of NSCLC, which could be reversed by inhibiting the Notch signaling with γ -secretase inhibitor.

Conclusions: SIX1 could facilitate multiple malignant biological behaviors by activating the Notch signaling pathway and function as a promising prognostic biomarker.

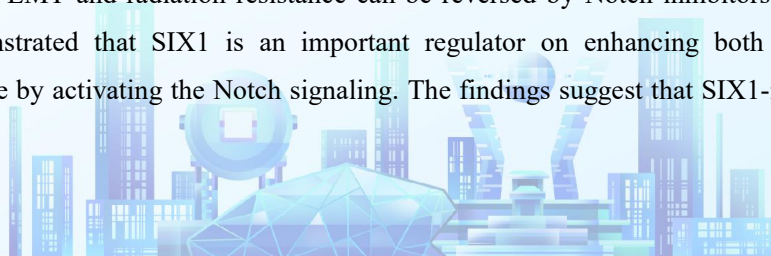
Key words: SIX1; non-small cell lung cancer; Notch signaling; epithelial-mesenchymal transition.

223. SIX1 contributes to EMT and radioresistance in NSCLC cells by activating the Notch signaling

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Radiotherapy remains one of the major treatments for non-small cell lung cancer (NSCLC) patients; whereas intrinsic or acquired radioresistance limits its efficacy. The newly discovered RDGN network is closely related to the occurrence of lung cancer and plays a regulatory role through the DACH1/EYA1/SIX1 pathway. However, the effect of RDGN network on the radiobiology of NSCLC is unknown. In this study, we found that SIX1 has multiple roles as an oncogenic gene in NSCLC. SIX1 overexpression promotes EMT and radioresistance, accompanied by enhanced DNA damage repair. We further demonstrated that SIX1 regulates downstream Notch signaling pathway and the SIX1-induced EMT and radiation resistance can be reversed by Notch inhibitors. In summary, these results demonstrated that SIX1 is an important regulator on enhancing both NSCLC EMT and radioresistance by activating the Notch signaling. The findings suggest that SIX1-induced EMT might



significantly contribute to the enhanced radioresistance. Therefore, SIX1 may serve as a potential biomarker or therapeutic target for NSCLC radiotherapy.

Key words: Non-small-cell Lung Cancer; SIX1; Notch Signaling; epithelial-mesenchymal transition; radiosensitivity

224. 三阴性乳腺癌相关成纤维细胞调控癌细胞 PD-L1 表达分子机制研究

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目的: 三阴乳腺癌 (Triple negative breast cancer, TNBC) 是高度异质性和侵袭性恶性肿瘤, 癌细胞与间质成纤维细胞共进化是影响 TNBC 演进的重要因素, 尤其是免疫抑制微环境形成及癌细胞过表达 PD-L1 是 TNBC 产生免疫逃逸的机制之一。但 TNBC 间质癌相关成纤维细胞 (Carcinoma-associated fibroblasts, CAFs) 如何参与调控癌细胞 PD-L1 表达, 目前机制未完全阐明。本研究主要通过体外共培养试验体系探讨 CAF 调控癌细胞 PD-L1 表达的可能机制, 为 TNBC 免疫治疗提供实验依据。

方法: 通过 TCGA 公共数据库分析乳腺癌患者常见生长因子、细胞因子和趋化因子与临床预后的相关性。以 qPCR array 检测活化成纤维细胞中生长因子、细胞因子、趋化因子及其受体表达水平。分别以不同浓度 CXCL1、CXCL5 和 CXCL8 单独或联合 RAS/MAPK、PI3K/AKT 和 STAT3 特异性抑制剂处理 PD-L1 低表达的 TNBC 细胞系, qPCR 和 Western Blotting 检测 PD-L1 的表达水平; 同时以 Western Blot 检测 ERK、AKT、STAT3 和 P65/P105 的磷酸化水平。

结果: 体外实验结果显示 TNBC 细胞系 (MDA-MB-231) 条件培养基与成纤维细胞共培养 7 天后, 相关炎性细胞因子表达明显升高, 其中 CXCL1、CXCL5 和 CXCL8 等明显过表达 ($P < 0.001$), 且 CAFs 促进 TNBC 细胞迁移能力增强 ($P < 0.05$)。TCGA 数据挖掘发现 CXCL1、CXCL5 和 CXCL8 过表达与 RAS/MAPK、RTK 和 PI3K/AKT/mTOR 等信号通路活化, 并与细胞凋亡、细胞周期异常及 EMT 调控密切相关, CXCL1 过表达与 TNBC 预后不良有关 ($P < 0.05$)。体外实验进一步发现不同浓度 CXCL1、CXCL5 和 CXCL8 促进 PD-L1 过表达 ($P < 0.05$), 并伴 RAS/MAPK、PI3K/AKT 和 STAT3 信号通路过度激活, 而相应信号通路特异性抑制剂能明显抑制 CXCL1、CXCL5 和 CXCL8 诱导癌细胞表达 PD-L1。

结论: 本研究初步证实 TNBC 细胞系 (MDA-MB-231) 条件培养液能促进乳腺成纤维细胞活化并获得癌相关的成纤维细胞表型, 并促进 CXCL1、CXCL5 和 CXCL8 等一系列炎性细胞因子和趋化因子过表达, 同时可能通过 RAS/MAPK、PI3K/AKT 和 STAT3 信号通路促进 TNBC 细胞过表



达 PD-L1。提示靶向 CXCL1/CXCL5 和 CXCL8 相关信号传导通路可能逆转 TNBC 细胞免疫逃逸表型。

关键词：三阴性乳腺癌；癌相关成纤维细胞；肿瘤微环境；趋化因子；免疫抑制因子

225. Development of exosome-based cancer vaccination using transcription-induced chimeric RNA as a neoantigen

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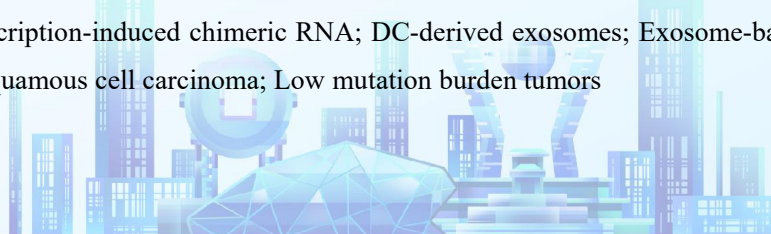
Background: Esophageal squamous cell carcinoma (ESCC) is an extremely aggressive malignancy with a dismal prognosis, indicating urgent need for development of alternate and/or complementary immunotherapeutic treatment options in advanced ESCC. Although somatic mutations are important sources of cancer-specific neoepitopes to generate cancer vaccine, recent studies revealed that somatic mutations commonly occur in many normal tissues, particularly in aging normal esophageal tissues. Transcription-induced chimeric RNAs (chiRNAs) are fused transcripts from unrelated genes generated through aberrant read-through/splicing or trans-splicing. These chiRNAs may be suitable to serve as targets in cancer vaccines for cancer types known to have low mutation burden and in which mutation-based immunogenic neoantigens are rare or even non-existent. Furthermore, a cell-free exosome-based vaccine approach offers several practical advantages over a cell-based vaccine, including long shelf-life when frozen, scalability and genetic modifiability. Previously, we reported a group of chiRNAs enriched in human ESCC. We wondered whether the ESCC-enriched chiRNAs could be exploited for the development of exosome-based therapeutic vaccine.

Methods: We developed a novel cell-free anticancer vaccine based on exosomes from the chiRNA-transduced dendritic cells (DC). Survival and tumor growth were monitored in mice bearing syngeneic chiRNA-expressing ESCC.

Results: We confirmed that chiRNA specifically expressed in cancer, suggesting it may be developed into an immunogenic neoantigen. Vaccination of immunocompetent mice bearing syngeneic chiRNA-expressing ESCC with exosome-based vaccine potently inhibited tumor growth and prolonged survival.

Conclusion: Our data demonstrate that transcription-induced chiRNA can be used as a source of cancer-specific neoantigen for cancer types known to have low mutation burden and in which mutation-based immunogenic neoantigens are rare or even non-existent. Moreover, the result showed that exosome-based vaccines have stable immunomodulatory capacity and can induce anticancer immunity.

Key words: Transcription-induced chimeric RNA; DC-derived exosomes; Exosome-based cancer vaccine; Esophageal squamous cell carcinoma; Low mutation burden tumors



226. MicroRNA 和外泌体 (Exosome) 作为新的肿瘤标志物与乳腺癌的研究进展

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乳腺癌是导致世界各地妇女高死亡率的遗传性疾病之一。尽管有先进的诊断工具和治疗策略，乳腺癌的发病率仍在逐年增加。这是由于缺乏准确可靠的肿瘤标志物，而这些肿瘤标志物的缺乏导致了早期乳腺癌识别、耐药监测和转移预测的困难。虽然肿瘤标志物如 CA153,CEA 可用于乳腺癌的诊断，由于这些标记物的异质性、敏感性和特异性，提高乳腺癌的早期诊断仍是一个挑战。因此，迫切需要一种新的生物标志物用于治疗诊断和改善预后。最近，越来越明显的是，miRNAs 和外泌体可能作为良好的非侵入性生物标记物，与癌变中的不同事件相关。本文对 miRNA 和外泌体与乳腺癌转移相关、乳腺癌早期诊断及化疗效果关系的研究进展进行综述。

关键词 乳腺癌；MicroRNA；外泌体；肿瘤标志物；化疗；转移；早期诊断

227. Association of carbonic anhydrase 10 hypermethylation with the risk of gastric carcinoma

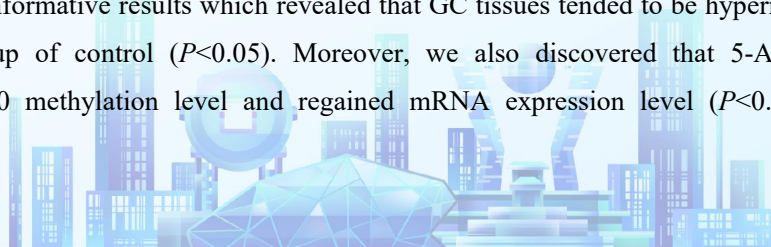
Jing Wang*

The First Affiliated Hospital of USTC

Background and Objectives: The incidence of gastric carcinoma (GC) is increasing in the worldwide. However, the specific and effective biomarkers for early diagnosis and survival predicting in GC are still in considerably need. The association between the hypermethylation of the zinc-related gene, carbonic anhydrase 10 (CA10), and GC remains unknown. This study aims to investigate the methylation function of CA10 in patients with GC.

Methods and Materials: In this study, we collected methylation data of CA10 in GC in datasets of the cancer genome atlas, and gene expression omnibus. 6 GC cell lines and 30 pairs of tumor tissues were studied for the purpose of elucidating the epigenetic function of CA10. Methylation results derived from Sequenom were validated by bisulfite sequencing. The expression levels of CA10 were tested by reverse transcription PCR quantitatively and western blot. The cell function was assessed by the cell proliferation, transwell and colony forming assay.

Results: The present research showed the elevated level of CA10 methylation in GC ($P<0.05$), consistent with the Bioinformative results which revealed that GC tissues tended to be hypermethylated of CA10 than the group of control ($P<0.05$). Moreover, we also discovered that 5-Aza-2'-deoxycytidine reduced CA10 methylation level and regained mRNA expression level ($P<0.05$), except protein



($P>0.05$). The area under the curve of CA10 methylation for GC diagnosis was 0.96. The sensitivity and specificity were 90.0% and 95.0% respectively. No correlation was found between CA10 methylation and tumor differentiation, TNM stage, CEA, etc ($P>0.05$). In vitro, CA 10 can inhibit the proliferation, colony formation, invasion and migration of GC cells ($P<0.05$).

Conclusions: The results of the present study suggest that the hypermethylation of CA10 is significantly associated with the risk of gastric carcinoma.

Key words: Gastric carcinoma; carbonic anhydrase 10; hypermethylation

228. 单细胞转录组测序揭示胶质母细胞瘤独特的免疫微环境

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天津医科大学总医院

目的: 作为发病率和死亡率极高的肿瘤,胶质母细胞瘤(GBM)一直是临床诊疗的重大难题。

GBM中浸润的免疫细胞主要是肿瘤相关巨噬细胞(TAM),T细胞含量很少,因此其也被定义为“冷肿瘤”。到目前为止,关于TAM在GBM中激活状态的研究主要局限于单个肿瘤组织的RNA测序分析,尚无更加深入清晰的研究。

方法: 我们综合分析9个GBM样本共16201个细胞的单细胞转录组测序结果,使用特定标志基因确定TAM的来源和激活状态,进一步使用SCENIC方法分析关键调控子信息,并刻画不同GBM亚型的TAM特征,最后明确靶向TAM关键调控基因的潜在药物靶点。

结果: TMEM119和MHC-II可作为TAM细胞来源和激活状态的重要标志基因。在混合型GBM中,绝大多数浸润的TAM为骨髓来源的巨噬细胞,而在前神经元亚型GBM中,TAM主要由激活型小胶质细胞组成,经典亚型GBM中主要浸润的是抑制型小胶质细胞。研究进一步发现,SPI1是TAM的核心转录调控因子,在TAM成熟和极化过程中发挥重要作用,可作为GBM免疫治疗的潜在药物靶点。

结论: 我们在单细胞水平描绘了人类GBM免疫全景图,重新定义了GBM中的TAM激活类型,并发现SPI1有望作为GBM免疫治疗靶点。

关键词: 胶质母细胞瘤;单细胞转录组测序;巨噬细胞极化;SPI1

229. 整合多维组学数据探究乳腺癌个体异质性

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研究目的：乳腺癌是一类高异质性的癌症，对乳腺癌进行分子分型可以为临床治疗提供研究基础。

目前乳腺癌分子分型依赖于识别群体水平的差异表达基因，该类方法受批次效应等技术因素影响，且无法反映个体水平的差异表达基因。本研究基于基因表达秩序关系筛选乳腺癌个体差异表达基因，识别乳腺癌新亚型，探究亚型间分子机制差异。

材料方法：本研究采用 TCGA (The Cancer Genome Atlas) 乳腺癌的多维组学数据，包括基因组的突变与拷贝数变异,表观组的甲基化水平和转录组的基因表达数据。利用 RankComp (Rank Comparision) 方法识别乳腺癌个体差异表达基因。在乳腺癌个体中不仅发生转录组差异表达，且在其他组学被检测到变异的基因，定义为乳腺癌个体驱动差异表达基因。基于个体驱动差异表达基因聚类识别乳腺癌新亚型，比较新亚型间临床特征与分子变异特征；利用独立 METABRIC 乳腺癌数据集验证亚型特异基因的预后相关性；利用秩和检验比较新亚型的免疫微环境差异。本课题分析流程详见附图。

结果：本研究发现乳腺癌个体中 7.3% 的差异表达基因基因组变异或者表观组变化，个体中基因差异表达与拷贝数变异,差异甲基化水平显著相关。个体驱动差异表达基因显著富集癌相关基因,转录因子和蛋白质互作网络的关键节点，说明乳腺癌个体驱动差异表达基因具有可靠性。基于乳腺癌个体驱动差异表达基因谱识别到具有预后显著差异的四类乳腺癌亚型。基于乳腺癌亚型的临床特征分析，cluster 1 亚型预后最差，而 cluster 4 预后最好；cluster 2 和 cluster 3 亚型分别与 PAM50 分型中的 Luminal 和 Basal 亚型相关。基于乳腺癌亚型的分子变异分析，在 cluster 1 亚型中 11 号染色体长臂 23 区域高频缺失，且该区域与乳腺癌预后的相关性在独立数据集中得到验证。Cluster 1 和 cluster 2 亚型发生荷尔蒙激素受体相关功能的高频改变；cluster 3 亚型具有 DNA 损伤修复功能异常特征，包括 BRCA2 基因高频差异下调,高肿瘤突变负荷和同源重组缺陷高打分。Cluster 4 亚型具有免疫相关基因失调。乳腺癌亚型间免疫微环境分析揭示淋巴细胞在 cluster 4 亚型高度浸润，且 cluster 4 亚型的免疫原性和免疫抑制检查点基因高频差异上调，为免疫检查点抑制剂的乳腺癌用药预测提供理论依据。

结论：本研究识别的乳腺癌个体驱动差异基因具有可靠性，新乳腺癌亚型在预后,基因组不稳定性与免疫微环境等方面存在差异，为乳腺癌个体化治疗提供新的策略。

关键词：差异表达基因；多维组学；乳腺癌亚型；个体异质性

230. The significance of Calmodulin-like protein 3(CALML3) in esophageal squamous cell carcinoma.

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Background: Esophageal cancer is one of the top 10 malignant tumors in the world. Lack of effective early diagnosis strategy are the main causes of death of esophageal squamous cell carcinoma (ESCC). As a new type of treatment, targeted therapy plays an important role in the treatment of ESCC. The identification of key molecular targets related to the occurrence and development of esophageal cancer is very important for the prognosis of ESCC. Calmodulin-like protein 3(CALML3) is an epithelial-specific calcium-sensitive protein. CALM3 is highly expressed in normal tissues such as breast, prostate, skin and oral mucosa. Previous studies have demonstrated that CALML3 is a potential biomarker for diagnosis and prognosis of malignancies. However, relationship between CALML3 and the development of ESCC has not been reported.

Methods: We identified the differential expression of proteins between ESCC tissues and matched normal paracancer tissues by proteomic analysis. The expression of CALML3 in ESCC tissues was assayed by Western Blotting and qRT-PCR. Furthermore, Immunohistochemical analysis was also used to analyze the expression difference of CALML3 in ESCC, and the association between CALML3 expression and TNM stage and prognosis was also confirmed. Using CRISPR/Cas9 editing, we created stable CALML3 knockout EC109 cell line. Finally, CALML3 on the proliferation and migration of ESCC cells were investigated by Cell Counting Kit-8 assay(CCK8), Wound healing assay and Cell migration assay, respectively.

Results: The abundance of CALML3 in ESCC tissues was much decreased than that in matched normal tissues ($P < 0.05$), and the low expression of CALML3 was correlated with advanced TNM stage ($P < 0.05$), and poor prognosis. Functionally, knockdown of CALML3 increased migration and proliferation of ESCC cells.

Conclusion: Our data indicate that CALML3 is considered a potential biomarker for ESCC diagnosis and prognosis, and it is a potential therapeutic target for ESCC treatment.

Key words: Esophageal squamous cell carcinoma; ESCC; CALML3; Biomarker

231. 不同分化程度早期胃癌的临床相关因素分析

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目的: 探讨早期胃癌分化程度的临床特点及影响因素。

方法: 收集 2011 年 1 月-2019 年 3 月武威市三甲医院收治的 455 例早期胃癌患者临床资料。回顾性分析早期胃癌患者不同临床特征与分化程度的关系及影响分化程度的相关因素。

结果: 455 例早期胃癌患者中, 分化型 381 (83.74%) 例, 未分化型 42 (9.23%) 例, 混合型 32 (7.03%) 例。不同分化程度在不同年龄段, 病变部位, 浸润深度, 病变大小, 脉管浸润方面差异有统计学意义 ($P < 0.05$), 未分化型和混合型的浸润深度 SM, 病变大小 $> 2\text{cm}$, 有脉管浸润的比率高于分化型; 未分化型术后追加手术比率最高 (69.05%), 其次是混合型 (50.00%), 三组之



间差异有统计学意义 ($P<0.0167$)；多分类 Logistic 回归分析显示，相对于分化型，病变大小 $>2\text{cm}$ ($\text{OR}=2.537$)，年龄 55 岁以下 ($\text{OR}=2.952$) 为未分化型早期胃癌患者的危险因素，病变大小 $>2\text{cm}$ ($\text{OR}=3.263$)，有脉管浸润 ($\text{OR}=3.802$)，病变部位贲门部 ($\text{OR}=2.963$) 为混合型早期胃癌的危险因素；相对于未分化型，病变部位贲门部 ($\text{OR}=12.322$) 为混合型早期胃癌的危险因素。

结论：病变大小，年龄，病变部位与未分化型早期胃癌有关；病变大小，脉管浸润，病变部位与混合型早期胃癌有关；混合型早期胃癌恶性程度介于分化型和未分化型之间。

关键词：早期胃癌；分化程度；影响因素

232. 内镜黏膜下剥离术治疗不同浸润深度早期胃癌的可行性及相关因素分析

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目的：探讨内镜黏膜下剥离术 (ESD) 治疗不同浸润深度早期胃癌的临床安全性及其相关影响因素。

方法：收集 2012 年 1 月 1 日至 2018 年 12 月 31 日在武威市三甲医院行 ESD 术的早期胃癌患者的临床相关资料，根据 ESD 术后病理，比较黏膜内癌组 (M) 与浅层黏膜下癌 (浸润深度 $\leq 500\mu\text{m}$, SM1) 组患者的临床特征及临床预后，运用 Logistic 回归模型分析影响 ESD 术治愈性切除的相关因素。

结果：276 例患者中，M 组 247 例，SM1 组 29 例。M 组与 SM1 组在病变大小，病变部位，术后病理类型方面差异有统计学意义 ($P<0.05$)；M 组治愈性切除率远高于 SM1 组 (94.74% vs 65.52%， $\chi^2=29.007$, $P<0.05$)；M 组与 SM1 组 3 年生存率 (96.21% vs 86.67%)，差异无统计学意义 ($\chi^2=0.540$, $P=0.463$)，术后并发症的发生差异也无统计学意义 ($P=0.572$)；有溃疡和浸润深度 SM1 是影响 ESD 术治愈性切除的相关因素。术后需要追加外科手术 40 例，其中追加手术 18 例，发生淋巴结转移 1 例，其他患者均定期随访。

结论：与 M 组相比，SM1 组短期预后相对较差，但总体生存率差异无统计学意义，因此，综合考虑患者基本情况及术后生存质量，在 SM1 早期胃癌患者中，ESD 可以作为一种治疗的选择。

关键词：内镜黏膜下剥离术；早期胃癌；影响因素

233. Hsa circ 0000594 作为肝母细胞瘤新的生物标志物和治疗靶点的研究

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各种研究表明, 环状 RNA (circRNAs) 的异常表达在多种癌症中起着关键作用。然而, circRNA 在肝母细胞瘤中的作用尚不清楚。在本研究中, 我们试图探讨 has_circ_0000594 在肝母细胞瘤中的潜在机制及其临床意义。在我们的研究中, 通过原位杂交和 RT-qPCR 确定 has_circ_0000594 在肝母细胞瘤组织和匹配的正常肝组织中的表达模式。通过 CCK-8, 克隆形成实验, transwell 和流式细胞术检测肝母细胞瘤细胞的增殖, 细胞活力, 迁移和凋亡。通过双荧光素酶报告分子测定研究了 has_circ_0000594 与 miR-217 的相互作用。生物信息学分析表明, SIRT1 可作为 miR-217 的靶基因。与成对的正常肝组织相比, has_circ_0000594 的表达水平在肝母细胞瘤组织中显著上调, 并且与肝母细胞瘤的亚型显示出显著的相关性。敲除 has_circ_0000594 可抑制肝母细胞瘤的恶性表型。通过 has_circ_0000594 / mir-217 / SIRT1 调节轴, has_circ_0000594 在肝母细胞瘤发育中起关键作用, 这可能成为肝母细胞瘤的新型诊断标志物和潜在的治疗靶标。

关键词: 环状 RNA; 肝母细胞瘤

234. 结直肠癌患者分离细胞的有机培养

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背景: 结直肠癌(CRC)是一种异质性疾病; 目前的研究依赖于癌细胞系和动物癌症模型, 这些模型可能不能精确地模仿人类内部肿瘤和指导临床医学。

目的: 我们研究的目的是探索和进一步改进了三维(3D)器官样模型的产生过程, 并推动了个性化治疗的发展。

方法: 我们在皮下将从患者身上进行手术切除的 CRC 组织注射到 BALB/c-nu 小鼠中, 以构建患者衍生的异种移植物(PDXs)。将适当肿瘤大小的 PDX 分离细胞与骨髓混合, 然后播种在 4 个细胞密度 (500, 1000, 2000 和 4000 个单细胞/井) 的超低附着 96 井板中。用先进的杜尔贝科改良鹰培养基/F12 培养基培养细胞, 并添加各种因子以维持肿瘤的生物特性和生长活性。在培养 24 小时至 25 天后, 测量了这 4 个细胞密度的生长曲线。

结果: 我们通过细胞滴定®发光细胞活性评估了四种化疗药物对细胞模型的影响。

关键词: 结直肠肿瘤; 药物治疗; 肿瘤移植; 三维印刷

235. 在肝癌中 AMOT 是高糖诱导 YAP 功能的必需的因素

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背景与目的：肝癌是威胁人类健康的主要疾病之一，YAP 是肝癌发展中很重要的经典基因。AMOT 已被确定为 YAP 交互者。然而，AMOT 如何管理 YAP 仍然不清楚争议。

材料和方法：使用肝癌细胞 Bel-7402 以及 SMMC-7721 进行体外实验，使用抗 O-GlcNAc, 抗 AMOT 进行免疫沉淀实验，明确 AMOT，OGT 与 O-GlcNA 的关系与用抗 TAMRA 测量被标记的 O 糖基化的 AMOT。使用不同浓度的葡萄糖浓度对细胞进行处理设置不同的药物处理诱导的实验组，用蛋白印迹法以及免疫沉淀进一步分析相对处理之下 AMOT 和 O 糖基化相关参数的变化。按要求诱导建造高糖小鼠模型，使用蛋白印迹法进一步验证体内高糖状态下的肝组织中 AMOT 以及 YAP 的表达量。使用免疫荧光实验更加直观的显示这些分组对 YAP 表达定位的影响。对 O 糖基化的 AMOT 进行细胞功能实验探究对肿瘤的作用，并且用免疫荧光技术表示正常和高葡萄糖小鼠肝脏中 AMOT 和 YAP 的亚细胞定位。

结果：在这里，我们发现除了 YAP 之外，AMOT 是另一个 Hippo 信号核心因素可能是 O-GlcNAcylated。此外，HG 能够增强表达和 O-AMOT 的 GlcNAcylation。我们还发现 HG 刺激核积累，转录活动，通过 AMOT 与转录因子的相互作用和 YAP 靶基因的转录，而 AMOT 在正常葡萄糖水平中充当 YAP 的抑制剂。最后，我们观察到上调和核 AMOT 和 YAP 在链脲佐菌素（STZ）诱导的高葡萄糖小鼠中的积累。

结论：我们发现 AMOT 在高葡萄糖水平中充当 YAP 刺激物。针对异常调节 Hippo 途径的核心因素可能是同时患有糖尿病肝癌相关的更有效的治疗方法。

关键词：AMOT；肝癌；YAP

236. IL17 在肿瘤预后中的重要性的 meta 分析

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目的：炎症因子是抑制肿瘤炎性作用的重要介质，能够促进肿瘤相关性炎症，使肿瘤细胞逃避免疫监控。IL17 是近年来新发现的促炎症细胞因子，已在多种恶性肿瘤中发现 IL17 呈高表达。肿瘤的进展及转移受到肿瘤微环境中相关的细胞因子影响。本研究旨在相关临床研究的基础上，采用 Meta 分析方法对其进行分析和评价，以明确 IL17 对于肿瘤患者预后中是否有价值。

方法：通过系统性的回顾和 meta 分析来评估 IL17 作为一个肿瘤预后标志物的作用。使用危险比 (hazard ratios, HRs) 和 95% 可信区间 (confidence intervals, CIs) 作为评价标准, 来综合分析计算 IL17 的表达与肿瘤生存预后的关联程度。以总生存率 (Overall survival, OS) 作为肿瘤预后的评价标准。

结果：通过纳入了 19 个研究共包含了 2390 例肿瘤患者的综合 meta 分析，我们发现在肿瘤中 IL17 的表达和总生存率没有明显相关性 (HR=1.29, 95% CI: 0.94-1.76; $P=0.12$)。但通过综合 meta 分析比较数据，显示出 IL17 高表达可以预测非小细胞肺癌和肝细胞癌的总生存率低，非小细胞肺癌和肝细胞癌的 HRs 和 95% CIs 分别为 (HR=2.30; 95% CI: 1.45-3.64; $P<0.001$; $I^2=0\%$)

和 (HR=2.02; 95% CI: 1.44-2.83; $P<0.001$; $I^2=0\%$), IL17 的高表达也与食管鳞癌预后相关 (HR=0.63; 95% CI: 0.51-0.79; $P<0.001$; $I^2=0\%$)。结果显示, 纳入的研究没有明显异质性, 单个研究对总体效应指标没有显著影响, 各研究不存在明显发表偏倚。

结论: meta 分析显示 IL17 很有可能成为一个新的肝细胞癌、非小细胞肺癌和食管鳞癌的预后的预测因子。

关键词: IL17; 肿瘤

237. Sirtuin 6 在食管癌中发挥致癌作用并诱导自噬

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目的: Sirtuin6 (Sirt6) 是 Sirtuin 家族成员, 通过催化启动子区域组蛋白脱乙酰化来抑制 HIF1 α 和 MYC 诱导的基因转录, 进而抑制有氧糖酵解过程以及细胞生长。有文献报道 Sirt6 在前列腺癌、乳腺癌以及非小细胞肺癌中表达升高, 表明其可能在不同癌种中发挥特定作用。目前, Sirt6 在食管癌中的作用尚不明确, 本研究旨在探索 Sirt6 在食管癌细胞中发挥的作用, 阐明其作用机制。

方法: 采用 RT-qPCR、免疫组织化学检测 Sirt6 在食管鳞状细胞癌组织中的表达水平。分析 Sirt6 表达与临床特征相关性。通过生物学实验研究 Sirt6 影响细胞增殖的机制和下游分子。通过 LC3II/I 和自噬通量研究 Sirt6 对自噬的影响。采用 WB 和 IP 鉴定与 Sirt6 互作的蛋白。

结果: Sirt6 在食管鳞状细胞癌组织中表达上调, 其上调与临床特征密切相关, 如肿瘤淋巴结转移、细胞分化等。Sirt6 促进细胞增殖, 并诱导食管癌细胞中的关键抗凋亡因子 Bcl2 表达, 且明显诱导细胞自噬。Sirt6 与 ULK1 特异性相互作用, 并通过调节 mTOR-ULK1 信号通路诱导自噬。

结论: Sirt6 的 mRNA 和蛋白水平在食管鳞状细胞癌组织中均显著升高, 其过表达与临床病理、分期和细胞分化密切相关。Sirt6 能够促进细胞增殖, 并通过调节 mTOR-ULK1 信号通路诱导自噬。

关键词: Sirt6; 食管癌

238. 可解吸附型多功能纳米材料在液体活检中的应用

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背景和目的: 近年来液体活检在癌症的临床实践中迅速发展, 它可以为实现个性化治疗及监测提供有力的支撑。液体活检是指通过微创的方法收集患者体液, 并对其中的循环肿瘤细胞 (Circulating Tumor Cells, CTCs)、外泌体 (EVs)、循环肿瘤 DNA (ctDNA) 进行检验。本文利



用肿瘤细胞表面带负电的特性设计制备一种可解吸附型多功能纳米材料，捕获并纯化患者体液中的 CTCs。

材料和方法：材料制备以 Fe₃O₄ 纳米颗粒为磁核，可在磁力作用下富集；以 SiO₂、硅烷偶联剂 APS 为中间层稳定并偶联蛋白；以等电点约为 7 的牛血红蛋白（BHb）为修饰层，可实现在不同 pH 条件下电位的改变实现 CTCs 高效的捕获及释放。在确定材料使用条件后，对五种常见的循环肿瘤细胞进行捕获及释放的效率探究，包括人肺腺癌细胞 A549、人乳腺癌细胞 MDA-MB-231-GFP、人慢性髓性白血病细胞 K562、人膀胱癌细胞 5637、人胰腺癌 sw1990。

检测材料在不同 pH 下的电位，在 pH 为 6.5 时电位为 +25mv 左右，在 pH 为 8.5 时电位为 -10mv 左右。

结果：实验结果显示对 A549 捕获效率为 98.2%，释放效率为 78.6%；对 MDA-MB-231-GFP 捕获效率为 91%，释放效率为 55.9%；对 K562 捕获效率为 85.7%，释放效率为 97.2%；对 5637 捕获效率为 98.3%，释放效率为 34.8%；对 sw1990 捕获效率为 86.1%，释放效率为 93.6%。

结论：可解吸附型多功能纳米材料可高效灵敏地捕获及释放体内微量的 CTCs，在液体活检中具有巨大的发展前景，同时为后续基因分析等深入研究提供基础。

关键词：可解吸附型多功能纳米材料；液体活检；CTCs

239. Arene Ruthenium(II) Complex suppresses transcription of BCR-ABL fusion oncogene via binding and stabilizing c-Myc G-quadruplex DNA and induces apoptosis in imatinib-resistant CML cells

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Aims: Tyrosine kinase bcr-abl fusion protein is the pathogenic factor of chronic myeloid leukemia (CML).

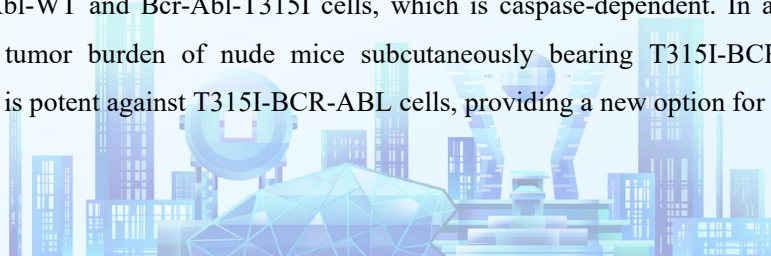
The gate-keeper T315I mutation is the predominant mechanism of acquired resistance to most tyrosine kinase inhibitors (TKI). Therefore, it's pressing to find alternative strategies and develop new drugs of which specifically target T315I-BCR-ABL for the treatment to CML patients harboring such mutation. Given that c-Myc can bind to the Bcr promoter and positively regulate Bcr-Abl fusion gene. [(η⁶-C₆H₆)Ru(p-BrPIP)Cl]Cl (R7) is a kind of aromatic ruthenium complexes, which can specifically bind and stabilize the G-quadruplex of c-Myc through groove binding mode, thereby down-regulating the expression of c-Myc. The assay aimed to assess the in vivo and in vitro effects of R7 on IM-resistant CML cells and its underlying mechanism.

Methods: The stabilizing effect of R7 on G4 DNA of c-Myc gene was determined by circular dichroism. Western blot and RT-qPCR were applied to detect the protein and message RNA level. The Bcr-Abl transcriptional activity of the transfected cells was detected by dual luciferase reporter assay kit.

AnnexinV-FITC /PI double staining assay was used to determine the apoptosis of CML cells exposed to R7. The morphological changes of living cells were observed by inverted fluorescence microscope and the apoptotic cell death was detected by flow cytometry. The mitochondrial membrane potential of CML cells after R7 treatment was determined by NIR detection kit. Co-immunoprecipitation assay was performed to confirm the interaction between c-Myc and Max. MTS assay and xenograft models were established to evaluate the effects of R7 on cell viability and tumors growth in nude mice.

Results: We first examined the effects of R7 on the viability of IM-sensitive and IM-resistant CML cells, and the results showed that R7 had an evident inhibitory effect on CML cell viability. The circular dichroism (CD) studies proved that R7 stabilized the c-Myc G-quadruplexes. Next, we examined the effect of R7 on c-Myc transcription and protein levels in CML cells and patients CML cells, and results showed that R7 significantly inhibited c-Myc transcription and protein levels. Also, R7 down-regulated the mRNA levels of Bcr-Abl in CML cells and patients CML cells. And dual-luciferase reporter assay indicated that R7 inhibited the transcription activity of Bcr-Abl gene. Luciferase activity analysis suggested that overexpression of c-Myc can up-regulate the transcription of Bcr-Abl, while R7 can block the transcription of Bcr-Abl mediated by c-Myc. Meanwhile, knockdown of c-Myc can inhibit the transcription of Bcr-Abl. In addition, the phosphorylation of RNA pol II was diminished to a certain extent in CML cells by R7 treatment. To further confirm the positively regulatory role of c-Myc on Bcr-Abl expression, CML cells were infected with lentiviral c-Myc. The protein level of Bcr-Abl was elevated in the c-Myc-overexpressed CML cells, but declined by R7 treatment. Conversely, the cells treated with c-Myc inhibitor 10058-F4, the level of Bcr-Abl was decreased and the reduction was more obvious after combining treatment with R7. Furthermore, the IP/WB assays indicated that R7 can inhibit c-Myc-Max interaction in CML. Furthermore, R7 decreases the expression of Bcr-Abl and its downstream signaling proteins such as stat5, AKT and Crkl. To further explore the mechanism of R7-induced Bcr-Abl decline, we studied its dependence on the caspase activation. Specifically, we observed that pan-caspase inhibitor zVAD-fmk could reverse R7 induced cell death. Then we detected the effect of R7 on growth of CML cells. Results showed that R7 induce cell apoptosis and inhibit cell proliferation in CML cell and patients CML cells. And it is related to the activation of Caspase pathway and the down-regulation of anti-apoptotic protein expression. In addition, the in vivo effect of R7 on KBM5 and KBM5-T315I cell-derived mouse xenograft models, which was consistent with the experimental results in vitro.

Conclusions: R7 is a kind of aromatic ruthenium complexes, which can specifically bind and stabilize the G-quadruplex of c-Myc through groove binding mode, thereby down-regulating the expression of c-Myc. Treatment of WT- and T315I-BCR-ABL CML cells by R7 inhibited c-Myc expression and c-Myc-Max interaction, thus decreased Bcr-Abl transcription and its downstream signaling molecules such as STAT5 and Akt. Moreover, R7 significantly inhibited the proliferation and induced apoptosis in both Bcr-Abl-WT and Bcr-Abl-T315I cells, which is caspase-dependent. In addition, R7 notably inhibited the tumor burden of nude mice subcutaneously bearing T315I-BCR-ABL CML cells. Therefore, R7 is potent against T315I-BCR-ABL cells, providing a new option for CML treatment.



Key words: CML; R7; Bcr-Abl; c-Myc; Imatinib resistance

240. miR-31 和 miR-145 作为子宫内膜异位症患者潜在的非侵入性调节生物标志物

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目的: 子宫内膜异位症是一种流行的妇科疾病,影响 10% 的育龄妇女。子宫内膜异位症通过腹腔镜检查诊断,然后进行组织学确认。早期诊断将导致更有效的治疗,发病率低得多。由于 miR-31 和 miR-145 被证明与参与子宫内膜异位症的生物学过程直接或间接相关,因此本研究的目的是检查血浆中 miR-31 和 miR-145 表达与子宫内膜异位症存在之间的关联。

材料与方法: 在本病例对照研究中,收集、提取 55 例子宫内膜异位症患者和 23 例无子宫内膜异位症女性的血浆样本,采用实时定量聚合酶链反应(qPCR)分析 miR-145 和 miR-31 的表达。

结果: 我们的研究表明,miR-31 在第 3 或 4 阶段和第 1 或 2 阶段的表达水平显著下调(小于 0.01 倍, $P < 0.05$),而 miR-145 的表达水平在子宫内膜异位症处于 1 或 2 期的女性。

结论: 不同的细胞生物学过程,如分化、增殖、线粒体功能、活性氧(ROS)产生、侵袭和蜕膜化,在子宫内膜异位症中失调。miR-31 和 miR-145 是具有潜在作用的微 RNA(miRNA),如癌症等病理学所示。我们发现 miR-31 在子宫内膜异位症患者中低表达,而 miR-145 在阶段 1 或 2 中过度表达,表明它们在更严重的形式中相对下调。我们的研究表明,这两种 miRNA 可能被认为是潜在的生物标志物,可能对子宫内膜异位症患者的早期诊断甚至随访有影响。

关键词: 生物标志物; 子宫内膜异位症; miRNA

241. ANGPTL4 facilitates the symbiosis between fusobacterium nucleatum and colorectal cancer cells by promoting glycolysis

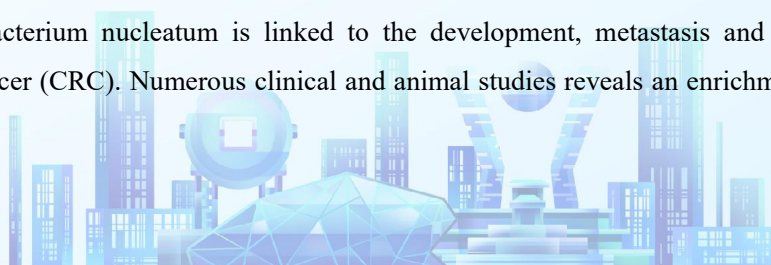
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Objective: Fusobacterium nucleatum is linked to the development, metastasis and chemoresistance of colorectal cancer (CRC). Numerous clinical and animal studies reveals an enrichment of F. nucleatum



in the tumor tissue compared with adjacent normal tissue. Nonetheless, the mechanism underlies the colonization and persistence of *F. nucleatum* in CRC tissue is not fully clarified.

Design: The mechanism of how *F. nucleatum* stimulates glycolysis activity of CRC cells and facilitates its own colonization was investigated in vitro and confirmed with the Cancer Genome Atlas (TCGA) datasets, clinical tissues, and a xenograft model. The relationship between histone acetylation, ANGPTL4 induction, glycolysis activity of CRC cells and *F. nucleatum* persistence were further elucidated in vitro and in vivo.

Results: We demonstrated that *F. nucleatum* infection remarkably promoted glucose uptake and glycolysis activity in CRC cells by elevating the ANGPTL4 expression in vitro and in vivo, which were necessary for the colonization of *F. nucleatum* itself. Furthermore, overall increased acetylation of histone H3 lysine 27 was observed in *F. nucleatum* infected CRC cells and clinical tumors, which was specifically responsible for the corresponding transcriptional regulation of ANGPTL4.

Conclusion: This study suggests the metabolic reprogramming of CRC cells is essential for the persistence of *F. nucleatum*. By interfering ANGPTL4-mediated glycolysis enhancement of CRC cells, the *F. nucleatum* colonization and its tumor-promoting effects could be eradicated in CRC patients.

Key words: *Fusobacterium nucleatum*; colorectal cancer; glycolysis; metabolic reprogramming; histone acetylation; ANGPTL4

242. TIGIT-PVR 抑制途径介导人乳头瘤病毒 16 型感染免疫逃逸机制研究

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研究目的: 人乳头瘤病毒是寄生人体的一类 DNA 病毒, 可引起表皮和黏膜上皮内瘤变, 高危亚型 HPV 持续感染被认定是推动宫颈上皮内瘤变甚至癌变的关键因素。宫颈癌筛查及疫苗制剂由于地区经济及疫苗自身只有预防而无治疗作用等因素的限制, 宫颈癌前病变及宫颈癌仍然是女性健康的重大威胁, 尚缺少潜在药理治疗及预警诊断的生物标志物。这项研究目的是揭示 HPV 持续感染的关键机制, 确定可操作的 HPV 所致宫颈癌前病变的免疫检查点, 以用于早期诊断或治疗策略。

材料与方法: 多中心收集宫颈 CIN 患者外周全血样本 82 例, 宫颈组织学样本 40 例, 分组: HPV (-), HPV (+) 炎症, HPV (+) CIN1, HPV (+) CIN2-3, 流式细胞学进行淋巴细胞表型及功能检测, 免疫组织化学进行宫颈原位免疫标记物染色强度检测, 研究采用 Graphpad8.0.1, Dunn's 检验等进行数据统计, $P < 0.05$ 认为具有统计学意义。



研究结果：① 循环 CD56brightNK 细胞计数增多：CD56brightNK 细胞绝对计数在 HPV（+）炎症、HPV（+）CIN1、HPV（+）CIN2-3 组中存在显著差异（ $P=0.036$ ），多重比较发现相比于 HPV（+）炎症组患者，其在 CIN2-3 组绝对计数升高显著。② CD56brightNK 细胞分泌 IFN- γ 能力降低：利用 IFN- γ 和 TNF- α 抗体进行胞内染色，流式细胞学计算阳性细胞百分比，验证 HPV 感染所致宫颈病变 NK 细胞功能。结果提示：HPV（-）组发现 CD56brightNK 细胞分泌 IFN- γ 能力较 CD56dimNK 细胞高（ $P=0.033$ ），CD56dimNK 细胞分泌 TNF- α 比例显著高于 CD56brightNK 细胞（ $P=0.028$ ）。HPV16（+）组中 CD56brightNK 细胞分泌 IFN- γ 比例显著减少，HPV16（+）CIN2-3 组尤其显著（ $P=0.004$ ）。③ HPV16（+）患者 TIGIT+CD56brightNK 细胞比例升高：Dunn's 检验发现，TIGIT+CD56brightNK/CD56brightNK 细胞值在各组之间的差异具有统计学意义（ $P=0.026$ ），尤其 HPV16（+）CIN2-3 组升高显著。提示：随病变进展，TIGIT 表达呈现增高趋势。④ HPV16（+）患者 TIGIT 及其配体 PVR 随病程进展表达增加：流式及免疫组织化学染色发现，随着 HPV（+）宫颈 CIN 病程进展 TIGIT 及其配体在宫颈原位组织中染色强度增加，提示 TIGIT-PVR 途径可能是导致 HPV（+）宫颈 CIN 患者 NK 功能受损的关键环节。

研究结论：本研究表征与健康供者相比，HPV（+）宫颈 CIN 患者随病程进展循环 CD56brightNK 细胞比例增加，证明 CD56brightNK 细胞在抵御 HPV 感染过程中极为重要。其次，本研究发现随感染进程 CD56brightNK 细胞分泌 IFN- γ 减少，证明细胞功能受损。此外，本研究发现 HPV（+）宫颈 CIN 中 NK 细胞表面抑制性受体 TIGIT 及其配体 PVR 表达与 CD56brightNK 细胞比例变化一致，提示 TIGIT-PVR 途径参与了 HPV 持续感染宫颈的致病过程。研究揭示了 HPV 持续感染导致病毒清除障碍的关键环节，证实除 PD-1/PD-L1、CTLA-4 等免疫检查点外，TIGIT 作为 HPV 所致宫颈 CIN 及宫颈癌免疫检查点的巨大潜力，对研制治疗性疫苗，有效预警宫颈癌具有重要的研究意义和临床价值。

关键词：HPV；宫颈 CIN；NK 细胞；TIGIT-PVR；免疫检查点

243. Detection of ANO1 mRNA in PBMCs is a promising method for GISTs diagnosis

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Background & purpose: ANO1 is a calcium-activated chloride channel protein that has been used to diagnose GISTs after tissue biopsy. Recently, ANO1 mRNA amplification in the blood has received considerable attention as a useful method for the diagnosis of GISTs. The aim of this study was to evaluate the diagnostic ability of ANO1 mRNA in distinguishing GIST patients from healthy subjects.

Methods: We constructed a logistic regression model for examining the diagnostic ability of ANO1 mRNA in comparison with conventional tumor markers, including CEA, CA199, and CA724.

Results: Our results showed that ANO1 mRNA was significantly amplified in PBMCs, the average expression level and range of ANO1 mRNA in the blood were increased along with the expression of ANO1 in the tissues, and the extent of amplification of ANO1 was associated with tumor size. In addition, ROC curve analysis showed that ANO1 mRNA in the blood had the highest specificity when compared with conventional tumor markers. Moreover, a combined analysis with ANO1mRNA and conventional tumor markers had the highest sensitivity in diagnosing GISTs.

Conclusions: Our study indicated that detection of ANO1 mRNA in PBMCs is a promising method for diagnosis of GISTs in vitro

Key words: ANO1; diagnosis; GISTs

244. Clinical usefulness of high levels of C - reactive protein for diagnosing epithelial ovarian cancer

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The purpose of the present study was to evaluate the diagnostic role of CRP in ovarian cancer and to assess whether CRP can be combined with tumor markers to enhance the diagnostic efficacy toward ovarian cancer. Area under the curve, sensitivity, and specificity were calculated to assess the diagnostic ability of each singly and combined as markers for ovarian cancer. The CRP cut-of value was then calculated to evaluate the diagnostic efficacy of CRP for ovarian cancer. Our results showed that values for all markers were significantly higher in the cancer group than in the control group. Receiver operating characteristic curve results showed that CA125 had the highest diagnostic efficacy for ovarian cancer, while the sensitivity for CRP was higher than for CA125, and the specificity for CRP was equal to that of CA125. The combination of CRP, CA125, and HE4, however, provided the strongest diagnostic capability. Furthermore, the diagnostic cut-of value for CRP with regard to ovarian cancer was 9.8 mg/L, and high levels of CRP were correlated with stage and tumor size of ovarian cancer. Our study indicated that CRP is valuable in the diagnosis of ovarian cancer, and that combining CRP with CA125 and HE4 improved the diagnostic efficacy with respect to ovarian cancer.

Key words: CRP; ovarian cancer; Diagnosis

245. Autophagy promotes the stemness of pancreatic ductal adenocarcinoma by impairing the nuclear translocation of EHF

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Background & purpose: Cancer stem cells lead to recurrence and drug resistance in pancreatic ductal adenocarcinoma (PDAC). The suppressive role of EHF in the regulation of PDAC stemness has been confirmed. Subsequently, we found a positive relationship between the expression of EHF and P62, which acts as a degradation substrate of autophagy and is negatively correlated with the level of autophagy. However, whether autophagy interacts with EHF remains unclear. This study aimed to explore the crosstalk between autophagy and EHF, and their roles in the regulation of PDAC stemness.

Methods: PDAC samples were collected and PDX mice models were constructed. Double labeled fluorescent autophagy flow monitoring system, western blotting and flow cytometry were used to detect autophagy. Regular function experiments were conducted to determine stemness. Co-immunoprecipitation and luciferase analyses were performed to explore molecular mechanism.

Results: Contrary to the inhibitory role of EHF in the regulation of stemness in PDAC cells, autophagy exhibited promotable roles. As a transcription factor, EHF could transactivate the expression of P62 through direct bind to its promoter. Simultaneously, P62 boosted the nuclear translocation of EHF via the direct protein interaction, followed by the increased transcriptional activity of EHF, thus forming a positive feedback loop. Furthermore, autophagy could also reduce the transcriptional activity of EHF by decreasing the expression of P62, resulting in the activation of downstream Wnt/ β -catenin signaling pathway, thereby enhancing the stemness of PDAC cells. Autophagy inhibitor ULK-101-1 effectively controlled the growth of PDAC cells by inhibiting its stemness characteristics in vivo, and high expression of EHF could be an indicator of benefits from ULK-101-1. Subsequent preclinical PDX mice cohorts demonstrated that ULK-101-1 could sensitize PDAC to gemcitabine therapy.

Conclusions: Autophagy leads to the loss of P62, followed by the decreased nuclear translocation of EHF, thus promoting PDAC stemness. Autophagy inhibitors can hinder tumor growth by suppressing the stemness of PDAC, which clues to the future clinical application of autophagy inhibitors.

Key words: pancreatic ductal adenocarcinoma; EHF; stemness; autophagy; P62

246. 肿瘤和遗传基因组医学筛查软件平台系统

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针对肿瘤和遗传专科病种精准医疗实际应用需求, 设计开发和验证了 10 多种医学基因应用筛查软件, 主要针对高通量测序和全基因组芯片检测样本产生的海量基因突变和染色体 CNV 改变等全基因组大数据, 按照国际开放共识性的政府生物数据库和肿瘤、遗传行业学会临床诊疗规范需求, 进行全面的生命医学学科整装性筛查、分析、聚类 and 图示, 报告病人的靶向治疗, 预报预



测和分子分型，临床鉴别等应用内容，利用计算机精准重复性，在数 10 秒内快速完成患者全基因组变异大数据筛查，将筛查到的相关信息整合到各种肿瘤和遗传病医学诊疗规范和临床方案形成辅助诊断报告。

关键词: 肿瘤遗传；全基因组；临床大数据；软件筛查报告

247. CircMYOF triggers progression and facilitates glycolysis via VEGFA/PI3K/AKT axis by absorbing miR-4739 in pancreatic ductal adenocarcinoma

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Emerging evidences have exhibited that circRNAs take part in the initiation and development of pancreatic ductal adenocarcinoma (PDA), a deadly neoplasm with extremely low 5-year survival rate. Reprogrammed glucose metabolism is a key feature of tumor development, including PDA. In this research, we designed to evaluate the role of circRNAs in reprogrammed glucose metabolism in PDA. RNA sequencing under various glucose incubation circumstance was performed. A new circMYOF was identified. Sanger sequencing and RNase R treatment confirmed its circular RNA characteristics. Real time PCR indicated that it was highly expressed in PDA clinical specimens and cell lines. Gain-of and loss-of function assay implied that circMYOF induced progression in PDA. Mechanically, RNA pull down and luciferase reporter experiment elucidated that circMYOF, exhibiting as a competing endogenous RNA for miR-4739, facilitated glycolysis via VEGFA/PI3K/AKT pathway. Taken together, our finding indicates that circMYOF may work as a desirable biomarker and therapeutic target for PDA patients.

Key words: circMYOF; pancreatic cancer; glycolysis

248. HER-2 阳性乳腺癌新辅助治疗腋窝淋巴结疗效预测标志物研究

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目的: HER-2 阳性乳腺癌新辅助治疗（neoadjuvant therapy, NAT）后乳房原发灶与腋窝淋巴结（axillary lymph node, ALN）疗效并不完全相同，因此单用原发灶疗效预测基因来预测 ALN 疗



效并不全面。本研究旨在探索 HER-2 阳性乳腺癌原发灶疗效相关差异表达 lncRNA 能否预测 ALN 疗效。

方法：本研究入组 3 对术后病理为 ypT0N0 和 ypT+N+ 的 HER-2 阳性乳腺癌 NAT 前原发灶穿刺组织行 lncRNA 芯片检测，筛选差异表达 lncRNA。选取 2015 年 9 月-2020 年 9 月于山东省肿瘤医院接受 NAT 的 137 例 HER-2 阳性乳腺癌患者术前穿刺组织进行差异表达 lncRNA 验证。ROC 曲线评估差异表达 lncRNA 作为预测原发灶和 ALN 疗效诊断标志物的能力。选用 HER-2 阳性乳腺癌细胞系 SK-BR-3 和 BT474 细胞，检测乳腺癌细胞加入紫杉醇作用后 lncRNA 的表达水平变化，进一步验证预测得到的 lncRNA 在药物敏感性调控中的作用。并通过调控 lncRNA 的表达水平，利用 CCK-8 药敏实验观察不同表达水平的 lncRNA 对乳腺癌细胞化疗药物敏感性的影响。

结果：lncRNA 芯片检测共筛选出 27 个上调的差异 lncRNA 和 20 个下调的差异 lncRNA。选取差异倍数 > 1.5 的 lncRNA 进行验证，结果显示，与 ypT0 组织相比，ypT+ 组织中 POTEH,AC00975.1 和 RUVB-AS1 的表达水平显著升高（均 $P < 0.05$ ）；与 ypN0 组织相比，ypN+ 组织中 AL390243.1 的表达水平显著升高（ $P = 0.0014$ ）。结合临床、病理、实验室指标及基因表达水平，多因素分析显示，RUVB-AS1 表达水平是预测 HER-2 阳性乳腺癌 NAT 原发灶疗效的独立预测因素（AUC 值=0.692）；临床 ALN 分期、穿刺病理分级和 AL390243.1 表达水平是预测 HER-2 阳性乳腺癌 ALN 疗效的独立预测因素（AUC 值=0.793）。随后我们进一步在 87 对癌组织和癌旁组织中分析 RUVB-AS1 和 AL390243.1 的表达水平，结果显示 RUVB-AS1 和 AL390243.1 在癌组织中的表达水平高于癌旁组织，同时 RUVB-AS1 和 AL390243.1 在 HER-2 阳性亚组的表达水平高于 HER-2 阴性亚组。随着药物作用浓度的升高，乳腺癌细胞 RUVB-AS1 的表达水平逐渐升高，即 RUVB-AS1 表达水平的升高可降低乳腺癌细胞药物敏感性。通过转染来上调 RUVB-AS1 的表达水平，应用 CCK-8 方法检测细胞对紫杉醇的敏感性，发现 RUVB-AS1 表达水平的上调可显著增加降低细胞对紫杉醇的药物敏感性。

结论：RUVB-AS1 表达水平可作为 HER-2 阳性乳腺癌 NAT 原发灶疗效预测标志物，AL390243.1 表达水平可作为 ALN 疗效预测标志物。联合临床、病理、实验室指标及基因表达水平可进一步完善乳腺癌降阶梯处理理念。

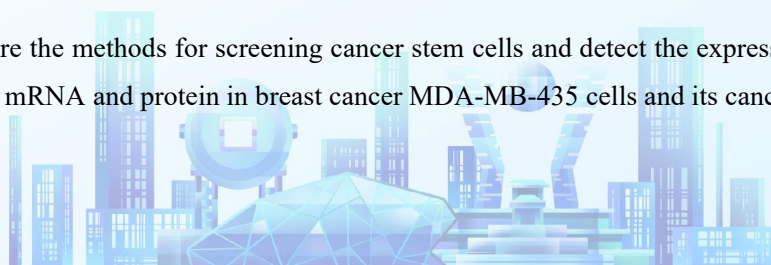
关键词：乳腺癌；新辅助治疗；LncRNA；腋窝淋巴结；生物标志物

249. The expression of RecQ helicases in breast cancer stem cells

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Purpose: To explore the methods for screening cancer stem cells and detect the expression of RecQ family helicases with mRNA and protein in breast cancer MDA-MB-435 cells and its cancer stem cells.



Methods:(1) Breast cancer stem cells were screened and cultured in serum-free medium. (2) The percentage of side population cells in breast cancer stem cells stained with Hoechst33342 was measured with flow cytometry. (3) The ability of colony formation in breast cancer stem cells was identified by using soft agar assay. (4)Total RNA of MDA-MB-435 cells and its tumor stem cells, normal liver L-02 cells, umbilical cord mesenchymal stem cells and normal lymphocytes were extracted respectively and reverse transcribed to their cDNA. The mRNA quantity of RecQ family helicases(RecQL, BLM, WRN, RecQ4, RecQ5) in these cells were detected by Real-time quantitative PCR. (5) The expression of BLM helicase protein and RecQ4 helicase protein were detected by Western Blot in MDA-MB-435 and its tumor stem cells, normal liver L-02 cells, liver cancer HepG2 cells and normal leucocytes.

Results:(1) Breast tumor stem cells were successfully screened and cultured in serum-free medium. (2) The percentage of side population cells in breast cancer stem cells accounted for over 95%. (3) The colony numbers formed from breast cancer stem cells (253 ± 6 colonies/1000 cells) are significantly more than that from MDA-MB-435 cells (126 ± 5 colonies /1000 cells, $P < 0.001$). (4) Comparing with MDA-MB-435 cells, the mRNA expression of RecQL, BLM, WRN in breast cancer stem cells are significantly decreased ($P < 0.05$), on the contrary, the mRNA expression of RecQ4, RecQ5 in breast cancer stem cells are significantly increased. ($P < 0.05$). (5) The expression of BLM helicase protein is followed from low to high in normal leucocytes, breast cancer stem cells, MDA-MB-435 cells, L-02 and HepG2. The expression of RecQ4 helicase protein is from low to high followed in normal leucocytes, MDA-MB-435 cells, breast cancer stem cells, L-02, HepG2. Comparing with MDA-MB-435 cells, the expression of BLM helicase protein in its cancer stem cells is declined and the expression of RecQ4 helicase protein in its cancer stem cells is increased. **Conclusions:** Breast cancer stem cells can be screened and cultured by using serum-free medium. RecQ4, RecQ4/BLM and RecQ5 may be expected to be the new and specific markers of breast cancer stem cells. RecQ4 and RecQ5 may be the new targets for breast cancer stem cells inhibition.

Key words: Breast cancer; Serum -free culture; Tumor/cancer stem cell; RecQ family helicases; Hoechst33342 dyeing; Soft agar assay

250. Gastric cancer prognostic marker DDX54 plays an important role in gastric cancer immunity

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Background: The high expression of DEAD-Box Helicase 54 promotes the occurrence of colorectal cancer, however, the relationship between its role in gastric cancer and immune cell infiltration remain unclear.

Methods: Use ENCORI and GEPIA databases to determine the relationship between DDX54 and CASC19. Use Oncomine, TIMER, The Human Protein Atlas to find the difference between DDX54 in normal tissues and cancer tissues, use Kaplan-Meier Plotter, UALCAN, PrognoScan database for prognostic analysis, and finally use TIMER Database for immune infiltration analysis.

Results: Gene and protein levels proved that DDX54 is expressed differently in a variety of cancers, especially in gastric cancer and colorectal cancer, and the prognosis is poor in gastric cancer (OS, HR=1.61, $P=1.4E-05$; PFS, HR=1.41, $P=0.0077$). DDX54 is positively correlated with CD4⁺ T cells, and negatively correlated with the other 5 immune cells, regardless of STAD or COAD. Immune marker analysis DDX54 is associated with a variety of immune cells. There is a strong positive correlation between gastric cancer and Regulatory T cell.

Conclusion: DDX54 is highly expressed in gastric cancer tissues, and the higher the expression, the worse the prognosis, which may be related to the suppression of the anti-tumor effect of normal immune cells and the recruitment of Treg infiltration. This indicates that it is a valuable prognostic and tumor marker for gastric cancer.

Key words: Gastric cancer; DEAD-Box Helicase 54 (DDX54); Prognosis; Bioinformatics analysis; Immunology

251. Keap1 在非小细胞肺癌中调控 PD-L1 的分子机制研究

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目的: 研究 Keap1 在非小细胞肺癌细胞中的表达水平, 以及在非小细胞肺癌细胞增殖中的作用, 和 Keap1 与 PD-L1 在非小细胞肺癌中的相互关系。

方法: 应用 TCGA 数据库和辽宁省 34 对癌和癌旁组织进行分析, 比较其中 Keap1 含量的表达差异。

采用人非小细胞肺癌细胞株进行体外培养, 构建 Keap1 的敲低和高表达稳转细胞系, 通过细胞增殖 CCK-8 实验, 探究 Keap1 对非小细胞肺癌细胞增殖能力的影响。利用 Keap1 敲低和高表达细胞系, 通过 Western Blot 实验方法检测细胞内信号通路的变化以及对 PD-L1 的调控作用, 筛选出差异明显的信号通路, 并研究该通路对非小细胞肺癌细胞的调控作用。

结果: TCGA 数据库分析结果显示, 在非小细胞肺癌患者的组织标本中, Keap1 在癌组织中的表达明显高于癌旁组织, 差异有统计学意义 ($P<0.01$)。在 34 对癌和癌旁组织中, 也得到相同的结果。在 CCK-8 实验中, 与对照组相比, Keap1 敲低组的增殖能力显著提高, 而 Keap1 高表达组的增殖能力明显下降, 差异有统计学意义 ($P<0.01$)。通过 Western Blot 实验方法的结果显示, 在非小细胞肺癌细胞系中, Keap1 的表达含量与 PD-L1 呈负相关趋势。



结论: Keap1 在非小细胞肺癌组织中呈高表达状态。Keap1 具有抑制非小细胞肺癌细胞增殖的作用。

Keap1 可能对 PD-L1 具有负向调控作用。

关键词: keap1; 非小细胞肺癌; 增殖; PD-L1

252. Bioinformatic identification of afatinib potential drug resistance gene BIRC5 in non small cell lung cancer

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Background: Resistance to second-generation epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI), afatinib, is the most challenge in clinical management of non small cell lung cancer (NSCLC), and the underlying mechanisms remain unclear.

Methods: Identification of genomic signatures that may confer afatinib resistance in non-small-cell lung cancer (NSCLC) was conducted through data mining of public database and integrative bioinformatic analyses. Furthermore, acquired afatinib-resistant lung adenocarcinoma cell lines (HCC827 AR) were established by long-term exposure of afatinib in vitro for stepwise escalation. The expression of baculovirus IAP repeat protein 5 (BIRC5) was detected by Western blot, and cellular viability and invasion of HCC827 AR was determined by CCK8 and Transwell assay.

Results: Based on the integrative bioinformatic analyses of public datasets, we demonstrated that overexpression of baculovirus IAP repeat protein 5 (BIRC5) was identified in both afatinib-resistant NSCLC cells and tissues, and BIRC5 was positively correlated with lymph node metastasis as well as pathological stage in NSCLC. Furthermore, NSCLC patients with BIRC5 overexpression was present poorly survival outcome. Immune infiltration analysis suggested that BIRC5 expression was significantly inversely correlated with tumor-infiltrating cells and immune biomarkers in NSCLC. The functions of BIRC5 co-expressed genes were mainly enriched in cell cycle mitotic phase transition, double-strand break repair, negative regulation of cell cycle process signaling pathway. In addition, overexpression of BIRC5 protein levels was detected in afatinib-resistant cells by western blot, while BIRC5-expressing cells treated with BIRC5 inhibitor, YM155, was sensitive to afatinib.

Conclusions: In this study, we showed that overexpression of BIRC5 result in resistance to afatinib in NSCLC, and BIRC5 specific inhibitors may overcome the resistant phenotype, indicating that dysregulation of apoptotic cell death pathway may be the key mechanism underlying TKI resistance in the development of NSCLC.

Key words: Bioinformatic analysis; NSCLC; Afatinib resistance; BIRC5

253. 肝细胞癌合并门静脉癌栓的治疗进展



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肝细胞癌为临床常见的恶性肿瘤，其高度恶性及易于侵犯和转移的生物学特性，致使患者生存率极低，其中最常见也是临床最棘手的一种情况是肝细胞癌合并门静脉癌栓，通常这类患者病情进展迅速，其治愈率极低，因此这类患者死亡率极高，而生存率极低。现阶段随着医疗水平和科学技术进步，肝细胞癌的相关治疗取得了显著进展，对于肝细胞癌的治疗也是采用多学科综合治疗模式，对于各期肝癌患者制定个体化治疗方案，采用联合治疗疗法，最大化改善患者的生活治疗和生存率。本文将从现有的治疗方法论述其在肝细胞癌治疗过程中的应用。

关键词：肝细胞癌；门静脉癌栓；多学科治疗

254. 不同级别脑膜瘤组织中 BAP1 和 H3K27me3 的表达情况及临床意义

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目的：探讨 BAP1 和 H3K27me3 在不同级别脑膜瘤组织中的表达及其临床意义。

方法：选择 2018 年 5 月至 2019 年 12 月郑州大学第一附属医院手术切除的 140 例脑膜瘤患者的肿瘤标本为研究对象。采用免疫组织化学法检查不同级别和组织学亚型脑膜瘤组织中 BAP1 和 H3K27me3 蛋白的表达，并分析 BAP1 和 H3K27me3 蛋白表达与患者临床病理学参数的关系。

结果：脑膜瘤组织中 BAP1 蛋白阳性表达率随着 WHO 级别升高逐渐增强，两两比较差异均有统计学意义($P<0.05$)；脑膜瘤组织中 H3K27me3 蛋白阳性表达率随着 WHO 级别升高逐渐降低，两两比较差异均有统计学意义($P<0.05$)；脑膜瘤组织中 BAP1 蛋白和 H3K27me3 的表达与膜瘤患者的年龄、性别及肿瘤的组织学亚型均无关($P>0.05$)。

结论：脑膜瘤组织中 BAP1 蛋白的表达随着 WHO 级别升高逐渐增强；脑膜瘤组织中 H3K27me3 蛋白阳性表达率随着 WHO 级别升高逐渐降低，其检测有助于脑膜瘤分级的病理诊断。

关键词：脑膜瘤；BAP1；H3K27me3；免疫组化

255. eIF2 α 的磷酸化减轻急性肝损伤中的内质网应激和肝细胞坏死

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目的：已经明确坏死和内质网（ER）应激与急性和慢性肝损伤有关。激活的真核生物起始因子 2 α （eIF2 α ）减少了蛋白质的合成，降低了 ER 中蛋白质折叠的负荷。本研究旨在分析 eIF2 α 磷酸化对急性肝损伤中肝细胞坏死的影响。

方法：给雄性 BALB/c 小鼠注射衣霉素或 d-半乳糖胺，并将 LO2 细胞与衣霉素共孵育以诱导急性肝损伤。利用 4-苯基丁酸（PBA）和 salubrinal 分别抑制内质网应激和 eIF2 α 的去磷酸化。分析小鼠和细胞模型中的 eIF2 α 磷酸化、内质网应激和肝细胞坏死情况。

结果：衣霉素或 d-半乳糖胺可在小鼠和 LO2 细胞中显著诱导 ER 应激和坏死，以及 eIF2 α 磷酸化。内质网应激加剧了衣霉素诱导的小鼠和 LO2 细胞肝细胞坏死。升高的 eIF2 α 磷酸化可显著减轻小鼠和 LO2 细胞的肝细胞 ER 应激和肝细胞坏死。有趣的是，肿瘤坏死因子受体 1（TNFR1）蛋白水平与坏死并不完全同步。在经 d-半乳糖胺处理的小鼠中，TNFR1 表达降低，而细胞与衣霉素孵育 12 和 24h，发现内质网应激可在衣霉素培养的细胞中部分恢复 TNFR1 的表达并增加坏死的发生。

结论：这些结果表明，ER 应激可介导独立于 TNFR1 信号的肝细胞坏死，而升高的 eIF2 α 磷酸化可减轻急性肝损伤期间的 ER 应激。

关键词：eIF2 α 磷酸化；急性肝损伤；内质网应激；肝细胞坏死

256. Elevating histone H3K27me3 level is an available biomarker for HCC

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Hepatocellular carcinoma (HCC) is the most common form of liver malignancy, which remains a global health challenge with ceaseless incidence and high fatality [1]. With the conceptual and technological advances in epigenetics and epigenomics, the role of epigenetic events including DNA methylation, histone modification and non-coding RNA regulation in HCC tumors has been gradually revealed [2]. DNA methylation and DNA methylation-induced epigenetic alterations, due to their potential reversibility, open the access to develop novel biomarkers and therapeutics for HCC [3]. Given that post-translational modification (PTM) of histone tails including lysine acetylation and methylation profoundly influenced carcinogenesis by altering chromatin structure and conferring a differential gene expression program [4]. It is necessary to better understand the new molecular targets of HCC epigenetics in HCC diagnosis, prevention, and treatment. Tri-methylation of the 27th lysine residue on histone H3 (H3K27me3), while just one of many such modifications, plays an important role in developmentally driven gene silencing and in cancer initiation and progression. H3K27me3 is distributed widely across enhancers and promoters, the global levels and genome-wide redistributions of which have been changed in multiple cancer types [5,6]. The expression dynamics of H3K27me3 and its clinical significance in HCC has also referred its potential that serves as a pathological or

prognostic biomarker. Previous studies in HCC demonstrated that high levels of H3K27me3 correlated with aggressive features and poor prognosis and could serve as a prognostic marker for HCC [7,8]. Deregulation in HCC of enzymes mediating the methylation and de-methylation of H3K27 is the main cause for this histone modification. The primary “writer” of H3K27me3, enhancer of zeste homolog 2 (EZH2), has been known to be involved in HCC progression in an oncogenic capacity [9,10]. Small-molecule inhibitors of EZH2 methyltransferase activity have been shown to decrease global H3K27me3 concentrations, reactivate silenced EZH2 target genes, and inhibit cell proliferation and tumor progression[11,12], which exhibit therapeutic promise in EZH2 high-expressed or gain of function mutation HCC patients. H3K27me3 “erasers”, lysine demethylase 6A/6B (KDM6A/KDM6B), were significantly decreased in HCC and might be potential tumor suppressors [13,14]. Apart from the altered expression of or mutations in H3K27me3 writers and erasers, alterations in readers and dysregulation of other chromatin regulators are also tied to H3K27me3 regulation [15]. Considering the strong associations between H3K27me3, EZH2, KDM6A, KDM6B and the development of HCC, the role of H3K27me3 as a diagnostic as well as a prognostic biomarker in HCC is anticipated. As promising as the current epigenetic cancer therapies are, significant challenges remain. The precise role of H3K27me3 at different stages of cancer progression is not well understood, and epigenetic modifications at the H3K27 locus are variable and reversible. In addition, different epigenetic modification states of the same lysine residue occur in different contexts and may have distinct functional consequences. Thus, in the future, a better comprehension of how H3K27me3 are disrupted in HCC could guide a more mechanistic-based rationale for the use of H3K27me3 as a diagnostic and prognostic biomarker.

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Acknowledgments

This work was supported by the grants from National Natural Science Foundation of China (81972664, 81672414)

Key words: H3k27me3; HCC; biomarker

257. 肿瘤出芽及癌相关成纤维细胞与乳腺癌临床病理特征关系研究

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目的：乳腺癌是女性高发的恶性肿瘤，侵袭与转移是患者预后不良的主要原因。肿瘤出芽（tumor budding, TB）和癌相关成纤维细胞（carcinoma-associated fibroblasts, CAF）是肿瘤侵袭转移中的引领细胞（leader cells），其在乳腺癌转移过程中发挥重要作用，然而关于 TB 与 CAF 在乳腺癌中的确切作用及其与患者临床病理参数之间关系尚未完全阐明，本研究通过免疫组织化学检测，分析 TB 与 CAF 和乳腺癌临床病理特征关系。

方法：收集 160 例乳腺浸润性导管癌（非特殊类型）根治术手术标本。通过免疫检测 CDH1,CDH2,VIM,TNC 和 VIM 等蛋白标记物在肿瘤细胞及其间质成份中表达情况，判断乳腺癌细胞上皮-间质转化（epithelial-mesenchymal transition, EMT）表型及间质 CAF 状态。采用 2016 年国际肿瘤出芽共识标准评估 TB 级别，采用卡方检验,Kaplan-Meier 检验及 COX 回归模型分析 EMT 及 CAF 相关蛋白表达水平与乳腺癌患者临床病理特征,及生存预后关系。

结果：结果显示，乳腺癌 TB 等级与脉管内癌栓,淋巴结转移,临床分期相关（ $P < 0.05$ ）。肿瘤主体中癌细胞 CDH1 蛋白表达水平与 ER/PR,Ki67 表达状态及 T 分期相关（ $P < 0.05$ ）；而 TB 中 CDH2 和 VIM 表达与 ER/PR 状态,分子分型，组织学分级,Ki67 相关（ $P < 0.05$ ），且三阴性乳腺癌（triple negative breast cancer, TNBC）中更显著。此外，VIM 蛋白表达水平与 TB 等级相关（ $P < 0.05$ ）。肿瘤浸润性前沿 TNC 蛋白表达与 ER/PR 状态,分子分型,Ki67 相关（ $P < 0.05$ ）其中 TNBC 中最为突出。在肿瘤内间质 TNC 蛋白表达亦与 ER/PR 表达水平相关（ $P < 0.05$ ）；而肿瘤细胞中 TNC 表达与 HER-2 过表达,分子分型,淋巴结转移密切相关（ $P < 0.05$ ），尤其是 TNBC 中表达最高；肿瘤内间质 VIM 蛋白表达与分子分型,T 分期相关（ $P < 0.05$ ），其中在 Luminal B 中高表达。通过综合分析发现 TB 等级和肿瘤浸润性前沿 TNC 蛋白表达与无转移生存率（metastasis-free survival, MFS）相关（ $P < 0.05$ ），COX 风险回归分析显示，TB 等级与 MFS 相关（HR 3.538，95%CI 1.747~7.167 $P=0.000$ ）。提示 TB 等级和肿瘤浸润性前沿 TNC 蛋白表达水平可能成为乳腺癌预后判断的重要生物标志物。

结论：本研究结果表明高等级 TB 与不良临床病理特征相关，并提示 TB 等级是乳腺癌患者的独立预后因素，而肿瘤浸润性前沿 TNC 蛋白表达水平亦可能成为乳腺癌预后判断的重要生物标志物。

关键词：乳腺癌；肿瘤出芽；癌相关成纤维细胞；肿瘤侵袭；肿瘤转移

258. 去乙酰化酶 SIRT1/2 抑制剂 Tenovin-6 通过下调葡萄糖吸收抑制结直肠癌细胞恶性增殖

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背景：能量代谢的改变以满足不受控制的增殖已成为肿瘤中最重要的标志之一。Sirtuin 家族是Ⅲ型的组蛋白去乙酰化酶，在肿瘤细胞增殖与代谢的调控中扮演重要角色。因此，组蛋白去乙酰化酶抑制剂有很好的抗癌前景。Tenovin-6 是 Sirtuin 家族中 SIRT1/2 的抑制剂，能够抑制其去乙酰化活性。通过临床样本分析，我们发现结肠癌广泛高表达 SIRT1/2，且其表达与预后呈负相关。因此，本研究拟进一步验证 Tenovin-6 抗结直肠癌的功效。

方法：通过 MTT,iCELLigence,BrdU,软琼脂实验,平板克隆等实验在结直肠癌细胞系 HCT116 和 SW480 中检测 Tenovin-6 对增殖的影响；利用流式细胞术检测细胞周期和凋亡；利用 2-NBDG 染色法检测细胞对葡萄糖的吸收；利用 qRT-PCR 和 Western blot 检测细胞周期相关因子及 GLUT4,PGC-1 α 的表达。过表达 PGC-1 α 和 PGC-1 α 特异性激活剂 ZLN005 处理来检测 PGC1 α /GLUT4 信号通路是否是 Tenovin-6 的下游通路。最后，利用 BALB/c-nu 裸鼠模型检测 Tenovin-1 与 ZLN005 对癌细胞体内成瘤的影响。

结果：Tenovin-6 能够抑制结肠癌细胞增殖，引起结肠癌细胞周期阻滞，下调周期相关蛋白的表达，并诱导了细胞凋亡。结肠癌细胞在 Tenovin-6 处理后对于葡萄糖的吸收能力和 ATP 水平都显著降低，线粒体生物功能转录共激活因子 PGC-1 α 和葡萄糖转运蛋白 GLUT4 呈现下调趋势。在此基础上过表达 PGC-1 α 并使用 Tenovin-6 处理结肠癌细胞，发现结肠癌的增殖能力和代谢水平以及 GLUT4 的 mRNA 水平和蛋白水平得到一定程度的恢复。体内实验结果也显示 PGC-1 α 特异性激活剂 ZLN005 处理后能够显著恢复 Tenovin-6 引起的结肠癌肿瘤细胞成瘤性抑制。

结论：Tenovin-6 能够通过下调 PGC-1 α /GLUT4 通路从而抑制结肠癌细胞代谢水平和增殖。

关键词：结肠癌细胞；Tenovin-6；细胞增殖；细胞代谢；PGC-1 α ；GLUT4

259. 小细胞肺癌患者化疗前后血清 ApoB/ApoA1,NLR,PLR 水平联合检测的临床意义

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目的：探讨 ApoB/ApoA1（载脂蛋白 B/载脂蛋白 A1），中性粒与淋巴细胞比率（neutrophil to lymphocyte ratio, NLR），血小板淋巴细胞比值（platelet to lymphocyte ratio, PLR）在小细胞肺癌患者外周血水平变化及化疗疗效相关性。

方法：选取 2017 年 1 月至 2019 年 12 月我院住院的无法手术的小细胞肺癌患者 67 例，其中局限期 26 例，广泛期 41 例，分别于化疗前及依托泊苷联合铂类 2 周期化疗后，清晨空腹抽取静脉血，测 ApoA1,ApoB,中性粒细胞计数,淋巴细胞计数,血小板计数，计算 ApoB/ApoA1,NLR,PLR，并对监测检测结果进行分析。



结果：局限期与广泛期血清 ApoB/ApoA1,PLR 水平无统计学意义（均 $P>0.05$ ），局限期与广泛期 NLR 水平差异有统计学意义（ $P<0.05$ ）；在治疗有效组，化疗后与化疗前相比，ApoB/ApoA1,NLR 水平均显著下降，差异具有统计学意义（均 $P<0.05$ ），PLR 水平下降，但差异无统计学意义（ $P>0.05$ ），在无效组，化疗后与化疗前相比，ApoB/ApoA1,NLR,PLR 水平差异无统计学意义（均 $P>0.05$ ）。

结论：NLR 可以作为在小细胞肺癌初诊分期的标记物之一，血清 ApoB/ApoA1,NLR 联合检测，可以评估小细胞肺癌患者化疗疗效,观察患者病情动态变化。

关键词：小细胞肺癌；载脂蛋白 B/载脂蛋白 A1；中性粒与淋巴细胞比率；血小板淋巴细胞比值；化学疗法；疗效评估

260. 去氧地胆草素通过细胞凋亡途径抑制细胞生长并增强结肠癌对 5-氟尿嘧啶的化学敏感性

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背景：结肠癌是人类癌症死亡的主要原因之一，主要通过手术和化疗进行治疗。然而，晚期病人的预后仍然很差，迫切需要有效治疗结肠癌的新策略。地胆草及其提取物去氧地胆草素（DET）具有抗炎和抗癌活性。然而,它们的抗癌机制尚不清楚。本研究分析了 DET 对结肠癌的抑制作用，并进一步探讨了潜在的分子机制。

材料与方法：采用 qRT-PCR 检测结直肠癌细胞中 Bcl-2 和 miRNAs 的表达；构建稳定过表达 Bcl-2 的两个结直肠癌细胞系；MTT 增殖试验,克隆形成,Edu 实验用于评估 DET 对结直肠癌细胞的增殖作用的影响。细胞流式试验用来测定周期阻滞和凋亡水平；Western Blot 检测两组细胞 G2/M 期阻滞的周期蛋白和凋亡蛋白的表达水平；IHC 实验检测体内实验肿瘤块的增值能力。

结果：DET 能够抑制结肠癌细胞的增殖,集落形成,细胞周期和诱导凋亡，并抑制了免疫缺陷小鼠的肿瘤生长。从机制上讲，DET 降低了抗凋亡蛋白 Bcl-2 的水平，Bcl-2 的过表达抑制 DET 诱导的细胞凋亡。此外，我们发现 DET 可以增强结肠癌对 5-氟尿嘧啶 (5-Fu) 的化疗敏感性。

结论：DET 通过 Bcl-2 凋亡途径抑制结直肠癌发展。此外，我们揭示了 DET 可以增强结肠癌对 5-氟尿嘧啶的化疗敏感性。

关键词：去氧地胆草素；结直肠癌；细胞凋亡；Bcl-2；5-氟尿嘧啶

261. 去甲泽拉木醛调控胃癌细胞增殖和迁移侵袭的机制研究

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背景: 胃癌是人类最常见的消化系统恶性肿瘤之一。去甲泽拉木醛是从雷公藤中提取的一种天然功能单体,对包括胃癌在内的多种癌症具有抗肿瘤作用,但其潜在机制尚不清楚。本研究目的即为探究去甲泽拉木醛抑制胃癌细胞发生及其可能的机制。

方法: 采用 MTT, BrdU 和 Western blot 实验检测去甲泽拉木醛对胃癌细胞增殖能力的影响;采用划痕实验, Transwell 实验和 Western blot 实验检测去甲泽拉木醛对胃癌细胞迁移侵袭能力的影响;随后 Western blot 实验检测胃癌细胞中 c-Myc 蛋白, FBXW7 蛋白, 周期相关蛋白 (CDK4, CDK6, cyclinD1) 和迁移侵袭相关蛋白 (N-cadherin, E-cadherin, MMP9, Vimentin) 的表达情况;异种移植瘤模型实验检测去甲泽拉木醛对胃癌的体外克隆形成能力和体内成瘤能力的影响;最后,通过 MTT 实验, BrdU 实验以及金氏公式等实验方法对去甲泽拉木醛能否增强胃癌细胞对 5-氟尿嘧啶和阿霉素的化疗敏感性进行检测。

结果: 去甲泽拉木醛能够抑制胃癌细胞的增殖和迁移侵袭能力,这是通过下调 c-Myc 蛋白的表达水平介导的。机制上是去甲泽拉木醛通过上调 E3 泛素连接酶 FBXW7 来降低 c-Myc 蛋白的稳定性。此外,在异种移植瘤模型实验中,去甲泽拉木醛抑制肿瘤的生长,这依赖于抑制 c-Myc 的表达。最后,去甲泽拉木醛增强了胃癌细胞对 5-氟尿嘧啶和阿霉素联合治疗的体外化疗敏感性。

结论: 去甲泽拉木醛通过 FBXW7/c-Myc 通路抑制胃癌细胞的增殖和迁移侵袭能力,并且还能增强胃癌细胞对化疗药物 5-氟尿嘧啶和阿霉素的体外化疗敏感性,为其在未来胃癌治疗中的应用奠定了理论基础。

关键词: 去甲泽拉木醛;胃癌;FBXW7; c-Myc; 细胞增殖; 细胞迁移; 化疗敏感性

262. Ki67 阳性指数与肝细胞癌切除及术后辅助经动脉化疗栓塞治疗的预后关系研究

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背景与目的: 对于可切除的肝细胞癌 (HCC), 肝切除术为标准治疗方法, 但术后复发率仍居高不下。术后辅助经动脉化疗栓塞术 (PA-TACE) 是目前推荐的延长无瘤生存期 (TFS) 的局部治疗方法, 特别是对于有复发高危因素的患者。但很多数据表明其只对部分患者有益, 确切疗效仍有争议。前期研究表明 Ki67 阳性指数与伴有 MVI 的肝细胞癌患者的早期复发密切相关。然而, Ki67 并未纳入 PA-TACE 术前评估的常用指标。本研究评估肝细胞癌患者 Ki67 阳性指数与肝切除术及肝切除术联合 PA-TACE 治疗的预后相关性, 旨在探索 Ki67 在 PA-TACE 获益人群筛选中的潜在价值。



方法：回顾从 2012 年 1 月到 2020 年 12 月接受 R0 切除术（HR）联合或不联合 PA-TACE 治疗的 716 名肝细胞癌患者的临床资料，运用 Cox 回归方法对总体患者进行单因素和多因素分析以评估 PA-TACE 与 Ki67 等因素对 TFS 的预后价值。并以 Ki67 阳性指数等级及肝切除术后是否联合 PA-TACE 治疗将总体样本分为不同亚组，探讨 PA-TACE 在总体及各亚组中对 TFS 影响并对早期复发率及不同复发模式进行比较。

结果：接受或不接受肝切除术后联合 PA-TACE 治疗的患者在 TFS 方面没有显著差异。然而，在 Ki67 指数低度（<30%）或中度（30%~59%）的患者分组中，PA-TACE 在 TFS 上体现出显著的统计学优势。Ki67 高表达的患者显示出较高的总体复发率、早期复发率、肝内多发复发率和肝外转移率。所有患者的不良反应发生率仅为 7.9%，与化疗栓塞相关的最显著的副作用是发烧、恶心/呕吐和短暂的肝毒性。

结论：术后辅助经动脉化疗栓塞术（PA-TACE）是一种耐受性良好的术后辅助治疗方法，适用于 Ki67 指数水平相对较低的患者。在 Ki67 水平相对较高的患者中则难以达到预期疗效。

讨论：Ki67 的高表达预示肿瘤的高增殖/侵袭能力，且患者术前可能即有微小癌灶的播散，则 PA-TACE 难以将其扼杀在萌芽之中。Ki67 指数可能是预测 HCC 患者预后的潜在标志物，也是决定是否推荐患者接受 PA-TACE 以降低术后复发风险时需要考虑的额外因素。

关键词：Ki67 指数；术后辅助经动脉化疗栓塞 (PA-TACE)；早期复发；复发模式；精准治疗

263. snoRD4A 作为肾透明细胞癌新型标志物及调控其生物学行为的研究

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背景：肾细胞癌（Renal Cell Carcinoma, RCC，简称肾癌）是起源于肾小管上皮的恶性肿瘤，占肾脏恶性肿瘤的 80%-90%，其最常见的病理类型为透明细胞癌，近年来肾癌的全球发病率以每年 2%-3% 的速度持续增长，已经成为全球男性第六大常见癌症。多项研究表明 snoRNAs 的异常表达直接影响着肿瘤的发生、发展及预后。在多种肿瘤中普遍存在有 snoRNAs 异常表达，但在特定肿瘤中只有特定 snoRNAs 表达异常，这表明 snoRNAs 表达却具有肿瘤类型特异性。

目的：验证尿沉渣中 snoRD4A 作为肾透明细胞癌（Clear cell renal cancer cell, ccRCC）新型标志物能力，并探索 snoRD4A 对 ccRCC 发生发展的驱动作用。

研究方法：①通过肾癌组织 TCGA 数据，筛选出与肾癌发生发展密切相关的 snoRNAs，RT-PCR 验证肾癌患者和健康志愿者之间血浆、尿沉渣 snoRNAs 分子表达差异情况，计算诊断效能；②进行肾癌恶性生物学行为体外功能实验，包括 CCK8 实验，克隆形成实验，细胞凋亡实验等；



③慢病毒构建过表达或沉默表达 snoRD4 稳筛细胞株，进行裸鼠皮下成瘤实验；④蛋白质谱分析差异蛋白，WB 验证差异蛋白表达。

结果：①snoRD4A 在肾癌石蜡组织、血浆以及尿沉渣中表达升高。②在肾癌细胞中沉默 snoRD4A 表达，细胞的增殖、克隆形成能力减弱，凋亡能力增强；在肾癌细胞中过表达 snoRD4A，细胞的增殖和克隆形成能力增强，凋亡能力减弱；③在动物体内沉默 snoRD4A 的表达，肿瘤体积明显减小；④蛋白质谱实验、western blot 实验以及拯救实验表明 snoRD4A 可能通过 Wnt 信号通路调控肾癌恶性生物学行为。

结论：尿沉渣 snoRD4A 可作为 ccRCC 的一种无创性诊断标志物。且 snoRD4A 通过 Wnt 信号通路调控 ccRCC 恶性生物学行为。

关键词：肾透明细胞癌；snoRNAs；标志物；snoRD4A

264. NRAGE 与 RNF8/BARD1 形成复合体参与同源重组修复介导食管癌化疗抵抗

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目的：NRAGE 是一种神经营养素受体相关的黑色素瘤抗原基因同源物，其表达在化疗抵抗的食管肿瘤细胞的细胞核中显著增加，并促进食管癌细胞的增殖。在肿瘤细胞中，DNA 损伤修复可促进细胞生长并抵抗 DNA 损伤类的化疗药物。在这项研究中，我们旨在研究 NRAGE 在 DNA 损伤修复中的作用和潜在机制，并为食管癌的治疗提供可能的靶标。

方法：采用彗尾实验、同源重组修复（HR）及非同源末端连接（NHEJ）报告系统，并建立了紫外线照射的皮肤肿瘤模型，以研究 NRAGE 在 DNA 损伤修复中的直接作用。通过体外药物敏感性实验、体内裸鼠成瘤实验，免疫印迹和免疫组织化学实验，评估了敲减 NRAGE 的食管癌细胞在体外和体内对 DNA 损伤药物的敏感性。采用荧光实时定量 PCR（qRT-PCR）和免疫印迹分析，测定 NRAGE 干扰的食管癌细胞中 DNA 损伤修复相关因子的表达水平。通过 GST pull-down 实验和免疫沉淀，以探究 NRAGE 在同源重组修复中的机制。

结果：NRAGE 促进同源重组修复，可在体内和体外调节食管癌细胞的化疗耐药性。NRAGE 通过泛素-蛋白酶体途径调节 RNF8 和 BARD1 的稳定性，并与两个蛋白质的 RING 结构域相互作用，形成复合体，参与 DNA 损伤修复。此外，在食管鳞癌组织中，NRAGE 蛋白的表达与 RNF8 和 BARD1 密切相关。

结论：上述结果表明，核定位的 NRAGE 与 RNF8 和 BARD1 相互作用以介导食管癌细胞的化疗抵抗，并有望成为食管癌的生物标志物和治疗靶点。

关键词：NRAGE；DNA 损伤修复；食管鳞癌



265. 靶向 circFARSA 的新型纳米药物 pSiNPs-PEI-siRNA-circFARSA 对胰腺癌的治疗作用及机制研究

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研究目的: 胰腺癌作为全球致死性极高的几大疾病之一,一直备受科研工作者的关注。虽然手术疗法及多种化疗药物已广泛应用于胰腺癌的临床治疗策略中,但由于多数胰腺癌的晚期诊断及耐药现象,导致其致死率一直居高不下。因此,研发基于新靶点的抗胰腺癌药物迫在眉睫。在本项目的前期研究中,我们通过分析对比癌症患者及健康人的细胞外囊泡,发现癌症患者细胞外囊泡中显著高表达 circFARSA。因此本项目中,我们设计合成靶向 circFARSA 的抑制剂,目的是:(1)验证 circFARSA 是胰腺癌的新型抗癌靶点;(2)制备合成靶向 circFARSA 的新型胰腺癌抗癌药物,为未来胰腺癌的治疗提供更多选择。

材料与方法: 本项研究中,我们设计合成一种可特异性抑制 circFARSA 表达的 siRNA,并命名为 siRNA-circFARSA。利用脂质体(Liposome)作为 siRNA-circFARSA 的药物递送系统,我们制备了负载 siRNA-circFARSA 的脂质体药物(命名为: Liposome-siRNA-circFARSA)。利用 qRT-PCR 及 Western blot 实验,我们探讨了 Liposome-siRNA-circFARSA 的抗癌机制。利用细胞增殖曲线及迁移实验,我们探讨了 Liposome-siRNA-circFARSA 对胰腺癌增殖及迁移能力的抑制作用。为进一步提升纳米药物的抗癌功能,我们将多孔硅纳米颗粒(pSiNPs)代替脂质体,制备负载 siRNA-circFARSA 的多孔硅纳米药物(命名为: pSiNPs-PEI-siRNA-circFARSA)。本项研究中,我们不但探讨了 pSiNPs-PEI-siRNA-circFARSA 对胰腺癌增殖及迁移能力的抑制作用,还利用 PDX 模型小鼠分析对比两种纳米药物的体内抗癌作用。

结果: 体外数据证实, Liposome-siRNA-circFARSA (Si: 0.7 $\mu\text{g/mL}$) 展示出显著的抗胰腺癌作用:如显著抑制胰腺癌细胞 PANC-1 及 SW1990 增殖,迁移能力。机制探讨证实, siRNA-circFARSA 递送至胰腺癌细胞内后,可通过抑制 circFARSA 的表达,进而抑制 Bcl-2 蛋白表达,最终导致胰腺癌细胞凋亡。为优化 siRNA-circFARSA 的药物递送系统,进而提升其抗癌功能,我们进一步合成了 pSiNPs-PEI-siRNA-circFARSA 纳米药物。表征数据显示, pSiNPs-PEI-siRNA-circFARSA 的水合粒径范围为 91.28 nm ~ 615.1 nm, 平均水合粒径约为 257 nm; 表面电位约为 27.1 mV。体外抗癌数据显示, pSiNPs-PEI-siRNA-circFARSA (Si: 0.7, 5.6 $\mu\text{g/mL}$) 均可显著抑制胰腺癌细胞 COLO-357 及 SW1990 的生长,且这种抑制作用呈剂量依赖性。机制讨论部分显示, pSiNPs-PEI-siRNA-circFARSA (Si: 0.7, 5.6 $\mu\text{g/mL}$) 均可抑制 circFARSA 的表达,且这种抑制作用呈剂量依赖性。最后,体内实验显示, pSiNPs-PEI-siRNA-circFARSA (Si: 22.4 $\mu\text{g/mL}$)

可显著抑制 PDX 模型小鼠肿瘤的生长。且 pSiNPs-PEI-siRNA-circFARSA 的抗癌功能及生物安全性显著高于 Liposome-siRNA-circFARSA。

结论: ①本项研究证实了 circFARSA 是胰腺癌的新型抗癌靶点; ②本项研究中合成的 pSiNPs-PEI-siRNA-circFARSA 是一种靶向 circFARSA 的新型胰腺癌抗癌药物, 为未来胰腺癌的治疗, 提供了更多候选药物。

关键词: 胰腺癌; circFARSA; siRNA; 多孔硅; 脂质体

266. HPV16 integration regulates ferroptosis resistance via the c-Myc/miR-142-5p/HOXA5/SLC7A11 axis during cervical carcinogenesis

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Ferroptosis, a novel form of regulated cell death driven by small molecules or conditions, plays an important role in virus-associated carcinogenic processes. However, whether tumours arising after high-risk HPV integration are associated with ferroptosis is unexplored and remains enigmatic. Here, we found that expression of the HPV16 integration hot spot c-Myc negatively correlates with ferroptosis during the progression of cervical squamous cell carcinoma (CSCC). We further confirmed that miR-142-5p, which was upregulated as a potent oncogene in HPV16-integrated CSCC cells, is a major downstream effector of c-Myc in its target network. Inhibitor of miR-142-5p drastically reduced the ferroptosis-suppressing effect mediated by c-Myc. By an integrated computational and experimental approach, HOXA5 was identified as an important downstream target gene of miR-142-5p. Ectopic expression of miR-142-5p suppressed HOXA5 expression, resulting in decreased lipid reactive oxygen species (ROS) and malondialdehyde (MDA) accumulation. HOXA5 increased the sensitivity of CSCC cells to erastin-induced ferroptosis via transcriptional downregulation of SLC7A11, which acts as a negative regulator of ferroptosis. Importantly, c-Myc knockdown increased the antitumour activity of erastin by enhancing ferroptosis both in vitro and in vivo. Collectively, these data indicate that the HPV16 integration hot spot c-Myc plays a novel and indispensable role in ferroptosis resistance by regulating the miR-142-5p/HOXA5/SLC7A11 signalling axis and suggest a potential therapeutic approach for HPV16 integration-related CSCC.

Key words: HPV16 integration; ferroptosis; cervical carcinogenesis; c-Myc; SLC7A11

267. 肿瘤医院 XN 血液分析流水线复检规则的建立与应用探讨

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目的: 为了统一我院血液分析的复检规则, 避免错检或漏检并提高工作效率, 对我院即将投入临床运行的 Sysmex XN 血液流水线准备引用的二套复检规则进行临床验证, 并根据临床验证的结果进行调整, 以期建立合适我院病人特点的血液分析复检规则。

方法: 随机选择我院 1003 例样本全部进行血涂片制备及显微镜镜检, 并将显微镜镜检结果录入到用于统计分析的 laboman 软件中, 该软件中已经装载有国际血液学 41 条复检规则及中华医学会检验分会推荐的 23 条复检规则; 分别用这两套规则进行统计, 得到复检率, 假阴性率和假阳性率, 及触发不同规则的病例信息, 再根据假阴性, 假阳性样本的检测结果及报警信息特点, 以及 XN 的 WPC 通道和 PLT-F 通道的功能特点对复检规则进行调整, 直到符合临床需求, 作为我院最终使用的自建规则。

结果: “国际血液学 41 条规则”条件下的推片复检率 51.25%, 假阴性率 1.79%, 假阳性率 34.30%; “中国 23 条规则”条件下的推片复检率 43.57%, 假阴性率 4.99%, 假阳性率 26.52%。“自建规则”的推片复检率 39.28%, 假阴性率 3.69%, 假阳性率 17.35%。应用“自建规则”对 300 例肿瘤患者进行验证, 推片复检率 33.49%, 假阴性率 1.40%, 假阳性率 25.58%。

结论: 由于不同品牌, 不同型号的血液分析仪的检测原理, 检测性能差异很大; 另外, 不同种类的医院病人特点也有差异, 因此, 在使用任何一款新的血液分析仪时, 必须建立其独特的复检规则, 才能在避免错检和漏检的情况下提高工作效率, 并为临床的诊疗提供可靠的检测结果及形态学信息。

关键词: 肿瘤医院; 血液分析仪; 复检规则; 外周血涂片

268. Analysis of the expression levels of m5C mRNA methylation-related enzymes in gastric cancer and the relationship with the prognosis

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5-methylcytosine (m5C) is one of the important RNA modifications and plays essential roles in nuclear export, transcript stability and translation initiation in eukaryotic cells, thus regulating cell division and protein synthesis. m5C can be dynamically and reversibly regulated by specific enzymes termed as ‘writers’ (methyltransferases), ‘readers’ and ‘erasers’ (demethylases). m5C RNA modification is catalyzed by ‘writers’ such as NOL1/NOP2/SUN domain (NSUN) family of proteins (NSUN1, NSUN2, NSUN3, NSUN4, NSUN5, NSUN6 and NSUN7) as well as the DNA methyltransferase (DNMT) homologue DNMT2, which use S-adenosylmethionine (SAM) as the methyl donor. However, among such diversified writers, only NSUN2 can install m5C on mRNA. Erasers (TET1 and TET3) are the protein factors responsible for removing modifications on mRNA. Aly/REF export factor

(ALYREF) and YBX1, two specific mRNA m5C-binding proteins that can read modifications and maintain the stability of target mRNA, were identified as readers of m5C.

It has been found that a variety of m5C regulators are associated with tumorigenesis and development. In order to explore whether the levels of m5C mRNA methylation regulators are related to gastric cancer, and the correlation between the expression levels of m5C mRNA methylation-related enzymes and the prognosis of gastric cancer patients, online TCGA analysis database UALCAN (<http://ualcan.path.uab.edu/analysis.html>) was used to compare the expression levels of m5C mRNA methylation-related enzymes across gastric cancer samples and normal tissues and study their association with the prognosis of patients. Besides, Gene Expression Profiling interactive Analysis GEPIA (<http://gepia.cancer-pku.cn/>) was employed to further analyze the connection between m5C mRNA methylation-related enzymes and hypoxia inducible factor HIF1A.

The results showed that the expression levels of Writers NSUN2, NSUN3, NSUN6, NSUN7, and DNMT2 were significantly up-regulated in gastric cancer compared with normal tissue, and the expression levels of Readers ALYREF and YBX1 were significantly increased in gastric cancer. In addition, the expression levels of Erasers ALKBH1, TET1, TET3 in gastric cancer were also significantly augmented. It was also found that the high level of Eraser TET1 was relevant to the poor prognosis for GC patients in the further analysis. In the correlation analysis with hypoxia-inducible factor HIF1A, it was revealed that the expression levels of Writers NSUN2, NSUN3, DNMT2 and Erasers ALKBH1 and TET3 were positively correlated with the expression level of HIF1A. Among them, the relationship between the expression of Writers NSUN3 and the expression of HIF1A was closest. ($R=0.34$).

The above results suggested that the m5C mRNA methylation-related enzymes were indeed involved in gastric cancer, and might promote the proliferation of gastric cancer cells and participate in the development of gastric cancer. The expression level of Eraser TET1 was related to the prognosis, and could be used as a prognostic indicator for patients with gastric cancer. It demonstrated that there was a link between the expression levels of Writers NSUN2, NSUN3, DNMT2 and hypoxia inducible factor HIF1A. The expression levels of Erasers ALKBH1 and TET3 were positively correlated with HIF1A, indicating that m5C mRNA methylation may interact with hypoxia. The interplay between the expression level of NSUN3, a more relevant molecule, and HIF1A expression was more desirable to be analyzed to explore the relationship between NSUN3 and hypoxia.

Key words: Gastric cancer; RNA methylation; m5C; Prognostic analysis; Hypoxia

269. 食管癌糖代谢异常研究进展

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食管癌是常见的消化道肿瘤，其发病率在全球恶性肿瘤中排第 6 位，死亡率排第 4 位。中国是食管癌高发国家，其新增病例和死亡率分别位于第 5 位和第 4 位，严重威胁人民健康^[1]。糖代谢异常是肿瘤发生的重要关联因素。近年研究发现，肿瘤细胞存在异常糖代谢并倾向于有氧糖酵解。与正常细胞相比，肿瘤细胞消耗更多的葡萄糖，即使在有氧条件下，肿瘤细胞仍然会优先选择糖酵解的方式提供肿瘤生长所需的能量，称为“瓦伯格效应”（Warburg 效应）^[2]。虽然有氧糖酵解过程中每分子葡萄糖产生的能量少于氧化磷酸化产生的能量，但是在葡萄糖量充足的情况下，有氧糖酵解产生 ATP 的速率可以超过氧化磷酸化产生 ATP 的速率^[3]。肿瘤细胞为适应外界环境，上调糖酵解催化酶，以代偿肿瘤细胞的生物能量及生物合成。糖酵解途径还可以产生乳酸，后者破坏肿瘤细胞周围的细胞基质，促进肿瘤细胞迁移。另一条葡萄糖代谢的重要途径是磷酸戊糖途径。磷酸戊糖途径的代谢产物可以用于生物大分子的合成，如核糖-5-磷酸则可用于 DNA 的合成，对于细胞的复制及其重要。同时它生成的 NADPH 也是细胞内维持细胞内氧化还原稳态不可或缺的还原剂。由于代谢加速，癌细胞通常比正常细胞显示更高水平的细胞内活性氧物质，后者过多将促进癌症的发展。故磷酸戊糖途径的失调会影响肿瘤细胞的生长与存活^[4]。对于食管癌发生发展中存在的糖代谢异常，Du 等^[5]人采用蛋白质组学技术对 41 例鉴定食管癌差异蛋白时，发现其中部分蛋白与糖酵解有关。食管鳞状细胞癌细胞 GLUT-1 过度表达，葡萄糖更易进入细胞，增强了有氧糖酵解，促进了肿瘤细胞的增殖与侵袭，患者生存率降低。Fang 等人发现对于食管鳞状细胞癌细胞，在缺乏葡萄糖时，NRF2/ATF4 的表达会增强，导致 ASNS 上调，一定程度上增强肿瘤细胞的增殖和迁移能力。Fukuda 等^[6]人发现提高丙酮酸激酶活性可能抑制食管癌肿瘤生长。Shuichi Fukuda 等的研究中发现，抑制 M2 型丙酮酸激酶，可以减少葡萄糖流入磷酸戊糖途径，导致顺铂治疗后细胞内活性氧自由基（ROS）水平升高，从而恢复顺铂的敏感性。这可能是克服耐药性的一种机制。Nrf2 可以通过对糖代谢进行重编程，主要是诱导磷酸戊糖途径，增强细胞生长所需的代谢合成原料，从而增强肿瘤细胞的增殖能力，可用作食管癌的靶向治疗靶点^[7]。总之，细胞代谢异常是肿瘤发生发展的关键特征，糖代谢异常是其中最基本的特征。通过靶向肿瘤细胞糖代谢过程，修正细胞代谢异常成为预防肿瘤发生发展和治疗肿瘤的新思路。目前关于食管癌的糖代谢研究还需要进一步深入。

关键词：食管癌；糖代谢；靶向治疗；

270. 线粒体 DNA 释放激活 cGAS-STING-NF κ B-TGF β 1 通路在放射反应中的作用

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目的: 放射诱导纤维化 (RIF) 是一种晚期并发症, 严重影响放射治疗后癌症幸存者的生活质量。

转化生长因子- $\beta 1$ (TGF- $\beta 1$) 是参与纤维化病理过程的原型纤维化细胞因子。然而, 辐射如何导致 TGF- $\beta 1$ 持续分泌, 进而诱导长期纤维化的分子机制仍不清楚。

方法: 本研究采用 6MV X 射线照射 EA.Hy926 细胞系 (40Gy/20F, 5F/W), 成功构建出持续分泌 TGF $\beta 1$ 的细胞模型, 并进一步对内在机制进行探索。

结果: 在本研究中, 我们发现在重复照射的 EAy926 细胞 (EA-R 细胞) 中, 线粒体功能障碍导致 TDP-43 以线粒体膜电位依赖性方式易位至线粒体, 从而进一步促进线粒体 DNA (mtDNA) 进入细胞质。细胞质中的 mtDNA 不断刺激 DNA 感受器 cGAS, 进而激活 cGAS-STING-NF κ B 信号, 增加 TGF- $\beta 1$ 的表达。这些是形成 RIF 的关键, 并已在临床组织中得到验证。同时, cox 抑制剂阿司匹林和 ACEI 药物卡托普利分别通过抑制 cGAS 和 NF κ B 来抑制 EA-R 细胞中 TGF- $\beta 1$ 的表达。更重要的是, 上调线粒体复合物 I 亚基 NDUFS1 的表达后, 可以逆转 TDP43-cGAS-STING-NF κ B-TGF- $\beta 1$ 信号通路。术前放疗的直肠癌患者组织中 TDP-43, STING 和 TGF- $\beta 1$ 的表达明显高于对照组。卡托普利治疗在放疗后 1-4 个月时抑制了血液中 TGF- $\beta 1$ 水平并减轻了癌症患者的急性毒性。

结论: 总的来说, 我们发现受损的线粒体和 cGAS-STING-NF κ B 通路与 RIF 密切相关。恢复线粒体功能并靶向该途径, 可能是预防 RIF 的潜在有效治疗策略。

关键词: 线粒体 DNA; 放疗导致的纤维化; TGF- $\beta 1$; cGAS-STING

271. 乳头状肾细胞癌 lncRNAs 风险预后模型建立与分析

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目的: 通过构建长链非编码 RNA (long non-coding RNA, lncRNAs) 风险模型用于评估乳头状肾细胞癌 (papillary renal cell carcinoma, PRCC) 预后, 探讨 lncRNAs 相关基因在 PRCC 临床应用价值。

方法: 基于 TCGA 数据库中 PRCC 的 lncRNAs 表达谱及临床数据, 采用 Cox 回归和 Lasso 回归分析对 lncRNAs 进行差异表达分析, 计算个体 lncRNAs 风险评分并建立可预测患者预后的 lncRNA 风险评分模型, 运用 Kaplan-Meier 生存分析, 时间依赖性受试者工作特征曲线 (receiver operating characteristic curve, ROC), C 指数 (concordance index, C-index) 评估该模型对患者预后的预测效能。采用共表达方法预测差异 lncRNAs 靶基因并进行筛选, 然后利用 KEGG 和 GO 富集分析预测 lncRNAs 靶基因功能。

结果: 从 TCGA 数据库共下载 289 例 PRCC 患者和 32 例健康对照者的 lncRNAs 表达谱及临床数据, 筛选获得 1002 个在 PRCC 组织和正常组织间差异表达的 lncRNAs。运用单因素 Cox 回归筛选得到 337 个与膀胱癌患者生存预后相关的 lncRNAs, 进一步通过 Lasso 回归分析得到 7 个与风

险预后模型紧密相关的 lncRNAs, 成功构建 lncRNAs 风险预后模型。模型风险评分 $= (1.87 \times \text{Exp AC010478.1}) + (1.82 \times \text{Exp AC015849.5}) + (0.39 \times \text{Exp AC024022.1}) + (0.66 \times \text{Exp AC084026.1}) + (3.13 \times \text{Exp AC090833.1}) + (2.59 \times \text{Exp AL499627.1}) + (1.19 \times \text{Exp MNX1-AS1})$ 。ROC 曲线显示, lncRNAs 模型的 3 年生存率 AUC=0.857, 5 年生存率 AUC=0.828, C 指数为 0.886, 提示风险预后模型具有较好的预测效能。K-M 生存分析提示模型评分越高的患者 5 年生存率越低。GO 和 KEGG 富集分析显示差异 lncRNAs 参与调控物质跨膜转运, DNA 复制, 酶活性调节等信号通路, 提示其在 PRCC 发生发展过程中具有重要的潜在作用。

结论:成功构建了 PRCC 的 lncRNAs 风险预后评估模型, 可用于预测 PRCC 患者的生存预后情况。

关键词: 乳头状肾细胞癌; 长链非编码 RNA; 预后; TCGA

272. Comprehensive analysis of TPX2 in Head and neck squamous cell carcinoma with prognostic values

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Objective: Targeting protein for Xenopus kinesin-like protein 2 (TPX2) is a microtubule-associated protein required for mitosis and spindle assembly. It has been revealed that TPX2 is overexpressed in various human cancers and promotes cancer progression, while its role in head and neck squamous cell carcinoma is unknown. We aimed to demonstrate the relationship between TPX2 and head and neck squamous cell carcinoma.

Methods: This study investigated the expression and roles of TPX2 in HNSC using Oncomine, The Cancer Genome Atlas, UALCAN, Human Protein Atlas, Clinical Proteomics Tumor Analysis Consortium, GeneMANIA, Tumor Immune Estimation Resource, GEPIA databases.

Results: High mRNA and protein expression of TPX2 were found to be significantly associated with clinical cancer stages, nodal metastasis status, and patient's gender in HNSC patients.

Conclusion: Taken together, these results indicated that TPX2 could be a potential target in the development of anti-HNSC therapeutics and an efficient marker of the prognostic value of HNSC.

Key words: head and neck squamous cell carcinoma; TPX2; public databases; prognostic value; comprehensive analysis

273. 膳食脂肪摄入与胰腺癌发病风险：基于剂量反应的系统综述与荟萃分析

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背景: 不当膳食脂肪摄入可能是胰腺癌 (pancreatic cancer, PC) 发生的潜在风险因素。但流行病学的调查结果一直存在争议或与实验室研究结论不一致。我们对近二十年的随机对照研究及队列研究进行了系统的回顾和剂量反应 meta 分析。

方法: MEDLINE (Pubmed), Embase, Web Of Science, Cochrane 用于检索 2000 年 1 月至 2020 年 12 月期间确定了已发表的随机对照研究及队列研究文献。随机效应模型用于估计相对风险 (Hazard ratio, HR) 和 95% 置信区间 (Confidence interval, CI)。我们还进行了亚组、敏感性和发表偏倚分析。

结果: 所收集的 1 项随机对照研究和 13 项队列研究中包括 4387 例 PC 和 1, 326, 517 例非 PC。通过比较最高和最低膳食总脂肪或脂肪酸摄入量, 我们发现较高的膳食总脂肪 [lgHR=0.17, 95%CI= (0.09, 0.24), I²=34.6%, P=0.074] 摄入量及饱和脂肪酸 [lgHR=0.15, 95%CI= (0.08, 0.22), I²=67.3%, P=0.000] 摄入量与 PC 发病风险呈显著正相关; 单不饱和脂肪酸 [lgHR=0.01, 95%CI= (-0.10, 0.13), I²=44.6%, P=0.094] 及多不饱和脂肪酸 [lgHR=0.05, 95%CI= (-0.06, 0.17), I²=59.7%, P=0.021] 与 PC 发病风险之间没有观察到显著关联。亚组分析发现, 在没有对混杂因素 Body Mass Index (BMI) 进行调整时, 单不饱和脂肪酸 [lgHR=0.20, 95%CI= (0.03, 0.37), I²=58.3%, P=0.048] 摄入可增加 PC 发生风险。在随访超过 10 年的研究中, 多不饱和脂肪酸摄入 [lgHR=0.21, 95%CI= (0.02, 0.40), I²=58.3%, P=0.048] 可显著增加 PC 发生风险。我们没有发现发表偏倚的证据。

结论: 膳食总脂肪及饱和脂肪酸摄入量与 PC 发病风险正相关, 其中饱和脂肪酸摄入量 (g/day 及 %energy) 越高, PC 风险越高, 呈线性剂量-反应关系。亚组分析显示, 在没有对混杂因素 Body Mass Index (BMI) 进行调整的研究及在随访超过 10 年的研究中, 不饱和脂肪酸可能会增加 PC 发生风险。

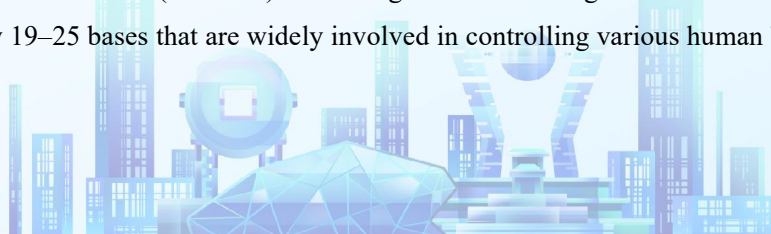
关键词: 膳食脂肪; 胰腺癌; Tumorigenesis; meta-analysis

274. DNMT1-induced miR-378a-3p silencing promotes angiogenesis via NF- κ B signaling pathway by targeting TRAF1 in hepatocellular carcinoma

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Background: Angiogenesis plays an important role in the occurrence, development and metastasis of hepatocellular carcinoma (HCC) and is a key target for pharmaceutical intervention in various malignancies. MicroRNAs (miRNAs) are endogenous noncoding RNA molecules with a length of approximately 19–25 bases that are widely involved in controlling various human biological processes.



miR-378a-3p participates in tumorigenesis and tumor metastasis according to previous studies, yet the exact role it plays in HCC angiogenesis remains poorly understood.

Methods: TCGA database, in situ immunohybridization, and qRT-PCR were used to investigate the expression miR-378a-3p in HCC tissues and cell lines. Its correlation with the clinicopathological characteristics and prognosis of HCC patients was analyzed. The effects of miR-378a-3p on HCC in vitro and in vivo were examined by CCK-8, transwell assay, tube formation and matrigel plug assay. RNA sequencing, bioinformatics analysis, luciferase reporter assay, immunofluorescence assay and ChIP assay were used to detected the molecular mechanism of miR-378a-3p-induced inhibition of angiogenesis.

Results: We confirmed that the expression of miR-378a-3p was significantly downregulated and was associated with microvascular density (MVD) in HCC, which indicated a short survival time of HCC patients, and reducing miR-378a-3p expression led to a significant increase in angiogenesis in vitro and in vivo. miR-378a-3p directly targeted TNF receptor associated factor 1 (TRAF1) to attenuate NF- κ B signaling, and then decreases secreted vascular endothelial growth factor (VEGF). DNA methyltransferase 1 (DNMT1) mediated hypermethylation of miR-378a-3p was responsible for downregulating of miR-378a-3p. Moreover, a series of investigation indicated that p65 initiated a positive feedback loop, which could up-regulate DNMT1 to promote hypermethylation of the miR-133a-3p promoter.

Conclusions: Our study indicates that miR-378a-3p is involved in HCC angiogenesis, which may be a biomarker for HCC.

Key words: Angiogenesis; HCC; miR-378a-3p; TRAF1; DNA methylation

275. DKK4 在结直肠癌中的功能和机制研究

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目的:1.检测 DKK4 在结直肠癌细胞和组织中的表达水平。2.明确 DKK4 对结直肠癌细胞恶性表型的影响。3.探讨 DKK4 调节结直肠癌恶性表型的分子机制及其自身的受控模式。

方法:1 结直肠癌芯片组织和细胞中检测 DKK4 的表达 1)实时定量荧光 PCR 检测结直肠癌多种细胞株及正常肠上皮细胞 FHC 中 DKK4 的 mRNA 表达水平, 根据表达水平筛选出符合构建细胞功能模型的细胞株。2)免疫组化方法检测结直肠癌芯片组织中癌和癌旁组织 DKK4 的表达, 分析 DKK4 在结直肠癌及癌旁组织中表达强度的差异, 以及与肿瘤分期、转移及预后等的关系。2.构建 DKK4 上、下调的结直肠癌细胞模型 3.检测 DKK4 对结直肠癌细胞增殖和转移能力的影响 1)Transwell 迁移和 transwell 侵袭实验及划痕实验通过结直肠癌上调和下调细胞模型检测结直肠癌细胞的体外迁移和侵袭能力。2)裸鼠尾静脉注射结直肠癌 DKK4 敲减细胞, 通过结合小动物活体成像技术, 进一步验证 DKK4 敲减细胞模型的体内转移能力。3)CCK8 法在 DKK4 上调和



下调的细胞模型中检测结直肠癌细胞增殖能力，并行裸鼠皮下成瘤实验进一步验证。4.DKK4 抑制结肠癌恶性表型发生的分子机制研究 1) Western blot 检测 DKK4 上调和下调细胞模型中 β -catenin, active β -catenin, phospho- β -catenin (Ser552), AKT1, AKT2, Phospho-AKT2, MMP2, MMP3 的表达情况。2) 实时定量荧光 PCR 检测 EGF, HGF, Wnt3a 对结肠癌细胞系 DKK4 表达的影响。5. 结直肠癌细胞中 miRNA 对 DKK4 的调控作用 1) miR-106a, miR-299-3p 和 miR-450b-5p 功能获得模型的构建。2) 双荧光素酶报告实验验证 miR-299-3p 和 miR-450b-5p 是否直接作用于 DKK4 发挥作用。3) CCK-8 法检测 miR-299-3p 和 miR-450b-5p 与 CRC 体外增殖能力的关系。4) Transwell 迁移和 transwell 侵袭实验验证 miR-299-3p 和 miR-450b-5p 与 CRC 细胞迁移, 侵袭能力的关系。

结果: 1. DKK4 在多种结直肠癌细胞系中高表达; DKK4 在多数结直肠癌中的表达高于癌旁组织, DKK4 高表达的结直肠癌患者生存期较长。2. 通过构建 DKK4 上下调细胞模型, 证实 DKK4 可以抑制结直肠癌细胞侵袭和转移, 但对结直肠癌细胞的增殖无明显影响。3. DKK4 可以抑制 Wnt/ β -catenin 信号通路及 AKT 信号通路活性, AKT 磷酸化 Ser552 位点 β -catenin 从而增强 β -catenin 转录活性, 进而抑制 MMP2 和 MMP3 的表达; Wnt 通路的配体 Wnt3a 以及细胞因子 EGF 可以促进 DKK4 的表达。4. miR-299-3p 和 miR-450b-5p 通过负性调控 DKK4 表达, 促进结直肠细胞的迁移和侵袭, 但对结直肠细胞增殖表型无影响。

结论: 1. DKK4 在多数结直肠癌细胞系和组织中高表达, DKK4 高表达组患者生存期长; 过表达 DKK4 可以抑制结直肠癌细胞侵袭和转移, 但对结直肠癌细胞的增殖无明显影响; DKK4 可以抑制 Wnt/ β -catenin 信号通路及 AKT 信号通路活性, AKT 磷酸化 Ser552 位点 β -catenin 增强 β -catenin 转录活性, 进而抑制 MMP2 和 MMP3 的表达。2. Wnt 通路配体 Wnt3a 及细胞因子 EGF 等可以促进 DKK4 的表达。Wnt/ β -catenin 通路激活促进 DKK4 表达是该通路的负反馈调节机制。在结直肠癌发生和进展过程中, Wnt/ β -catenin 通路异常活化使得 DKK4 表达升高, 以对这一通路进行抑制性负反馈调节。这一机制可解释“DKK4 在多数结直肠癌组织中高表达, 但 DKK4 高表达组患者反而生存期更长”的现象。3. 结直肠癌细胞中 DKK4 的表达水平还受到 miRNA 的调控。我们发现 miR-299-3p 和 miR-450b-5p 通过直接调控 DKK4 发挥作用, 促进结直肠细胞的迁移和侵袭, 但对结直肠细胞的增殖能力无明显影响。

关键词: DKK4; 结直肠癌; 迁移和侵袭; miR-299-3p; miR-450b-5p

276. 基于催化发夹 1 组装 DNA 酶的无酶双 DNA 步行器检测端粒酶活性

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端粒酶是一种潜在的肿瘤生物标志物。本文介绍了一种用于超灵敏检测端粒酶活性的无酶等温荧光策略,即基于催化发夹组装的 DNAzyme(CHA-DNAzyme)的双 3D DNA 步行器。当与端粒酶孵育时,端粒酶引物被拉长以形成端粒重复序列(TR)。延长的 TR 通过连续的链置换反应,沿着预先设计的轨道随机移动,组装完整的 DNAzyme(Cha Walker)。然后,被激活的 DNAzyme 通过水解 DNA 发夹从 AuNPs(DNAzyme Walker)释放荧光标记的 DNA 片段,自主地沿着另一条轨迹移动。因此,回收了大量的荧光来分析端粒酶活性。Cha Walker 和 DNAzyme Walker 的使用使该传感策略具有较高的灵敏度和信号传输效率。该策略的分析范围很广,从 10 到 1000HeLa 细胞 mL⁻¹,低检测下限为 7 细胞 mL⁻¹ 该策略不仅可以检测不同肿瘤细胞中的端粒酶活性,而且可以定量检测积累的正常细胞中的癌细胞的端粒酶活性。另外,通过检测人血清中的端粒酶活性,验证了该策略的实用性。

关键词: 端粒酶;催化发夹;DNA 酶

277. TPTEP1 exerts tumor-suppressive role functioning as a competing endogenous RNA to upregulate PDCD4 expression by competing for miR-196a-5p in esophageal carcinoma.

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Objective: In the present study, we initiated an investigation into the biological functions and the molecular mechanisms of TPTEP1 in esophageal carcinoma (ESCA).

Methods: Bioinformatics analysis was performed to find the differential genes in ESCA. Real-time PCR analysis used to examine the TPTEP1 expression in human ESCA tissues and cell lines. Functional studies were performed to elucidate the influence of TPTEP1 on the malignant behavior and epithelial-mesenchymal transition (EMT) in ESCA cells. Furthermore, we used luciferase reporter assay and RNA immunoprecipitation (RIP) to explore its underlying mechanism in ESCA.

Results: TPTEP1 expression was downregulated in ESCA tissues and positively correlated with the prognosis of patients, but not with tumor stage. Functionally, TPTEP1 suppressed ESCA cell migration and invasion and impaired EMT, indicating that TPTEP1 exerted tumor-suppressive role in ESCA. Through mechanism investigation, we revealed that TPTEP1 exerts tumor-suppressive role functioning as a competing endogenous RNA (ceRNA) to upregulate PDCD4 expression by competing for miR-196a-5p in ESCA.

Conclusion: Our study indicated a TPTEP1-miR-196a-5p-PDCD4 axis in regulating the malignant behavior of ESCA.

Key words: esophageal carcinoma; competing endogenous RNA; EMT



278. ULK2 通过调节 MCT1 和 MCT4 促进结直肠癌的侵袭,迁移

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目的: 研究 ULK2,MCT1,MCT4 在结直肠癌组织中的异质性表达以及 ULK2 对结直肠癌浸润的作用。

方法: 我们通过免疫组化分析了 ULK2,MCT1,MCT4 在 80 例结直肠癌组织中的表达以及与临床病理特征的关系,进一步通过对正常-肿瘤交界处的正常肠上皮,肿瘤以及肿瘤浸润前沿进行免疫组化分部位评分,评估了 ULK2,MCT1,MCT4 在结直肠癌组织不同部位的表达特征以及在浸润前沿的表达与临床病理特征的关系。同时,我们通过在线数据库 GEPIA (<http://gepia.cancer-pku.cn/>) 分析了 ULK2,MCT1,MCT4 在结直肠癌中 mRNA 的表达水平和三者的表达相关性。接下来,我们构建 ULK2 过表达细胞株,进行 transwell 细胞迁移和侵袭实验,检测 EMT 相关蛋白,并在体外分别转染 miR-224 的模拟物 (mimic) 及其阴性对照 (nc)。最后,检测了 LV-NC 和 LV-ULK2 组中糖酵解通路相关酶的 mRNA 表达,己糖激酶(HK)和乳酸脱氢酶 (LDH) 的酶活力,细胞外乳酸,MCT1 和 MCT4 的表达。在 LV-NC 组和 LV-ULK2 组中分别加入氯喹,检测 ULK2,SQSTM1,LC3II 的蛋白表达和细胞外乳酸水平。

结果: ①通过免疫组织化学评分,相较于正常肠上皮,ULK2 在肿瘤中低表达,MCT1 和 MCT4 在肿瘤中高表达($P=0.0257$, $P<0.001$, $P<0.001$)。细胞浆-细胞膜整体评分,MCT1 和 MCT4 的表达与临床病理特征并无相关性,细胞膜评分 MCT4 的表达与肿瘤浸润深度呈正相关($P=0.0212$)。对正常-肿瘤交界处正常肠上皮,肿瘤,浸润前沿进行分部位评分发现,MCT1,MCT4,ULK2 在浸润前沿高表达并且与肿瘤浸润深度呈正相关($P=0.0367$, $P=0.0475$, $P=0.0300$)。ULK2 和 MCT4 在结直肠癌浸润前沿的表达具有正相关性($P=0.0396$)以及在直肠腺癌 (rectum adenocarcinoma, READ) 中 ULK2 与 MCT1 的 mRNA 水平具有正相关关系($P=0.014$)。(2)相较于 LV-NC 组, LV-ULK2 组的细胞侵袭率和迁移率增加,MMP9,MMP2 蛋白表达增加,E-cadherin 膜表达降低和 β -catenin 的入核增加。相较于 LV-ULK2+miR-224 nc 组, LV-ULK2+miR-224 mimic 组中细胞侵袭和迁移能力降低。(3) LV-ULK2 组中 HK 的酶活性增加,细胞外乳酸增加,MCT1 和 MCT4 的 RNA 和蛋白水平均增加。加了氯喹后, LV-NC+CQ 组和 LV-ULK2+CQ 组中 LC3II 和 SQSTM1 蛋白表达以及细胞外乳酸水平并无差异。

结论: MCT1,MCT4,ULK2 在结直肠癌浸润前沿高表达并且与肿瘤浸润深度呈正相关。ULK2 可以通过自噬调节 MCT1 和 MCT4 的表达,增加细胞外的乳酸,促进结直肠癌的侵袭和迁移。外源性 ULK2 促进结直肠癌迁移和侵袭的作用可以被 miR224 逆转。

关键词: 结直肠癌; ULK2; MCTs; 肿瘤浸润

279. Tim-3 与肿瘤预后和免疫的泛癌分析: 一项生物信息学研究



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背景: T 细胞免疫球蛋白和粘蛋白结构域 3 (Tim-3) 因其在肿瘤中的免疫调节作用和预后价值而引起了较大的关注。本研究的目的是综合分析 Tim-3 在泛癌中的预后价值及其与免疫浸润的关系。

方法: HPA, Oncomine, TCGA, GTEx, TIMER 2.0, CCLE 数据库分析 Tim-3 在血细胞, 正常组织, 肿瘤组织和肿瘤细胞系中的表达水平及差异, Kaplan-Meier Plotter 和 Prognoscan 进行 Tim-3 和肿瘤患者预后分析。cBioPortal 数据库使用 TCGA Pan-Cancer 数据集分析 Tim-3 在各种肿瘤突变情况以及对预后影响。TIMER 2.0 和 TISIDB 数据库分析 Tim-3 与各种肿瘤免疫浸润的相关性。STRING 数据库构建 Tim-3 和与其正相关的免疫调节剂和趋化因子的 PPI 网络, 并用 DAVID 数据库对其进行 GO 功能注释和 KEGG 通路富集。

结果: 总的来说, 与配对的正常组织相比, Tim-3 在大多数肿瘤高表达。在肝癌 (LIHC), 睾丸生殖细胞肿瘤 (TGCT), 胸腺瘤 (THYM), 卵巢癌 (OV), 乳腺癌 (BRCA), 胰腺癌 (PAAD), 食管癌 (ESCA), 头颈癌 (HNSC) 和 结直肠癌 (CRC) 中高表达 Tim-3 患者预后较差, 而在膀胱癌 (BLCA), 宫颈癌 (CESC), 眼癌, 肾透明细胞癌 (KIRC), 肾乳头状细胞癌 (KIRP) 和 子宫内膜癌 (UCEC) 中预后较好。KIRC 患者 Tim-3 突变频率最高, 其次是 UCEC。在大多数肿瘤的肿瘤微环境中, Tim-3 与单核细胞, 巨噬细胞, CD8+T 细胞和树突状细胞以及免疫调节剂和趋化因子如 CCL2-5, CCR1, CCR2, CCR5, CCR7, CD27, CD28, CD48, CD86, CD96, CD244, CD274, CTLA4, CSF1R, CXCL9-12, CXCR3, CXCR6, IDO1, IL10, LAG3, LGALS9, PDCD1, PDCD1LG2, TGITFB1 和 TIGFB1 成正相关性。富集分析表明, 这些免疫调节剂和趋化因子富集在细胞因子-细胞因子受体相互作用, 趋化因子信号等免疫信号通路。此外, Tim-3 被确定为 PAAD 和 CESC 的危险和保护因素, 且在 CD8+T 细胞和 NK 细胞高浸润患者发挥预测预后作用, 在 CESC 中, Tim-3 相关基因主要参与免疫正调控, 而在 PAAD 中, Tim-3 同时参与免疫负调控如 T 细胞增殖和肿瘤坏死因子产生的负调控。

结论: Tim-3 在多种肿瘤中可作为预后预测因子, Tim-3 通过在免疫的调节作用影响恶性肿瘤的发生发展, 尤其 Tim-3 在一些肿瘤如 PAAD 中的免疫负调节和预后危险因素使其成为新的更有效的抗肿瘤免疫疗法的目标。

关键词: Tim-3; 泛癌; 表达; 突变; 预后; 免疫

280. 不同级别脑膜瘤中 PR 的表达及临床意义

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目的：研究 PR 在脑膜瘤中的表达情况。

方法：采用免疫组织化学方法检查不同级别和组织学亚型脑膜瘤组织中 PR 的蛋白表达，并进行数据分析。

结果：在脑膜瘤组织中 PR 的蛋白表达水平随着脑膜瘤 WHO 级别的升高而逐渐降低，三者间两两相比差异均有统计学意义($P < 0.05$)；脑膜瘤组织中 PR 的蛋白表达水平与相同 WHO 级别的不同组织学亚型间无明显差异($P > 0.05$)；脑膜瘤组织中 PR 的蛋白表达水平与年龄、性别无明显差异($P > 0.05$)。

结论：PR 的蛋白表达水平的检测有助于脑膜瘤分级的病理诊断。

关键词：脑膜瘤；PR；免疫组化

281. Glucose-6-phosphate dehydrogenase mutant K56C/D306C/D427C with higher inhibition rate for enzyme multiplied immunoassay of Cyclosporine A

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Background: The inhibition rate is a key parameter to accurately detect the concentration of small molecules such as Cyclosporine A (CsA) in patient sample with enzyme-multiplied immunoassay technique (EMIT). Several factors may contribute to the inhibitor rate in EMIT assay, such as the conjugation site on Glucose-6-phosphate dehydrogenase (G6PDH), the selection of the antibody, reaction buffer composition, etc. Here we use CsA as an example to investigate the influence of conjugation sites on the inhibition rate.

Methods: G6PDH (about 55.4 KDa) mutants with one to three cysteines mutations at different sites, including K56C, D156C, D200C, D259C, D306C, D427C, D480C, K56C/D306C, K56C/D427C, K56C/D306C/D427C and K56C/D306C/D454C were constructed. Site directed conjugation were carried out between the cysteine group from the mutants and the maleimide group from the CsA derivative. The molecular weight of the conjugate was confirmed by mass spectrometer, and the change of enzyme activity was measured by a Hitachi 7180 biochemical analyzer to evaluate the antibody inhibition rate. The inhibition rate was expressed as following:
$$\text{Inhibition rate} = [1 - \text{G6PDH Activity}(\text{antibody}) / \text{G6PDH Activity}(\text{without antibody})] \times 100\%$$

Results: The structure of the CsA derivative was shown in Fig. 1A, and the molecular weight of the CsA derivative was 1424.88. According to the Fig. 1B and Fig. 1C, the molecular weight of the G6PDH D427C-CsA conjugate was 56921.67, and the K56C/D306C/D427C-CsA was 59735.63, which indicated the mutants with single or triple cysteines were coupled with one and three derivatives, respectively. The inhibition rates of different G6PDH-CsA conjugates were shown in Table 1. Among the different single mutants, the inhibition rate of D427C-CsA was the highest (22%), D306C-CsA the

second (12%), and other sites showed little inhibition. Besides, one triple mutant, K56C/D306C/D427C, exhibited the highest inhibition rate (52%), which was approximately 2.36 times that of D427C-CsA.

Conclusions: For EMIT of CsA, the G6PDH triple mutant K56C/D306C/D427C-CsA had a higher inhibition rate of 52% which is better for assay development.

Key words: EMIT; Cyclosporine A; Inhibition rate

282. 中晚期胃癌患者中免疫微环境特征对免疫治疗的应用价值

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肿瘤免疫微环境对免疫治疗有较好的指导作用，然而受限于免疫组化对多标记精细分型的缺陷，并不能对肿瘤患者进行进一步的指导。我们收集了 148 例中晚期胃癌患者肿瘤组织，采用流式细胞术检测其肿瘤免疫微环境相关指标，并建立了相关方法学对免疫指标进行评估，同时联合各临床指标进行综合分析。我们根据胃癌的解剖位置进行分析，发现在远端胃中 CD8⁺CD279⁺细胞比例更高 ($P=0.024$)，而其余的淋巴细胞指标并无显著差异；然后，我们对这些胃癌患者根据 MMR 进行分组，结果发现 pMMR 和 MMR 患者具有不同的免疫微环境特征，其中 pMMR 患者的总淋巴细胞比例更低，NK 细胞比例更低，CD4/CD8 细胞比例更低 ($P=0.046$)；另外对采用免疫治疗的 49 例患者进行分析，发现 pMMR 患者的 2 年复发率更低，同时 CD8⁺CD279⁺high 的患者相对于 CD8⁺CD279⁺low 的患者的 2 年复发率更低。总体来看，采用流式细胞术对肿瘤患者进行免疫微环境评估具有一定的临床应用价值，较高比例 CD8⁺CD279⁺细胞的存在可能是远端胃癌免疫治疗疗效的影响因素之一。

关键词: 肿瘤免疫微环境；流式细胞术；胃癌；淋巴细胞

283. 血清 CEA,CA19-9,CA242,CA50,CA125 联合检测在胃部疾病中的诊断价值

姚汶励*

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目的: 探讨血清癌胚抗原 (CEA),糖类抗原 19-9 (CA19-9),糖类抗原 242 (CA242),糖类抗原 50 (CA50),糖类抗原 125 (CA125) 联合检测胃部相关疾病的诊断价值。

方法: 对 383 例不同良恶,恶性胃部相关疾病患者的血清采用安图 Auto Lumo A2000 Plus 磁微粒化学发光法 (CMIA) 均进行 CEA,CA19-9,CA242,CA50,CA125 水平检测,依据病理结果分为良性病变组与胃癌组,以临床诊断结果为“金标准”,分析统计各指标单独检测及五种联合检测的



特异性与灵敏度，采用 ROC 分析血清 CEA,CA19-9,CA242,CA50,CA125 水平对胃癌的诊断价值。

结果：383 例患者中，经临床诊断病理结果证实 208 例为良性病变，175 例为胃癌；与良性病变组比较，胃癌患者血清 CEA,CA19-9,CA242,CA50,CA125 水平显著升高，差异具有统计学意义（ $P<0.05$ ）；五项联合诊断的灵敏度、准确度、特异度、阳性预测值、阴性预测值均高于各项单独检测，差异具有统计学意义（ $P<0.05$ ）；ROC 曲线分析显示，血清 CEA,CA19-9,CA242,CA50,CA125 水平联合诊断胃癌的 ROC 曲线下面积明显大于单独指标诊断（ $P<0.05$ ）。

结论：血清 CEA,CA19-9,CA242,CA50,CA125 在诊断胃部相关疾病中具有重要意义，且五项联合检测诊断胃癌价值更高，利于评估病情、手术方案制订及预后判断，值得推广应用。

关键词：CEA；CA19-9；CA242；CA50；CA125；胃部疾病

284. Comprehensive evaluation of computational methods for predicting cancer driver genes

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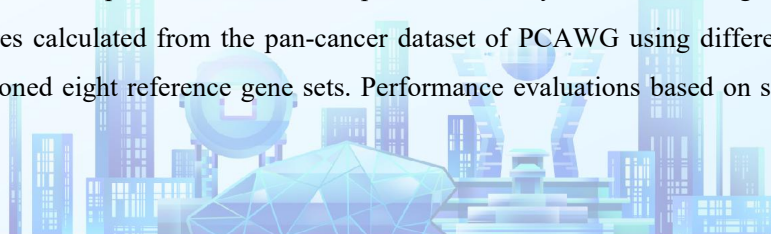
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Objective: Some studies have evaluated performance in some of algorithms for predicting pathogenic or driver mutations and genes. However, for the identification methods of tumor driver genes, several methods proved to have the best performance in the corresponding researches. Moreover, recently developed methods such as Moonlight, nCOP, OncoIMPACT, MutPanning, driverMAPS, WITER, and DriverML have not been compared with each other until now, and the comparison of network datasets for network-based approaches is still lack. Furthermore, the lack of accepted gold standard of driver genes and appropriate measurements limited the research on assessment of methods for predicting cancer driver genes. Thus, it is urgently needed to perform a comprehensive and systematic evaluation of computational methods for predicting cancer driver genes.

Methods: Herein, considering the novelty and practicality, we independently assessed the performance of 12 recently published approaches of driver gene prediction without our participation, including eight network-based, one functional-based, and three frequency-based methods. Then we integrated the gene driver scores which represent the possibility of cancer driver predicted by different tools into a website of cancer driver catalog. In total, we performed eight measurements of 12 methods with six network datasets based on eight benchmark datasets.

Results: Given that the importance of drivers in pan-cancer analysis have been highlighted, we obtained the AUC scores calculated from the pan-cancer dataset of PCAWG using different algorithms based on aforementioned eight reference gene sets. Performance evaluations based on somatic mutations of



pan-cancer dataset showed that a frequency-based method of driverMAPS outperformed other algorithms under most of reference datasets.

To further evaluate the ability of different algorithms for predicting cancer drivers in specific cancer types, we employed somatic mutation data from each of the 36 cancer types separately based on six independently developed networks. Performance evaluations of different methods based on somatic mutations of 36 cancer types showed that by AUC measurement, one of frequency-based methods, driverMAPS, showed the highest median value of AUC. However, network-based methods such as HotNet2, MaxMIF, NetSig, DNsum, DNmax, and OncoIMPACT showed much higher sensitivity than driverMAPS as well as other algorithms. we also assessed these algorithms using other six evaluation measurements including accuracy, specificity, precision, error rate, F1 score, and MCC to verify the performances of these softwares, which showed similar results to AUC.

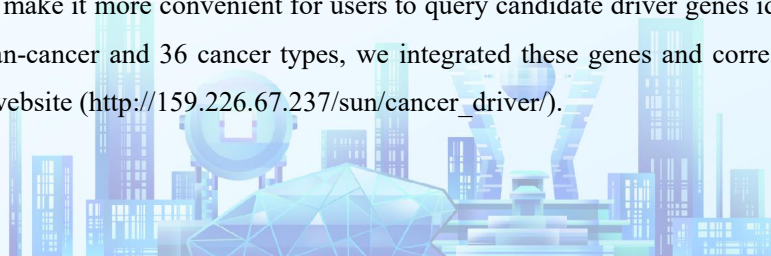
Performance effect of different networks on network-based methods for predicting driver genes showed that six network datasets showed similar performance according to accuracy, specificity, precision, error rate, and F1 score by using six network-based methods. However, they showed different performance based on AUC, sensitivity, and MCC.

Sample size is an indispensable factor to calculate mutational frequency and can affect the stability of software performance. For studying the influence of sample size on different methods to distinguish driver genes, we further assessed the performance of different algorithms and network datasets under different sample sizes across 36 cancer types. In terms of different sample sizes, each software showed similar performance. However, these methods presented different property trends with the increase of sample size.

Previous studies showed that the identification of driver genes was not only related to mutation frequency but also associated with gene length. So, it is essential to consider the impact of gene length in identifying driver genes. Our results showed that several computational methods such as MaxMIF, DNsum, DNmax, MutPanning, WITER preferred to predict similar length of genes compared with benchmark datasets, while the rest computational softwares prefer to longer or shorter genes. Our observation suggested that the normalization of gene length is an important step to eliminate the bias induced by gene length when calculating the mutation frequency of genes with different lengths.

To study the similarity of candidate driver genes identified by different computational methods, we compared the top 100 predictions obtained in the pan-cancer analysis. We found the stronger similarity existed among network-based methods, which implied that network-based methods are prefer to identify relative similar driver genes, while the methods of other two categories did not show similar feature. By comparing the similarity of candidate driver genes in different cancer types, we found that similar driver genes distribution pattern existed in cancers from related organs, especially in different subtypes of the same cancer type.

Finally, in order to make it more convenient for users to query candidate driver genes identified by these 12 methods in pan-cancer and 36 cancer types, we integrated these genes and corresponding possibility scores into a website (http://159.226.67.237/sun/cancer_driver/).



Conclusion : To our knowledge, this study assessed the performance of algorithms for predicting candidate driver genes, and compared the properties of different network datasets for the first time. In addition, the gene length and sample size were considered in the evaluation. Our results revealed that performance of some approaches varied under different conditions including networks, measurements, and the sample sizes, implicating that they were not always stable under all conditions. Overall, the frequency-based method driverMAPS and network-based method HotNet2 showed the best performance. Moreover, the network-based algorithms using protein-protein interaction networks outperformed the functional-based and the rest frequency-based approaches. Furthermore, the precision, F1 score, and MCC of most approaches were very low, suggesting that some algorithms require more stringent cutoff values to distinguish driver and non-driver genes. In summary, based on the advantages and limitations of each method, our findings provide a preliminary guidance for clinicians and researchers to select appropriate method to identify candidate driver genes.

Key words : cancer driver genes; computational methods; predicting algorithms; method assessments; TCGA

285. Diagnosis-navigation-treatment: a versatile biocompatible and biodegradable PDL1 platform for breast cancer early diagnosis, precisely surgery, and radiosensitization.

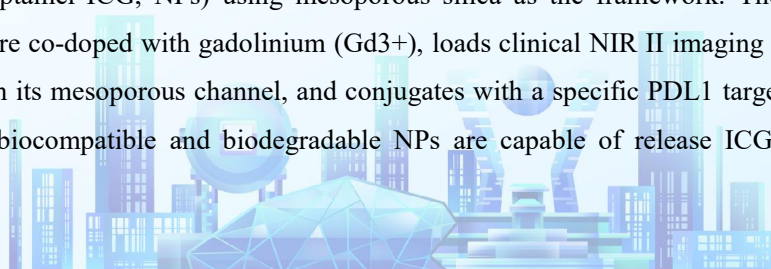
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Background: Triple-negative breast cancer (TNBC) has the highest recurrence and distant metastasis rates among breast cancer molecular types. In breast-conserving surgery, the insensitivity discrimination of negative margins correlating with locoregional recurrence and poor patient outcomes. As for immunotherapy, only 20 %-40 % of the patients respond to the atezolizumab treatment due to the change of PDL1 receptor. Meanwhile, TNBC has radiotherapy resistance. Novel radiosensitization targets need to be found to enhance both the local and systematic benefits of radiotherapy. Mesoporous silica nanoparticle (MSN) is recently recognized by the FDA as a safe material for human trials, thus it is extensively explored as promising theragnostic agent. Compared with antibody, aptamer has the advantages of high sensitivity, simplicity and cheapness, but its easy degradation limits the application in vivo.

Objectives and rationale: We aim to construct a PDL1 target “all in one” multi-functional nanoprobe (MSN-Gd@Aptamer-ICG, NPs) using mesoporous silica as the framework. The mesoporous silica nanospheres are co-doped with gadolinium (Gd³⁺), loads clinical NIR II imaging reagent indocyanine green (ICG) in its mesoporous channel, and conjugates with a specific PDL1 targeting aptamer on the surface. The biocompatible and biodegradable NPs are capable of release ICG by the reaction of



intracellular high GSH and tetrasulfide bonds in silica frame. In the diagnosis, NIR II fluorescent imaging of ICG with the high resolution and deep tissue penetration depth screens out PDL1 highly expressed tumors. In surgical resection, it can show a real-time cancerous tissues margin in intraoperative scenarios and the tumors are successfully remove under the navigation of NIR II fluorescent imaging. During metastasis therapy of post-operation, the released Gd³⁺ effectively deposits X-rays and produces abundant hydroxyl radicals ($\bullet\text{OH}$) and oxidative stress to induce radiosensitizing effects. More importantly, the therapy efficiency is monitored by NIR II fluorescent imaging. Therefore, our multifunctional NPs have roles in the accurate diagnosis of PDL1 expression of tumor in early stage, intraoperative navigation for radical excision, and metastasis eradication with radiosensitization efficiency enhanced, which lays a solid foundation for clinical TNBC therapy.

Methods: The probe was 50 nm and it was successfully synthesized and certified. MTT assay suggested that it was nontoxic to normal breast cells and TNBC cells. Transmission Electron Microscope images showed that the probe was stable at the extracellular fluid and was degradable at tumor intracellular conditions. The leaching of ICG and Gd³⁺ was negligible at the extracellular fluid. The tumor targeting capability of the probe in vitro was evaluated on 4T1 (TNBC, PDL1 low expressed) and MDA-MB-231 (TNBC, PDL1 high expressed) cells by flow cytometry and laser confocal microscope. In vivo, the NIR II fluorescence imaging with a high resolution and tissue penetration depth successfully distinguished 4T1 and MDA-MB-231 bearing mice indicated the superior diagnostic capability of PDL1 via aptamer. In the surgical resection, the NIR II fluorescence imaging of NPs guided to remove the tumor with precisely discriminate the boundary of the tumor. When combined with RT, IHC staining of Ki67 showed that the NPs exhibited superior radiosensitizing effects under NIR II fluorescent imaging guidance in comparison with undoped Gd mesoporous silica nanoprobe. TUNEL fluorescent staining and H&E staining further confirmed that NPs radiation therapy induced more $\bullet\text{OH}$ and extensive DNA double-strand breaks.

Results and Conclusion: Our biocompatible and biodegradable PDL1 platform is nontoxic, can screen out PDL1 high expression tumors, and navigate the precise resection in the operation. Besides, it enhances the radioimmunotherapy efficacy of breast metastasis. Our platform is a novel trial for the clinical application of PDL1 aptamer in breast cancer diagnostic, guiding resection, and radiosensitization under NIR II fluorescent imaging.

Key words: PDL1 aptamer platform; breast cancer; clinical application

286. Evaluating an enzyme multiplied immunoassay technique of a phenytoin kit on an ARCHITECT C16000

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Background : Phenytoin (PTN) is one of the most commonly used drugs in epilepsy, and its special pharmacokinetics and narrow therapeutic window make it necessary to monitor the concentration of PTN in the blood to help ensure appropriate therapy .

Object: The objective of this study was to evaluate the performance of an enzyme multiplied immunoassay technique (EMIT) PTN kit on an ARCHITECT C16000.

Method: The EMIT PTN kit was developed by Beijing Strong Biotechnologies (BSBE), Inc. All the following studies were performed on an ARCHITECT C16000 clinical chemistry analyzer. Tri-level controls and two serum sample pools were adopted to the precision studies according to Clinical and Laboratory Standards Institute (CLSI) EP05-A2, and the accuracy, linearity and specificity studies were evaluated according to EP15-A2, EP06-A2 and EP14-A2 separately.

Results: The repeatability, precision, spike recovery, specificity data are demonstrated in Table 1A, 1B, 1C, 1D. The linear range of the PTN kit is 2.0 to 40 $\mu\text{g/ml}$, and the linear equation is $y = 3.7355x - 1.8278$ with $R^2 = 0.999$. 16 kinds of compounds were tested for specificity studies, 15 compounds list in table 1D caused $\leq 10\%$ change in drug concentration when tested in the presence of 15 $\mu\text{g/ml}$ phenytoin. But the compound fosphenytoin, at a level of 60 $\mu\text{g/ml}$, caused a 22.98% change when tested in the presence of 15 $\mu\text{g/ml}$ phenytoin.

Conclusion: The EMIT PTN kit developed by BSBE has a good performance in repeatability, precision, accuracy, specificity and linearity which could be used for clinical phenytoin detection.

Key words: EMIT; PTN; evaluat

287. 索拉菲尼治疗肝细胞癌耐药机制的研究进展

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肝细胞癌 (Hepatocellular carcinoma, HCC) 是原发性肝癌中最常见的一类肿瘤, 由于其在早期无明显症状和体征变化, 出现症状时大部分 HCC 患者已到病程中晚期, 错过了手术切除的最佳时机, 预后较差, 死亡率较高。索拉菲尼 (Sorafenib) 是获得美国食品药品监督管理局 (Food and Drug Administration, FDA) 批准治疗中晚期 HCC 的分子靶向药物。然而, 接受索拉菲尼治疗后, 仅有约 30% 的晚期 HCC 患者表现出较好的治疗效果, 许多患者在六个月内逐渐进展成对索拉菲尼治疗的不敏感或耐药[1]。因此探究索拉菲尼对肝癌治疗的不敏感和耐药机制具有重要的意义。

最初, 索拉菲尼因其具有较强的 Raf-1 激酶抑制特性和较好的激酶选择性而被发现用于治疗 HCC, 后在实验中证实了索拉菲尼能有效阻断 Raf/MEK/ERK 经典信号通路, 表现出良好的抑制肿瘤细胞增殖等抗癌效果。随后研究发现, 索拉菲尼还具有抗肿瘤细胞增殖、抗血管生成、破坏肿瘤的微血管以及促细胞凋亡、增强免疫反应等作用抑制肿瘤生长[2]。然而, 索拉菲尼在临床应用中, 常表现出敏感性不佳和耐药性问题。①上皮间质转化 (Epithelial-mesenchymal transitions,

EMT)是指上皮样细胞向间质样细胞的转化的过程,调控 EMT 过程相关的信号通路及分子,如 TGF- β ,PI3K/AKT,Notch,Hedgehog 等信号通路的激活可能促进了索拉菲尼耐药性的升高[3]。

②肿瘤微环境在索拉菲尼耐药性的产生中发挥了重要作用。缺氧:肝癌细胞在索拉菲尼的持续作用下,由于其抗血管生成等作用,可造成癌细胞的缺氧环境,随后激活 NF- κ B 和 HIF-1 α 途径诱导索拉菲尼耐药[4],而 PI3K/AKT/HIF-1 α 信号通路的激活在缺氧条件下诱导肝癌细胞 EMT,增加了肝癌细胞的耐药性[5]。细胞自噬:研究发现索拉菲尼可诱导自噬标志物 LC3-I 到 LC3-II 的转变,诱导自噬体形成,增强细胞自噬活性,继而给肝癌细胞一定的生存优势[6]。此外,索拉菲尼可以通过独立于 MEK1/2-ERK1/2 途径的内质网应激途径诱导细胞凋亡和自噬,当自噬被抑制或自噬相关基因被敲除后能增强索拉菲尼的杀细胞效应[7]。外源性病毒感染:研究发现,HBV 病毒整合的肝癌细胞对各类药物耐受性升高。VBP1,一种 VHL 肿瘤抑制蛋白的结合因子,能够促进 HBx 蛋白诱导的 NF- κ B 信号的活化和细胞增殖[8]。NF- κ B 信号的持续活化在与炎症相关的癌症中对癌症的发展可起到促进作用[9],并使 HCC 细胞药物耐药性产生。

③除以上提及的信号通路,仍有多种信号通路被证实参与了或者可能影响了索拉菲尼耐药性的产生,如 JNK,HGF/c-Met,EGFR-SRC-STAT,Raf/MEK/ERK 等信号通路。同时,一些转录因子,微小 RNA (microRNA, miRNA) 和长链非编码 RNA 等,它们共同构成了一个转录调节性网络[10],也参与了 HCC 对索拉菲尼作用敏感性的调节。综上,鉴于索拉菲尼在治疗中晚期 HCC 中的重要地位,进一步研究索拉菲尼耐药性和敏感性问题的,将为提高晚期 HCC 患者的生存机会做出重要贡献。

关键词: 索拉菲尼;肝细胞癌;耐药性;上皮间质转化;微环境

288. LncRNA LINC00641 represses cell metastasis of esophageal squamous cell carcinoma through functioning as a sponge of miR-522-3p.

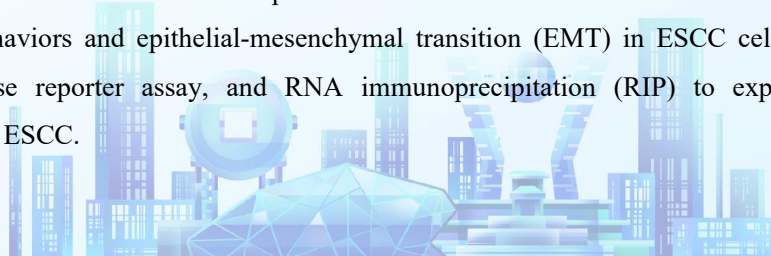
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Objective: In the present study, we initiated an investigation into the biological functions and the molecular mechanisms of long intergenic non-protein coding RNA 641(LINC00641) in esophageal squamous cell carcinoma (ESCC).

Methods: Real-time PCR analysis used to examine the LINC00641 expression in human ESCC tissues and cell lines. Functional studies were performed to elucidate the influence of LINC00641 on the malignant behaviors and epithelial-mesenchymal transition (EMT) in ESCC cells. Furthermore, we used luciferase reporter assay, and RNA immunoprecipitation (RIP) to explore its underlying mechanism in ESCC.



Results: In ESCC tissues and cell lines, LINC00641 was found to be downregulated. Functionally, LINC00641 suppressed ESCC cell migration and invasion and impaired EMT, indicating that LINC00641 exerted tumor-suppressive role in ESCC. Through mechanism investigation, we revealed that LINC00641 functioned as a competing endogenous RNA (ceRNA) to upregulate the suppressor of cytokine signaling-5 (SOCS5) expression by competing for miR-522-3p in ESCC cells.

Conclusion: Our study indicated a LINC00641-miR-522-3p-SOCS5 axis in regulating the metastasis of ESCC.

Key words: long intergenic non-protein coding RNA; esophageal squamous cell carcinoma

289. 新型转移性结直肠癌免疫微环境调节因子的筛选和分析

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目的: 结直肠癌是威胁人类健康的主要恶性肿瘤之一, 在确诊为结直肠癌的患者中, 大约 50%到 60%发生转移, 是其主要的致死原因。肿瘤微环境在调节肿瘤生长中起着关键作用, 影响肠癌的进展和预后。然而在结直肠癌肿瘤转移过程中, 肿瘤免疫微环境基因的改变和潜在的重塑机制目前尚不清楚。筛选转移性结直肠癌特异性的免疫微环境调节因子, 阐明转移性肠癌免疫微环境的重塑机制, 为开发新的预后预测模型及精准治疗靶点提供理论依据。

方法: 通过转移性结直肠癌转录组学数据差异表达分析和 KEGG 信号通路富集分析, 筛选转移相关免疫差异表达基因(DEGs)及相关通路。通过 PPI 蛋白网络构建, 寻找促进免疫微环境重塑及肠癌转移的关键因子。用芯片数据计算肠癌转移灶和原发肿瘤的免疫评分, 用 CIBERSORT 反卷积算法进行免疫细胞浸润分析。

结果: 筛选出转移相关免疫通路的 173 个 DEGs, 其中上调基因 60 个, 下调基因 113 个。在肝转移性肠癌的免疫微环境中, VEGF 信号通路,PD-1/PD-L1 表达与 PD-1 检查点通路,Th1,Th2 和 Th17 细胞分化,NF κ B 信号通路,IL-17 信号通路,趋化因子信号通路等信号通路激活和富集。蛋白 PPI 网络分析显示, 鸟嘌呤核苷酸结合蛋白 GNAI1,趋化因子 CXCL6,凝血因子 II 受体 F2R,黑素细胞刺激激素受体蛋白 MC1R 是其中关键节点, 其节点间连接数分别为 15,11,10,9 个, 其中 GNAI1 是连接多个蛋白作用网络的枢纽节点。此外, 还发现在肠癌转移灶组织中, 代表肿瘤组织中基质细胞数目的 stromal score, 代表肿瘤中免疫浸润细胞数目的 immune score, 以及代表肿瘤组织中肿瘤细胞数目和纯度的 estimate score 均显著高于原发肿瘤组织。CIBERSORT 反卷积算法显示, 在肠癌肝转移灶样本中, CD8⁺T 细胞,活化的 NK 细胞,单核细胞,活化的树突状细胞表达较高。

结论: 肝转移性肠癌的肿瘤微环境与原发肿瘤相比发生了较大的变化, 其中 GNAI1,CXCL6,F2R,MC1R 等免疫微环境的关键因子可能在转移过程起重要作用。

关键词: 结直肠癌; 肿瘤转移; 免疫微环境; 调节因子



290. m⁶A, m⁵C RNA 甲基化修饰酶表达与胃癌相关性分析

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胃癌是严重危害人类健康的常见恶性肿瘤之一，其发生发展受遗传变异、表观遗传修饰、转录组变化等多方面影响。RNA 甲基化修饰是表观遗传调控机制的重要途径之一，在肿瘤发生、进展和预后中起重要作用。m⁶A 和 m⁵C 是 RNA 甲基化修饰的主要位点，其异常修饰与多种肿瘤的发生有关。为探究 RNA 甲基化修饰异常在胃癌中的作用，本研究分析 RNA 甲基化 m⁶A 和 m⁵C 的相关修饰酶在胃癌中的表达模式及其与胃癌患者病理特征的相关性。

以 15 个 m⁶A 甲基化相关修饰酶基因和 14 个 m⁵C 甲基化相关修饰酶基因作为研究对象。下载 The Cancer Genome Atlas (TCGA) 数据库中胃腺癌患者的 RNA-seq 数据和病例临床信息，分析上述基因在患者肿瘤组织和癌旁组织中的表达水平，其中 25 个基因在肿瘤组织中表达显著上调，提示 RNA 甲基化修饰酶的异常表达可能与胃癌有关。利用 R 语言，通过 LASSO 套索回归，分析 29 个基因的异常表达与胃癌的预后关系并筛选关键基因，鉴定对患者预后起关键调控作用的 5 个基因：RBM15、ZC3H13、DNMT1、FTO、ALKBH5，确定回归系数，根据风险评分构建风险模型。其中，RBM15 和 DNMT1 可作为患者预后好的标志物，即其高水平表达有利于胃癌患者生存，而 FTO 则相反。以 ROC 曲线检验模型准确性，5 年生存期患者 ROC 曲线下面积为 0.692，提示该模型具有一定精准度。根据风险评分将胃癌患者分为高风险组和中低风险组，对两组患者做预后差异和临床病理特征分析，发现患者总体生存期和肿瘤病理分级存在显著性差异，且高风险组患者预后更差。风险评分和患者临床病理特征的单因素和多因素 Cox 回归分析表明，肿瘤确诊年龄和基于该风险模型所得的胃癌风险评分可作为胃癌患者预后的独立风险因素。

综上，本研究发现 5 个 RNA 甲基化修饰相关酶的异常表达可作为胃癌患者的预后评价指标。进一步解析 RNA 甲基化修饰酶在胃癌发生进展中的关键调控作用，将为胃癌患者的治疗策略指定和预后评估分析提供重要的指导意义。

关键词：胃癌；RNA 甲基化修饰酶；风险模型；预后

291. 基于生物信息学分析女性多发肿瘤 CDH1 的研究

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目的: 应用癌症基因组图谱(TCGA),GEO 数据库分析女性多发肿瘤(乳腺癌,卵巢癌,子宫内膜癌,子宫肉瘤,子宫颈癌) E-钙黏蛋白(CDH1)基因表达,改变和蛋白磷酸化以及相关通路的富集分析。

方法: 用 TIMER2 和 GEPIA2 联合分析基因在肿瘤与正常组织间表达差异,并用 GEPIA2 分析肿瘤不同病理阶段 CDH1 的表达;用 UALCAN 进行蛋白组学分析;当基因表达有意义时,应用 cBioPortal 网站对 CDH1 进行遗传变异,突变及生存期等分析;最后应用 KEGG 和 GO 进行通路富集分析。

结果: 1. 与正常组织相比,CDH1 在女性多发肿瘤中均高表达,且差异存在统计学意义,卵巢癌和子宫肉瘤中 CDH1 的表达与病理分期具有相关性($P<0.05$)。2.CDH1 总蛋白在乳腺癌,卵巢癌,子宫内膜癌中表达高于正常组织($P<0.05$),CDH1 的蛋白磷酸化差异表达仅在乳腺癌中有统计学意义($P<0.05$)。3.乳腺癌,子宫内膜癌,宫颈鳞状细胞癌中 CDH1 的遗传变异以“突变”为主,卵巢浆液性囊腺癌以“删除”为主;与 CDH1 无改变比较,CDH1 发生变异时,肿瘤患者总生存率,疾病特异性生存率,无病生存率和无进展生存率均有统计意义($P<0.05$)。4. 通过 KEGG 通路富集分析,发现有 35 条相关通路($P<0.05$),癌症相关主要有 EPK 信号通路,胞内磷脂酰肌醇激酶信号通路,缺氧诱导因子信号通路等。GO 富集分析显示 CDH1 主要参与细胞间的连接,细胞分裂等过程。

结论: 1.CDH1 在正常组织与肿瘤组织差异表达,可考虑研究作为诊断,治疗和预后的检测指标,CDH1 对卵巢癌,子宫肉瘤病理分期的确定具有潜在价值。2.在怀疑乳腺癌,卵巢癌,子宫内膜癌时可考虑检测 CDH1 蛋白表达作为辅助诊断。乳腺癌中的 CDH1 磷酸化蛋白的作用值得我们继续探讨。3.CDH1 的遗传变异和富集分析有可能为研究女性多发肿瘤的发病机制及诊治提供新思路。

关键词: E-钙黏蛋白; 女性多发肿瘤; 分析

292. 唾液 miRNA-144,miRNA-21 联合检测对食管癌的诊断价值

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目的: 探讨唾液中 miRNA-144,miRNA-21 的表达水平及其联合检测对食管癌的诊断价值。

方法: 选择 2015-01~2019-05 暨南大学附属广州市红十字会医院心胸外科收治的食管癌患者 85 例(病例组),均经病理活检与免疫组化检查确诊;另选择同期健康志愿者 32 名(对照组),两组年龄均 >60 岁。采用聚合酶链式反应(PCR)检测两组唾液的 miRNA-144,miRNA-21 表达水平。采用 ROC 法评估两者对食管癌的诊断价值。

结果: 病例组唾液中 miRNA-144,miRNA-21 的表达水平显著高于对照组($P<0.05$)。ROC 分析结果显示,唾液中 miRNA-21 诊断食管癌的曲线下面积为 0.785,miRNA-144 为 0.777,具有诊断价值,且联合两个指标进行检测可进一步提高诊断效能(曲线下面积=0.851)。

结论: 食管癌患者唾液中的 miRNA-21,miRNA-144 呈高表达, 联合两者检测具有应用于食管癌筛查诊断的前景。

关键词: miRNA-144; miRNA-21; 唾液; 食管癌; 联合检测

293. 血 β -HCG 值在侵蚀性葡萄胎诊断及治疗中的作用

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目的: 探讨血 β -HCG 值对侵蚀性葡萄胎诊断的早期预测及化疗耐药的影响。

方法: 回顾性分析南京医科大学附属妇产医院 2010 年 1 月至 2020 年 1 月期间诊治的葡萄胎病例 204 例, 148 例患者血 β -HCG 在清宫后监测自然降至正常为治愈组, 56 例进展为侵蚀性葡萄胎为恶变组。根据清宫前后血 β -HCG 值变化绘制下降率曲线, 研究不同时期血 β -HCG 值对侵蚀性葡萄胎的预测价值, 比较不同 β -HCG 截断值对侵蚀性葡萄胎化疗耐药的影响。

结果: 清宫前至清宫后一日血 β -HCG 下降率预测侵蚀性葡萄胎准确性的敏感度 45.2%, 特异度 76.7%。清宫前至清宫后一周血 β -HCG 下降率预测侵蚀性葡萄胎准确性的敏感度 69.3%, 特异度 58.9%。清宫后一日至清宫后一周血 β -HCG 下降率预测侵蚀性葡萄胎准确性的敏感度 78.6%, 特异度 83.2%。侵蚀性葡萄胎患者中, 耐药患者的平均血 β -HCG 值是敏感患者的 1.77 倍, 监测化疗过程中血 β -HCG 的下降时间, 化疗前血 HCG ≥ 10000 mIU/mL 组较血 HCG < 10000 mIU/mL 组下降时间延长, β -HCG ≥ 10000 mIU/mL 是耐药的高危因素。

结论: 清宫后一日至清宫后一周血 HCG 下降率是侵蚀性葡萄胎早期预测的最佳指标。侵蚀性葡萄胎患者中, 耐药患者的平均血 β -HCG 值是敏感患者的 1.77 倍, 化疗前 β -HCG ≥ 10000 mIU/mL 是耐药的高危因素。

关键词: β -HCG ; 侵蚀性葡萄胎; 早期诊断; 化疗; 耐药

294. 循环 miRNA 在多发性骨髓瘤诊断,预后评估中的作用及功能研究

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目的: 循环 miRNA 是液体活检分子标志物之一。循环 miRNAs 已被证实可作为多发性骨髓瘤 (Multiple Myeloma, MM) 的生物标志物, 但循环 miRNA 的功能目前尚未完全阐明。本研究拟探寻新的循环 miRNA 生物标志物并明确其在 MM 诊断及预后中的价值, 揭示循环 miRNAs 在 MM 发生及进展中的作用。



方法：对 15 例 MM 患者血清和 10 例 MM 细胞(CD138+, n=10)进行 RNA 测序分析。使用 Veen 分析寻找 MM 患者血清和肿瘤细胞中共有差异表达的 miRNAs, 随后进行 RT-PCR 验证。分别采用 ROC 分析和 Kaplan-Meier 分析评估循环 miRNA 在 MM 诊断和预后评估中的作用。探讨循环 miRNA 分子的生物学功能。

结果：miRNA 分子在 MM 患者血清和肿瘤细胞中均存在稳定而特异表达。MM 患者血清 miRNA 表达谱显示, 相较于健康供者, MM 患者血清中共检出 104 个差异表达的 miRNAs($P < 0.05$), 其中 75% 的差异 miRNAs 表达下调, 25% 表达上调。MM 细胞 miRNA 表达谱结果显示, MM 细胞中共检出 392 个 miRNAs 差异表达($P < 0.05$), 其中 23.1% 的 miRNAs 表达下调, 76.9% 表达上调。Veen 分析结果显示, 在 MM 患者血清和肿瘤细胞中存在 36 个共同差异表达的 miRNAs, 其中 22.3% 的差异 miRNAs 位于 1 和 17 号染色体上, 提示这些差异 miRNA 可能参与 MM 发生发展。RT-PCR 进一步证实 5 个循环 miRNAs (miR-27b-3p, miR-145-3p, miR-628-3p, miR-342-5p 和 miR-30e-3p) 在 201 例 MM 患者血清中差异表达。Kaplan-Meier 分析显示, 低表达 miR-27b-3p 或低表达 miR-145-3p, 低表达 miR-628-3p 的 MM 患者无进展生存和总生存时间较对照组明显缩短。此外, 我们的研究还发现血清中低表达 miR-27b-3p 的 MM 患者, 其外周血中 CD3+T 细胞和 CD3+CD4+T 细胞较血清中高表达 miR-27b-3p 的患者比例低。并且低表达 miR-27b-3p 的 MM 患者 T 细胞, 尤其是 CD8⁺T 细胞衰老 (CD3⁺CD57⁺CD28⁻T) 比例增加。值得注意的是, MM 患者血清中 miR-27b-3p 低表达者, 其血清外泌体则富含 miR-27b-3p。为明确 miR-27b-3p 水平与 T 细胞衰老的相关性, 我们分离了 MM 患者血清中外泌体, 并与正常供者外周血单个核细胞 (HD-PBMCs) 进行共培养。流式分析结果显示, 共培养后可明显降低 CD3 T 细胞上 CD28 表达水平。Q-PCR 检测发现 T 细胞中 miR-27b-3p 的表达水平升高。此外, 我们发现过表达 miR-27b-3p 可显著下调 Jurkat 细胞中 CD28 基因及蛋白水平。因此, 这些发现表明外泌体在 CD3 T 细胞衰老诱导中发挥了关键作用, miR-27b-3p 水平较低是 MM 患者免疫微环境抑制的标志, 也是 MM 患者预后较差的生物标志物。

结论：MM 患者存在稳定、特异的循环血清 miRNA 表达谱。本研究发现 5 个在 MM 与 HD 中显著差异表达的血清 miRNAs, 分别为 miR-27b-3p, miR-342-5p, miR-30e-3p, miR-145-3p, miR-628-3p。生存分析结果显示, 低表达 miR-27b-3p, miR-145-3p, miR-628-3p 的患者有较短的无进展生存 (PFS) 和总生存 (OS) 时间。血清 miR-27b-3p 是参与多发性骨髓瘤患者 T 细胞衰老的新的 MM 循环 miRNA, 提示 MM 患者预后较差。

关键词：循环 miRNA; 多发性骨髓瘤 T 细胞衰老

295. 多肿瘤全基因组检测临床软件辅助获益

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目的: 国内 NGS 多基因 fastq 文件挖获的各种肿瘤基因组数据临床治疗获益药物不足 30%，病理基因分型获益的病例不足 10%，但全基因组和临床软件改善了临床获益。

方法: 收集 2014 年来临床科研各型肺癌，肺结节，肠腺癌，胃腺癌，食道癌，淋巴瘤，肝癌，胆道癌，胰腺癌，乳腺癌，卵巢癌，宫内膜癌，输卵管癌，脑胶质瘤，肾癌，膀胱癌，前列腺癌，各种肉瘤，来源不明肿瘤，转移癌等 45 种肿瘤共 147 例石蜡或血 CTC 细胞样本。采用 Affymetrix GSC3000dx 芯片仪 Oncoscan 检测扩增缺失和突变，部分为 Illumina NGS 全外显子测序检测突变插入和框移，以 3500dx 测序验证。样本库的建立，质控，基因组杂交，漂洗，扫描和测序等流程同标准操作规程，检测原始数据达 3.6G，以 VCF 格式标准化分组，用国家软件著作权认证的临床肿瘤全基因组系列软件（WGM v1.0）和 WES 药物靶向软件处理源数据，按照癌症基因组(TCGA)和 WHO 肿瘤病理分类抓获临床病理大数据，辅助医师人机对话编辑分类病理条目下的基因分型和 NCCN 各临床靶向免疫治疗报告。

结果和讨论: 全基因组检测临床病理基因分型结果获益 91 例（62%），完成二线以上临床靶向药物检索为 143 例（97%）仅 4 例未检出获益药物，全面检索 FDA 靶向药物中染色体拷贝数变异加突变的获益率多于 NGS 基因单一突变药物获益率。

关键词: 肿瘤；全基因组；临床软件；循环肿瘤细胞

296. LncRNA MALAT1 promotes colorectal cancer progression through regulating the miR-150-5p/METTTL14 pathway

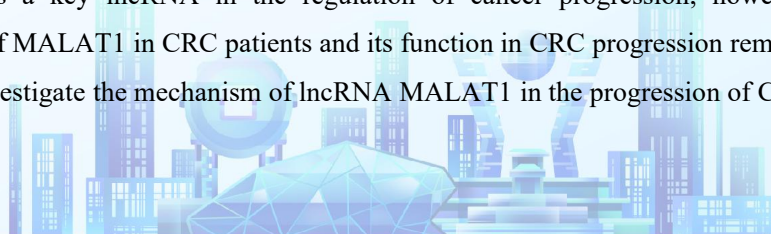
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Background: Long non-coding RNAs (lncRNAs) are involved in the development of many cancers, including colorectal cancer (CRC). Metastasis Associated Lung Adenocarcinoma Transcript 1 (MALAT1) is a key lncRNA in the regulation of cancer progression, however, the prognostic significance of MALAT1 in CRC patients and its function in CRC progression remain undefined.

Objectives: To investigate the mechanism of lncRNA MALAT1 in the progression of CRC.



Material and methods: Quantitative real-time polymerase chain reaction (qRT-PCR) was performed to measure MALAT1 and miR-150-5p expression. Cell proliferation, migration and invasion were analyzed using Cell Counting Kit-8 (CCK-8) and transwell assays. Protein expression of epithelial-mesenchymal transformation (EMT)-related markers and Methyltransferase Like 14 (METTL14) were determined using western blot analysis. The interactions among MALAT1, miR-150-5p and METTL14 were verified with dual-luciferase reporter assay. A xenograft model was constructed in vivo to confirm the role of MALAT1 in CRC tumor growth.

Results: We demonstrated that MALAT1 expression was upregulated in CRC, and its silencing reduced CRC cell proliferation, migration, invasion, and EMT. MiR-150-5p could be inhibited by MALAT1, which inhibitor could reverse the suppressive effect of MALAT1 silencing on CRC progression. METTL14 could be targeted by miR-150-5p, and the inhibitory effect of MALAT1 knockdown on CRC progression could also be eliminated by METTL14 overexpression. Furthermore, interference of MALAT1 reduced the tumor growth of CRC in vivo.

Conclusions: Our data demonstrate that MALAT1 regulated METTL14 expression to promote CRC progression via inhibition of miR-150-5p.

Key words: MALAT1; METTL14; colorectal cancer; miR-150-5p.

297. The Establishment of mRNA-Profile-Based Molecular Subtyping and Recurrent Risk Assessment Model — a Novel NanoString Method for Breast Cancer

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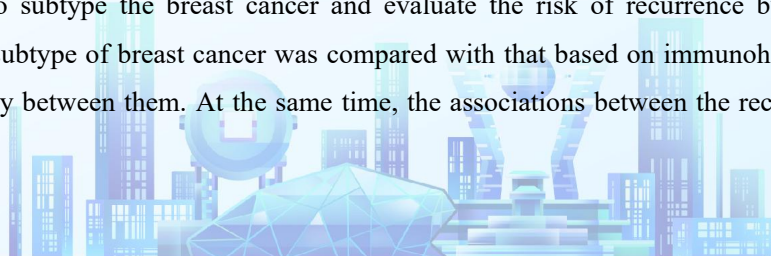
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Objective: Breast cancer represents one of the most common malignancies in Chinese women with a high incidence, for a majority of whom it develops to the advanced stage. In order to monitor the development of breast cancer postoperatively, it is required to figure it out what the subtypes of the breast cancer are, followed by the risk evaluation for the luminal subtype. Despite that it is available currently to subtype this cancer by immunohistochemistry, of which the type at an early stage could be assessed by certain commercial kits, it is still difficult to get it widely spread in offering the accurate risk score for large populations because of the unacceptable cost in China.

Methods: Molecular colored barcoding of Reporter and Capture probes by Nanostring nCounter technology was used to digitally detect the gene expression with our breast cancer gene panel, which was aiming to subtype the breast cancer and evaluate the risk of recurrence by the risk score. In addition, the subtype of breast cancer was compared with that based on immunohistochemistry to test the consistency between them. At the same time, the associations between the recurrence risk and the



disease-free survival or overall survival were analyzed using survival curves. Gene ontology was carried out to offer the judgement of our gene panel in subtyping breast cancer patients.

Results: The direct expressions of individual genes of the panel from 130 breast cancer patients were detected by a Nanostring assay and the subtypes were categorized according to the levels of ESR1, PGR, ERBB2 and MKI-67. It was shown that the molecular subtyping with our breast cancer gene panel was consistent with that using immunohistochemistry. In addition, the risk score evaluated by this panel was obtained through the bioinformatic analysis as well as was compared with the commercial kit. The data indicated that 20 of the 24 patients with the luminal type had the consistent prediction risk score. The gene ontology analysis showed that our breast cancer panel could be classified into four groups which functionally presented the individual subtype of breast cancer.

Conclusion: The breast cancer gene panel performed by a NanoString assay was capable of subtyping the breast cancer and predicting the recurrent risk of the early breast cancer. This technology was more efficient and cost-effective in the outcome prediction of post-surgical breast cancer patients.

Key words: Breast cancer; mRNA; Subtype; Recurrence risk score; NanoString

298. miR-144-3p 影响 NNK 诱导肺癌作用机制的研究

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研究目的: 肺癌的发展过程中微小 RNA (miRNA) 存在差异表达。NNK 作为香烟中致癌物之一,表现出肺癌诱导效应。因此研究 NNK 诱导肺癌过程中显著变化的 miRNA 可以为肺癌预防和诊断提供新思路。

研究方法: 在体内使用 NNK 诱导 A/J 小鼠构建肺癌形成模型。采用 MicroRNA 芯片和 RT-qPCR 检测 miRNA 的表达水平。体外采用 NNK 诱导小鼠正常肺上皮细胞 MLE-12 的肺损伤模型。流式细胞术检测细胞周期,凋亡。蛋白免疫印迹法与免疫荧光检测 CK19 蛋白表达, mimic 和 inhibitor 调节 miRNA 表达。

结果: 在 NNK 诱导的 A/J 小鼠中, miR-144-3p 的表达水平升高与体外 NNK 诱导 MLE-12 细胞变化一致。在 MLE-12 细胞中, 过表达 miR-144-3p 与 NNK 诱导对肺癌标志物 CK19 的表达产生相同的影响; 下调 miR-144-3p 逆转了 NNK 对细胞周期和细胞凋亡的影响。

结论: 本研究表明 miR-144-3p 参与了体内 NNK 诱导肺癌的发病机制, 并且在肺癌发生发展和逆转异位癌中起重要作用。通过调节 miR-144-3p 可能使预防肺癌的有效策略。

关键词: miR-144-3p; 非编码 RNA; NNK; 肺癌

299. 奥拉帕尼抑制患者源性肝母细胞瘤的生长

雷琴*



目的: 肝母细胞瘤 (HBL) 是一种致死性的儿童肝癌, 有多种治疗选择, 但最终需要手术治愈。

HBL 最恶性的形式是一种化疗耐药的侵袭性肿瘤, 其特点是快速生长、转移和治疗反应差。对于侵袭性 HBL 的机制知之甚少, 最近的焦点是发展替代治疗策略。在这项研究中, 我们检查了人类染色体区域——侵袭性肝癌域(ALCDs)在肝癌中的作用, 并评估了侵袭性 HBL 中 ALCDs 激活的机制。

结果: 我们发现 ALCDs 是人类基因组的关键区域, 位于所有的人类染色体上, 特别是在致癌基因和其他癌症相关基因的内含子区域。在侵袭性 HBL 和 HCC 患者中, JNK1/2 在 Ser6 位点磷酸化 p53, 这导致 ph-S6-p53 与含有 ALCDs 的癌基因上的 PARP1/Ku70 复合物相互作用并传递。ph-S6-p53-PARP1 复合物打开 ALCDs 周围的染色质并激活多种致癌途径。在侵袭性 HBL 患者来源的异种移植物中, 我们发现, FDA 批准的抑制剂奥拉帕尼能够抑制 PARP1, 显著抑制肿瘤生长。此外, 这与 ph-S6-p53/PARP1 复合物的减少以及随后对 ALCD 依赖的致癌基因的抑制有关。癌细胞的培养研究证实, 奥拉帕尼介导的 ph-S6-p53-PARP1-ALCD 轴的抑制作用抑制了癌细胞的增殖。

结论: 在本研究中, 我们发现 ALCDs 可调节侵袭性 HBL, 而 ALCDs 可被 ph-S6-p53/PARP1 通路激活。通过使用 PARP1 抑制剂奥拉帕尼, 我们抑制了 HBL-PDX 模型中的肿瘤生长, 这证明了它在未来的临床模型中的实用性。

关键词: 肝母细胞瘤; ALCDs; 奥拉帕尼

300. Construction and multi-omics analysis of prognostic Signature for esophageal adenocarcinoma based on m6A RNA methylation regulators

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Research Objectives: Esophageal adenocarcinoma (ECA) is a highly lethal tumor and one of the leading causes of cancer-related death. There is still a lack of effective diagnostic and prognostic markers. The main purpose of this study is to develop potential diagnostic and prognostic markers for ECA, and to provide theoretical basis for individualized treatment, so as to bring better efficacy.

Materials and Methods: We downloaded esophageal adenocarcinoma patient data from TCGA and used LASSO Cox regression to select five m6A RNA methylation Regulators to construct the optimal model. Patients were divided into high and low risk groups based on the median riskscore value. The specificity and sensitivity of the model were analyzed by the ROC curve. The differentially expressed

genes between the two groups were screened using R *edgeR* software package, and the significant enrichment pathways were analyzed by the Gene ontology (GO) analysis and gene set enrichment analysis (GSEA). Based on the data of CNV, SNP and Human Methylation 450 K Illumina Infinium Methylation Arrays, we respectively evaluated the relationship between CNV differences, SNP differences, Methylation differences and differentially expressed genes among high and low risk groups. Finally, we used the Connectivity Map (CMap) Database to screen for potential small-molecule drugs to treat ECA, and the "pRRophetic" package to predict the difference in half maximum inhibitory concentration (IC50) of commonly used chemotherapeutic drugs between high and low risk groups.

Results: In the prognosis model of ECA developed based on m6A RNA methylation Regulators, the low-risk group had a significantly better OS than the high-risk group ($P < 0.001$). The 1-year, 3-year and 4-year AUC of this model are 0.776, 0.793 and 0.854, respectively, which can accurately predict the OS of ECA of early stage (I-II), different ages and genders. Univariate and multivariate COX regression analyses showed that m6A RNA methylation Regulators based risk score was an independent prognostic factor for OS in ECA patients. GO analysis showed that the differentially expressed genes between the two groups were mainly involved in biological processes such as cell growth, immunity and metastasis. In the low-risk group, GSEA enrichment pathways were mainly FC- γ r-mediated phagocytosis and GNRH signaling pathway, while in the high-risk group, cell cycle regulation and spliceosome were the main pathways. There were 186 copy number different genes in ECA between high and low risk groups, among which CHIA was up-regulated in high risk group, and the expression level was positively correlated with copy number. A total of 76 cases of ECA patients developed SNP, and high frequency mutation genes and mutation rates were different between high and low risk groups. There were 50 differentially methylated genes between high and low risk ECA groups. By linear regression, we obtained 8 methylation driver genes. Among them, ASCL1, FABP1, G0S1, HOTTIP and NOX1 showed low methylation degree and up-regulated expression in the high-risk group; but KLF2, MAFB and PAX9 were highly methylated and down-regulated. In the study of the correlation between these genes and CpG site methylation status, we found that ASCL1, KLF2, MAFB and NOX1 had two CpG site methylation sites that were negatively correlated with their expression. G0S1, FABP1, PAX9 and HOTTIP had three, five, seven and twenty-one CpG site methylation sites respectively. In addition, CMap results showed that Podophyllotoxin is the most significant candidate for the treatment of ECA, and patients in the low-risk group were more sensitive to docetaxel than those in the high-risk group.

Conclusions: We constructed and verified a prognostic model based on a five-m6A RNA methylation regulators. Based on this model, we discovered the potential key genes that lead to different survival outcomes in EAC patients and the relationship between these key genes and multi-omics. In addition, we screened EAC potential therapeutic drugs, which will help the diagnosis of EAC patients and the development of individualized treatment.



Key words: esophageal adenocarcinoma; m6A RNA methylation regulators; SNP; CNV; methylation; CMap

301. 结肠炎相关肠癌的转录后调控

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长期的肠道炎症会增加癌症的风险, 8%~20%的炎症性肠病患者在未来 30 年内会发展成结肠炎相关肠癌 (colitis associated cancer, CAC)。目前许多研究表明 CAC 与炎症阶段异常表达的 miRNAs 密切相关, miRNAs 作为 CAC 疾病诊断及治疗的新靶点受到广泛关注。基于此, 我们使用 AOM/DSS 诱导的 CAC 小鼠模型探讨癌变过程中异常表达的 miRNAs。发现在肠道发育异常的过程中, miR-31-5p, miR-223-3p 和 let-7f-5p 失调。随后, 我们确定了这三个 miRNAs 在 CAC 中的作用, APC 为 miR-223-3p 的新靶标, SLC9A9 和 AMER3 为 let-7f-5p 的新靶点, miR-31-5p 可以靶向 LATS2 mRNA, 从而调节 Caco2 细胞中的 Hippo 通路。此外, 我们还发现了一种天然药物 (长梗冬青苷), 可以分别缓解 miR-31-5p 或 miR-223-3p 过表达引起的 LATS2 和 APC 的下调, 同时减轻 DSS/AOM 对小鼠肠道的损害。这些结果表明, miRNAs 引起的转录后调控与 CAC 的发病机理有关, 并且可以通过靶向在 CAC 中异常表达的关键 miRNAs 来预防 CAC。

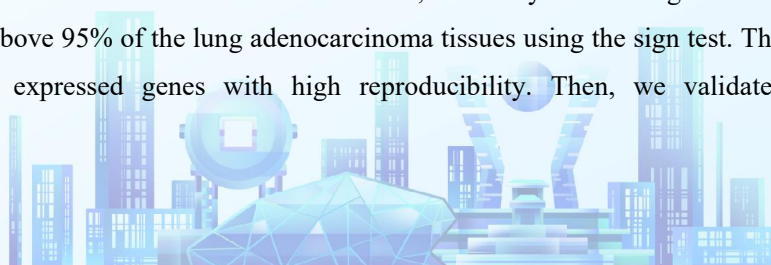
关键词: CAC; miR-31-5p; miR-223-3p; let-7f-5p

302. High Reproducibility Gene Characterization Analysis Based on Paired Data of Tumors and Normal Samples in Lung Adenocarcinoma

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Background: At present, most of the screening methods for differentially-expressed genes are based on the significance test method to judge differentially-expressed genes. Genes might be judged as differential genes, which were used as molecular markers, when more than 60% of samples up/down-regulated or contained extreme data in the test of significance. So these biomarkers are difficult to use in clinical application. In this study, with 129 lung adenocarcinoma tumors and adjacent normal tissues gene expression profile collected from GEO and TCGA, we firstly identified genes that were differentially expressed in above 95% of the lung adenocarcinoma tissues using the sign test. This gene is defined as differentially-expressed genes with high reproducibility. Then, we validated these DE genes



(Differential genes) in 57 lung adenocarcinoma tissues with paired adjacent normal tissues. From these DE genes of lung adenocarcinoma tissues, we found several interesting genes.

Methods: Differential genes with high reproducibility have two meanings. The first is the difference of gene expression value i.e., gene expression is up-regulated (or down-regulated) in the disease period compared with the normal period and has statistical significance. The second is reproducibility i.e., the proportion of people with a gene up-regulated (or down-regulated) in disease population is very large. In this study, high reproducibility ratio was defined as 95%.

Firstly, up-regulated (or down-regulated) genes with high reproducibility were identified by paired gene expression profiles of lung adenocarcinoma and adjacent non-malignant tissues. Results were then validated by independent data sets. Secondly, differentially-expressed genes were identified by Conventional differentially-expressed gene algorithms and compared with differentially-expressed genes with high reproducibility by consistency score. Finally, functions and potential roles of differential genes with high reproducibility were explored through differential co-expression analysis, functional enrichment analysis, network analysis and literature analysis. Research route is illustrated in Figure 1.

Results: There are 129 pairs of paired data genes in three datasets of lung adenocarcinoma gene expression profiles (GSE19804, GSE18842 and GSE27262, by GLP570 platform). For the same gene of paired data, the gene expression value of lung adenocarcinoma is higher than that of normal tissue, which is defined as up-regulation; the gene expression value of lung adenocarcinoma is lower than that of normal tissue, which is defined as down-regulation. In 129 pairs of the gene paired data, 54 highly reproducible dysfunctional genes (12 up-regulated and 42 down-regulated) with lower confidence limit greater than 0.95 were identified.

In this study, 54 high- reproducibility genes were analyzed for differential co-expression by Pearson correlation test and BH method ($FDR < 0.01$ or $FDR < 0.05$). Among the up-regulated highly-reproducible genes, some genes are characterized by a small or nonexistent number of related genes in the cancer-adjacent samples. This phenomenon indicates that this gene is not expressed or has low expression level in the cancer-adjacent samples. These genes were up-regulated in lung cancer samples, and the number of related genes increased significantly, indicating that they are capable of performing functions.

For example, gene COL11A1 (1301) was low expressed in normal samples (Mean gene expression ranked at the bottom 10%) and up-regulated in cancer samples compared with normal samples, showing high reproducibility. COL11A1 is also overexpressed in recurrent lung adenocarcinoma. Moreover, COL11A1 is associated with cell proliferation, migration, invasion and drug resistance. Similarly, COL11A1 gene is also predicted to be a target for diagnosis and treatment of lung adenocarcinoma by network analysis. High expression of COL11A1 gene is a marker of pancreatitis that has potential to transform into pancreatic cancer. Additionally, it has already been reported that the high expression profile of COL11A1 gene is a biomarker for recurrence of intraductal papilloma. Furthermore,



COL10A1 is a tumor biomarker which always up regulated in a wide variety of tumors including those of the breast, colon, bladder, stomach, esophagus, lung, testis, ovary and pancreas.

Differentially co-expressed genes with COL11A1 or COL10A1 were selected in the GSE27262 dataset.

Functional enrichment analysis of KEGG (Kyoto Encyclopedia of Genes and Genomes) pathways showed that these genes were significantly enriched in "Focal adhesion","ECM-receptor interaction","Protein digestion and absorption","PI3K-Akt signaling pathway","Drug metabolism – cytochrome P450 " and "Hippo signaling pathway " (FDR < 0.05, hypergeometric distribution model).

Conclusions: Based on the paired data, high reproducibility genes screened were the common characteristics of gene expression in more than 95% of cancer patients. Many of these genes had interesting characteristics. For example, COL11A1 were up-regulated in lung adenocarcinoma tissues universally but did not have any or just extremely low expression profile in adjacent normal tissues using differential co-expression analysis. MAP3K3 had a high degree (degree = 81) in PPI network, which indicated that it was a key node. KNOP1 had 100% of high reproducibility in all four datasets. If these genes are applied in clinical practice, more people will benefit.

Key words: Matching; Biomarkers; Order Relations; Reproducibility

303. 食管鳞癌细胞来源外泌体对巨噬细胞极化的影响

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目的: 探讨食管鳞癌细胞来源外泌体对巨噬细胞极化的影响

方法: 1.采用 ExoQuick-TC 法从食管鳞癌细胞上清液中提取外泌体, 电子显微镜观察外泌体的形态, 纳米颗粒追踪分析仪分析其直径, western blot 检测外泌体特异性表面标志物 CD63,CD81 的表达, 对外泌体进行鉴定。2. 将 THP-1 细胞 (人髓系白血病单核细胞) 与 PMA 共孵育, 诱导其成为巨噬细胞。用 PKH26 荧光标记食管鳞癌细胞来源外泌体, 并将其与巨噬细胞共培养。24h 后用 DAPI 标记巨噬细胞的细胞核, 然后在激光共聚焦显微镜下观察到外泌体被巨噬细胞摄取情况。3. 细胞分组培养: 巨噬细胞单独培养组, 食管鳞癌细胞来源外泌体与巨噬细胞共培养组。通过流式细胞仪分析两组巨噬细胞的 M2 型巨噬细胞表面标记物 CD206 的表达情况, 应用 qRT-PCR 检测两组巨噬细胞中 M2 型巨噬细胞标记物 (CD206,精氨酸酶-1,IL10 和 CD163) 的表达情况, 对两组巨噬细胞的表型进行鉴定。

结果: 1.电子显微镜下可以清楚地看到呈典型的脂质双层膜碟状结构的外泌体, 直径约为 50-150nm。CD63 和 CD81 在 ESCC 细胞的外泌体中高表达 ($P<0.01$)。2. 共聚焦显微镜下可见 PKH-26 红色标记的外泌体被巨噬细胞摄取。3. 流式细胞术结果表明, 与对照组单纯的巨噬细胞 (5.64%) 相比, 外泌体孵育的巨噬细胞中 CD206+巨噬细胞的比例明显增加 (22%)。qRT-PCR 结果表明, 与对照组单纯的巨噬细胞相比, 外泌体孵育的巨噬细胞中 M2 型巨噬细胞



标记物（CD206,精氨酸酶-1,IL10 和 CD163）的表达显著增加。这些结果提示食管鳞癌外泌体可以诱导巨噬细胞向 M2 型极化（ $P<0.01$ ）。

结论: 食管鳞癌细胞来源外泌体可被巨噬细胞摄取并诱导巨噬细胞向 M2 型极化。

关键词: 食管鳞癌；外泌体；巨噬细胞极化

304. 甲状腺乳头状瘤中潜在生物学标志物的筛选及生物信息学分析

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目的: 通过生物信息学技术筛选甲状腺乳头状瘤（Papillary thyroid carcinoma, PTC）中表达差异的基因，为甲状腺乳头状瘤的治疗提供新的思路和靶点。

方法: 从 GEO 数据库下载甲状腺乳头状瘤的芯片数据集 GSE58545,GSE35570,GSE33630,GSE27155,使用在线分析工具 GEO2R 筛选甲状腺乳头状瘤及其癌旁正常甲状腺组织间的差异表达基因,使用网络分析工具 Metascape 进行差异基因的 GO 分析及 KEGG 通路富集,通过 STRING 在线软件进行差异表达基因的蛋白-蛋白相互作用分析,并应用 Cytoscape 对蛋白-蛋白相互作用网络进行模块分析,提取核心基因。基于 TCGA-THCA 数据集提取核心基因表达数据,分析其表达水平。基于 ProteinAtlas 数据库比较正常甲状腺组织及甲状腺乳头状瘤组织中核心基因表达差异。

结果: 本研究共提取 159 例甲状腺乳头状瘤组织及 116 例正常甲状腺组织间共筛选出 28 个差异表达基因（DEGs）（ $|\log FC|>1$, $\text{adj.}P<0.05$ ），其中上调的 DEGs 共 18 个，下调的 DEGs 共 10 个。GO 分析和 KEGG 通路富集显示，这些差异表达的基因主要富集在多个代谢,免疫调节及 PPAR 信号通路等。通过蛋白-蛋白相互作用网络的构建及核心基因提取，我们筛选出 JUN,CTNNB1,KIT,CCR7,CCL21,NMU 六个枢纽差异表达基因。TCGA-THCA 数据集和 ProteinAtlas 数据库免疫组化分析结果均显示，与正常甲状腺组织相比，JUN,KIT,CCR7,CCL21 在肿瘤组织中表达下调，CTNNB1,NMU 在肿瘤组织中表达上调。

结论: 本研究为进一步深入理解甲状腺乳头状瘤的生物学机制,探索其治疗的有效方案提供了新思路。

关键词: 甲状腺乳头状瘤；GEO 数据库；差异表达基因；生物信息学分析



305. Lamp2a facilitated lipid droplet production and chemoresistance of colorectal cancer cells by maintaining ING5 protein stability

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Lamp2a is the lysosome-associated membrane glycoprotein, and acts as a receptor for substrate proteins of chaperone-mediated autophagy. Here, we found that Lamp2a was down-regulated in colorectal cancer at mRNA level ($P<0.05$), but down-regulated at protein level ($P<0.05$). Lamp2a protein expression was negatively correlated with lymphatic invasion, lymph node metastasis, liver metastasis and TNM staging of colorectal cancer ($P<0.05$), and unfavorable prognosis of the early colorectal cancer patients ($P<0.05$). Lamp2a knockdown suppressed proliferation, induced apoptosis, and decreased migration and invasion of colorectal cancer cells ($P<0.05$) with the underexpression of acetyl-CoA carboxylase (ACC), ATP-citrate lyase (ACL), Bcl-2, ING5 and NF- κ B, and Bax overexpression, while Lamp2a overexpression had the converse result. There was a positive relationship between Lamp2a and ING5 expression in colorectal cancer ($P<0.05$). The treatment with pyrrolidine dithiocarbamate, and Chloroquine decreased ING5 expression in lamp2a transfectants. ING5 degradation speed was delayed in Lamp2a transfectants after cycloheximide exposure ($P<0.05$). ING5 knockdown reduced the expression of ACC, ACL and NF- κ B, and the formation of lipid droplets, while it was opposite for their overexpression. The higher expression of ING5, lamp2a, ACC, ACL, and NF- κ B, and stronger lipogenesis was seen in 5-FU-resistant cancer cells. ING5 or lamp2a silencing caused the hypoeexpression of ACC, ACL, and NF- κ B, and lipogenesis in both 5-FU-resistant cancer cells. These findings indicated that lamp2a overexpression was positively correlated with colorectal carcinogenesis, aggressive behaviors and prognosis of colorectal cancer. Lamp2a might contribute to lipogenesis and subsequent chemoresistance by inhibiting lysosomal degradation of ING5 via NF- κ B signal pathway.

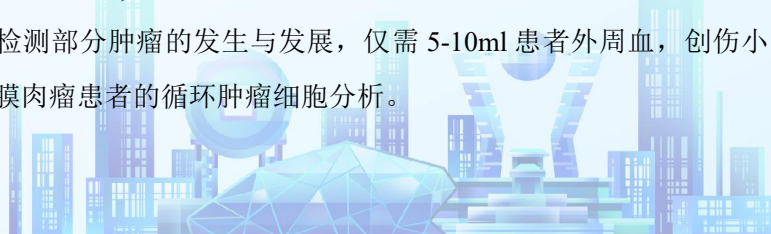
Key words: colorectal cancer; Lamp2a; ING5; NF- κ B; lipogenesis; chemoresistance

306. 对 10 例滑膜肉瘤患者的循环肿瘤细胞（CTCs）分析

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背景: 滑膜肉瘤是一种罕见的软组织肿瘤, 恶性度极高, 易于通过血液产生远处转移, 预后极差, 存在独特的 SYT-SSX1, SYT-SSX2 或其他极少见的 SYT-SSX 融合基因。CTCs 检测已作为“液体活检”技术检测部分肿瘤的发生与发展, 仅需 5-10ml 患者外周血, 创伤小, 步骤简单。本研究对 10 例滑膜肉瘤患者的循环肿瘤细胞分析。



方法：在抽血和分离核酸后，通过微滴式数字 PCR 和巢式 PCR 从循环肿瘤细胞或无细胞核酸中检测 SYT-SSX 融合基因。

结果：通过微滴式数字 PCR 仅 1 例检测出少量拷贝的 SYT-SSX2 融合转录本；巢式 PCR 无法检测 10 例滑膜肉瘤病例中的任何融合转录本。

结论：有文献报道 2 例滑膜肉瘤中检测到 CTCs，一例为低分化型，而另一例为原发性胃的滑膜肉瘤，其他尚无研究。故我们推测，使用 CTCs 检测滑膜肉瘤患者 SYT-SSX 融合基因是一种罕见的情况，虽显示出了最初的希望，但不能作为患者的有效潜在诊断和预后指标。可以监测其他可能的生物标志物，例如滑膜肉瘤特异性 miRNA，此内容还需进一步研究。

关键词：滑膜肉瘤；循环肿瘤细胞；CTCs

307. Comprehensive analysis of characteristics, detecting techniques and clinical outcomes of RET-rearranged NSCLCs from real-world practice in China

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Background: The discovery of therapeutically oncogenic drivers has led to significant improvements in the treatment of non-small cell lung cancer (NSCLC). Among these, *RET* have been described as rare oncogenic gene and recommended by consensus for routine testing. Recently, novel TKIs including selpercatinib and pralsetinib have been approved by the FDA for treatment of advanced *RET*-driven lung and thyroid cancer. However, due to the low prevalence of *RET* fusion, there is only limited information about the clinical characteristics of *RET*-rearranged NSCLC, especially in Asian populations. In addition, the optimal test strategy and clinical outcomes of *RET*-rearranged patients remain to be defined.

Methods: 9431 Chinese NSCLCs from two cancer centers who have undertaken targeted DNA NGS were enrolled. Intergenic and uncommon *RET* rearrangements were confirmed by targeted RNA NGS. Fluorescence in situ hybridization (FISH) and immunohistochemistry (IHC) were also performed in a subset of positive cases to assess their validity. Clinicopathologic characteristics, molecular profiling and treatment outcomes among different *RET* fusion variants were analyzed.

Results: A total of 167 *RET*-rearranged NSCLCs were identified with median age 57 years (range 30-83), who were mostly female, never smokers with lung adenocarcinoma. The prevalence of *RET* rearrangement was 1.52% in 9101 unfiltered Chinese NSCLCs while it was up to 8.8% in 330 *EGFR/KRAS/BRAF/ALK*-negative NSCLCs. Moreover, 40.3% (25/62) Stage IV *RET*-rearranged NSCLCs developed brain metastases. *KIF5B* (68.3%) was the most common fusion partner of *RET*,

followed by *CCDC6* (16.8%) and *NCOA4* (1.2%). Among 23 uncommon fusion subtypes identified by DNA NGS, 10 with sufficient samples were verified by RNA NGS, including *KIF5B-RET*, *GOLGA5-RET*, *TNIP1-RET* and *EPS8-RET*. The breakpoints of *RET* and its partners were relatively concentrated in our study, mainly in *RET* intron11, *KIF5B* intron15 and *CCDC6* intron1. The most common concurrent mutations were *TP53* mutations. Eight patients harboring concurrent driver oncogenic alterations including *EGFR* (N=5), *KRAS* (N=2), and *ALK* (N=1). In survival analysis, *CCDC6-RET* was proved to be an independent prognostic factor of prolonged PFS using multivariate COX analysis. The concordance of FISH and NGS was 83.3% (25/30), while the concordance of IHC and NGS was lower as 28.1% (16/57). We noticed that IHC had extremely low sensitivity on *RET* detection, while FISH also showed unsatisfying sensitivity in identifying non-*KIF5B-RET* mutation.

Conclusion: *RET* rearrangement occurs in 1.52% of Chinese NSCLCs and has identifiable clinicopathologic characteristics. *RET* IHC has a low sensitivity and is therefore not suitable for daily practice, while NGS and FISH has good performance in identifying *RET* rearrangement. Both IHC and FISH demonstrated lower sensitivity for *NCOA4*-/others-*RET* fusions. Clinical benefit with chemotherapy is different between *CCDC6-RET* and *KIF5B-RET* fusion patients, optimal treatment should be considered when selecting therapies for patients with *RET*-rearranged lung cancers.

Key words: *RET*; gene rearrangement; NSCLC; NGS; Chinese patients

308. The Ca^{2+} -activated chloride channel ANO1/TMEM16A: An emerging therapeutic target for epithelium-originated diseases?

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Anoctamin 1 (ANO1) or TMEM16A gene encodes a member of Ca^{2+} activated Cl^- channels (CaCCs) that are critical for physiological functions, such as epithelial secretion, smooth muscle contraction and sensory signal transduction. The attraction and interest in ANO1/TMEM16A arise from a decade long investigations that abnormal expression or dysfunction of ANO1 is involved in many pathological phenotypes and diseases, including asthma, neuropathic pain, hypertension and cancer. However, the lack of specific modulators of ANO1 has impeded the efforts to validate ANO1 as a therapeutic target. This review focuses on the recent progress made in understanding of the pathophysiological functions of CaCC ANO1 and the current modulators used as pharmacological tools, hopefully illustrating a broad spectrum of ANO1 channelopathy and a path forward for this target validation.

Key words: ANO1; TMEM16A; drug target



309. 梯形通道微流控芯片用于循环肿瘤细胞高效率,高纯度捕获,鉴定与分析

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研究目的: 循环肿瘤细胞(circulating tumor cell, CTC)是从原发性或转移性肿瘤脱落到外周血循环中的癌细胞。这些细胞的数量、表型和遗传信息可为治疗和预后提供重要信息。然而,目前的CTC富集技术存在效率低、通量低、下游分析困难等诸多局限性,为了解决这一难题,我们设计了一款具有梯形横截面通道的微流控芯片,可以高效、快速的富集CTC。

材料与方法: 本文设计的微流控芯片是由一个具有梯形截面的螺旋微通道组成,并利用了DeanFlow原理,根据大小差异将CTC与白细胞分离来富集CTC,并结合细胞大小、细胞形貌、细胞核质比以及多种细胞标记物DAPI、CD45、EpCAM/PanCK、N-cadherin等鉴别诊断阳性CTC。通过临床测试,对健康及肿瘤病人血液样本进行CTC检测,并将肿瘤病人血样中富集到的CTC进行蛋白检测和CTC单细胞基因测序分析。

结果: 该技术不依赖于肿瘤细胞表面标志物,可在4分钟内成功分离和富集4 mL血液样本中的肿瘤细胞。分离出的肿瘤细胞包括免疫荧光法鉴定的上皮和间充质两种表型,回收率80%以上,白细胞去除率99.99%以上。通过使用这种方法,我们测试了50名健康志愿者和786名癌症患者的血液样本。在健康志愿者中未发现CTC,在肿瘤患者中CTC检出率达到90%以上。此外,收集到的CTC可以直接进行蛋白检测(如PD-L1)以及下游CTC单细胞基因分析。其中对肝癌患者血液中的CTC进行单细胞测序并与原发肝癌组织全基因组测序进行对比,发现肝癌CTC基因组特征与原发肝癌组织基因吻合率达到73.2%。

结论: 我们开发了一种基于惯性聚焦的梯形微流控生物芯片,用于CTC高效富集与鉴定。通过对临床血样检测证明CTC检出率达到90%以上,且富集到的CTC可直接进行下游蛋白检测和单细胞基因分析。

关键词: 微流控; 循环肿瘤细胞; PD-L1, 单细胞测序, 精准医疗

310. The suppressing effects of ING5 expression on tumorigenesis and aggressiveness of colorectal cancer

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ING5 is involved in cell cycle arrest, DNA damage repair, the induction of apoptosis and senescence by targeting histone acetyltransferase or histone deacetylase activity. Here, we found that ING5

suppressed proliferation, glycolysis, mitochondrial respiration, migration, invasion, epithelial-mesenchymal transition and tumor growth, and induced apoptosis, senescence, fat accumulation, autophagy and chemoresistance to cisplatin, MG132, paclitaxel and SAHA in colorectal cancer cells. ING5 overexpression inactivated the β -catenin pathway via the ubiquitination and proteasomal degradation of β -catenin by forming ING5-APC- β -catenin, and inhibited the expression, phosphorylation, and the nuclear entry of NF- κ B and its binding promoter activity. Conditional ING5 deletion in intestinal epithelial cells might increase the sensitivity of chemically-induced colorectal carcinogenesis. ING5 mRNA expression was upregulated during colorectal carcinogenesis and negatively correlated with aggressive behaviors and unfavorable survival rate. These findings indicated that aberrant ING5 expression might contribute to colorectal carcinogenesis and reverse the aggressive phenotypes of colorectal cancer cells by inhibiting NF- κ B and β -catenin signal pathways.

Key words: colorectal cancer; ING5; aggressive phenotypes; progression; carcinogenesis

311. 原位微流控液滴数字 PCR 方法用于多重检测 EGFR T790M 和 C797S 的顺式/反式突变

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研究目的: 当肺癌患者的 EGFR T790M 和 C797S 突变位于不同染色体并形成反式结构时, 可联合第三代与第一代 EGFR 靶向药物进行治疗。当 T790M 和 C797S 突变位于同一条染色体上并形成顺式结构时, 目前尚无有效的靶向药物。为此, 我们设计了基于原位微流控的数字 PCR 系统实现 T790M 和 C797S 突变的精准多重检测。

方法: 基于原位微流控数字 PCR 平台, 通过生成液滴阵列, 开发了具有 FAM 标记的 T790M 特异性 TaqMan MGB 探针和两个 VIC 标记的 C797S 特异性 TaqMan MGB 探针的分子诊断系统。我们使用肺癌细胞系作为野生型和突变阳性对照, 从肿瘤组织、肿瘤细胞系和 PCR 产物中提取的 DNA 样本。

结果: 我们的基于微流控的数字 PCR 平台可以产生千数计的均匀稳定的直径为 40-60 μ m 的微液滴。系统制备时间仅需 5 分钟, 一个样品的工作时间为 5 分钟。并且从每个芯片上可以得到 40000 多个有效数据。基于我们的微流控数字 PCR 系统, 我们发现当 FAM 和 VIC 通道在同一样品孔中为阳性时, 说明该样品具有 T790M 和 C797S 突变位于同一条染色体上的顺式突变。当不同样品孔中的 FAM 和 VIC 通道为阳性时, 提示样品具有 T790M 和 C797S 突变位于不同染色体上的反式突变。在使用本数字 PCR 平台进行的大量型野生型背景的背景样本检测, 突变等位基因分数检测低至 0.1%。



结论：通过使用基于原位微流控的数字 PCR 系统，我们成功开发了利用临床组织样本进行 EGFR T790M 和 C797S 的顺式/反式突变多重检测的精准诊断方法。

关键词：微流控； 数字 PCR； EGFR 突变； T790M 和 C797S； 精准医疗

312. Long noncoding RNA SNHG9 promotes the progression of gastric cancer through sponging MicroRNA-760

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8. Shaanxi Provincial People's Hospital

9. Shaanxi Provincial People's Hospital

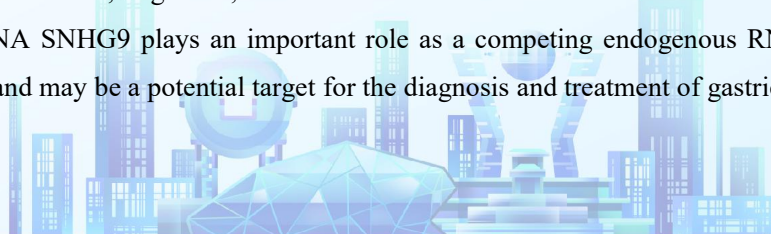
10. Shaanxi Provincial People's Hospital

Background: Multiple long noncoding RNAs (lncRNAs) were known to be closely associated with the tumorigenesis and progression in cancers. But the role of lncRNA SNHG9 in the pathogenesis and progression of gastric cancer is still unclear. The aim of this study was to investigate the function of lncRNA SNHG9 and the underlying mechanism in the pathogenesis and progression of gastric cancer.

Methods: qRT-PCR was used to evaluate the expression of lncRNA SNHG9 and miR-760 in gastric tumor tissues and cells. CCK-8 assay, transwell assay and flow cytometry analysis were used to evaluate the roles of lncRNA SNHG9 and miR-760 in cell proliferation, invasion, migration and apoptosis. The relationship between lncRNA SNHG9 and miR-760 was assessed by bioinformatics analyses and luciferase reporter assay, and the levels of SOX12, N-cadherin, E-cadherin, MMP9 and PCNA were detected by Western blot.

Results: The expression levels of lncRNA SNHG9 were significantly increased in gastric tumor tissues and cells, and miR-760 were significantly reduced in gastric tumor tissues and cells. Knocking down of lncRNA SNHG9 inhibited proliferation, invasion and migration of gastric tumor cells, and induced apoptosis of gastric tumor cells, and also significantly decreased the levels of SOX12, N-cadherin, MMP9 and PCNA, while upregulated the levels of miR-423-5p and E-cadherin. Furthermore, we found that miR-760 was a target of lncRNA SNHG9, and miR-760 could directly target SP1 and inhibit cell proliferation, migration, and invasion in HGC-27 and SUN-1 cells.

Conclusion: lncRNA SNHG9 plays an important role as a competing endogenous RNA in gastric tumor pathogenesis and may be a potential target for the diagnosis and treatment of gastric tumor.



Key words: lncRNA SNHG9; miR-760; SP; gastric tumor

313. The oncogenic roles of JC virus T antigen in breast carcinogenesis

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Purpose: JC virus (JCV) infects 80-90% of the population, and results in progressive multifocal leukoencephalopathy upon immunodeficiency. The study aimed to pathologically clarify the oncogenic roles of T antigen in human breast cancers.

Methods: Breast cancers, dysplasia and normal tissues were examined for T antigen of JCV by nested and real-time PCR. The positive rate or copy of T antigen was compared with clinicopathological parameters of breast cancer. JCV existence was morphologically detected by immunohistochemistry and in situ PCR. T antigen was examined by Western blot using frozen samples of breast cancer and paired normal tissues.

Results: According to nested PCR, the positive rate of breast ductal or lobular carcinoma was lower than normal tissue ($P<0.05$). T antigen existence was negatively correlated with E-cadherin expression and triple-negative breast cancer ($P<0.05$), but positively with lymph node metastasis, estrogen receptor and progesterone receptor expression ($P<0.05$). Quantitative PCR showed that JCV copies were gradually decreased from normal tissue, dysplasia to cancer ($P<0.05$). JCV T antigen copy was lower in ductal adenocarcinoma than normal tissue ($P<0.05$), in line with situ PCR and immunohistochemistry. JCV copies were negatively correlated with tumor size and E-cadherin expression ($P<0.05$), but positively with G grading of breast cancer ($P<0.05$). Western blot also indicated weaker T antigen expression in breast cancer than normal tissues ($P<0.05$).

Conclusions: JCV T antigen might play an important role in breast carcinogenesis. It can be employed as a molecular marker for the differentiation and aggressive behaviors of breast cancer.

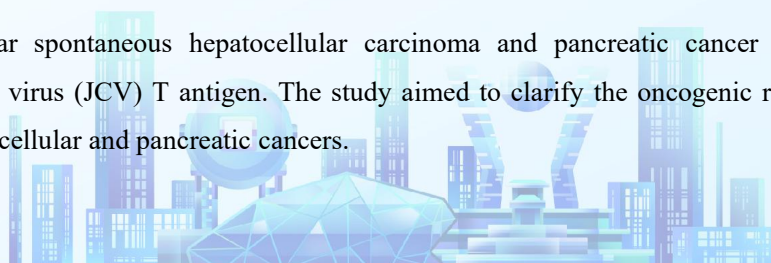
Key words: JC virus T antigen; oncogenesis; breast cancer

314. The oncogenic roles of JC virus T antigen in hepatocellular and pancreatic cancers

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Aim: There appear spontaneous hepatocellular carcinoma and pancreatic cancer in transgenic mice expressing JC virus (JCV) T antigen. The study aimed to clarify the oncogenic roles of T antigen in human hepatocellular and pancreatic cancers.



Methods: Specimens of hepatocellular and pancreatic cancers, and corresponding normal tissues were examined for T antigen of JCV by either nested- or real-time PCR. JCV existence was morphologically detected targeting T antigen by immunohistochemistry and in situ PCR. T antigen expression was also analyzed by Western blot using frozen samples.

Results: According to general PCR, the positive rate of T-antigen was lower in hepatocellular carcinoma than adjacent non-tumor tissue (79.0% vs 84.7%, $P<0.05$). It was the same for pancreatic cancer (76.0% vs 92.3%, $P<0.05$). In situ PCR demonstrated that positive cells were detectable in hepatocellular and pancreatic carcinoma cells, hepatocytes, and pancreatic ductal epithelial cells. A strong nuclear immunoreactivity against T antigen was observed in the nucleus of hepatocellular and pancreatic cancers, but not in hepatocytes and pancreatic ducts. A stronger T antigen expression was seen in hepatocellular and pancreatic cancers than paired normal tissues by Western blot.

Conclusions: The genomic insertion of T antigen preferred to occur in normal pancreatic and liver tissue in comparison with corresponding cancers. Its protein expression might play an important role in its carcinogenesis.

Key words: JC virus; T antigen; oncogenesis; hepatocellular carcinoma; pancreatic cancer

315. The effects of REG4 expression on the chemoresistance of ovarian cancer

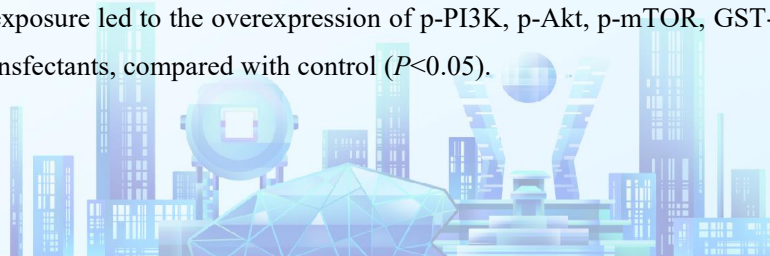
Liwei Xiang*, Hang Xue, Huachuan Zheng

承德医院附属医院

Objective: REG4 is a secretory protein involved in cell differentiation and proliferation, and up-regulated in gastrointestinal and ovarian cancers. This study aimed to clarify the effects of REG4 expression on the chemoresistance of ovarian cancer.

Methods : The expression of REG4 in ovarian cancer was analyzed by oncomine database, and the prognostic value of REG4 in ovarian cancer treated with platinum or paclitaxel was analyzed by KM plotter database. The effect of REG4 overexpression on drug resistance of ovarian cancer cell line CAOV3 was analyzed by MTT, flow cytometry, transwell and western blot.

Results: We found a higher REG4 expression in ovarian cancer than normal tissues ($P<0.05$) according to Oncomine, and REG4 expression was negatively associated with overall, progression-free or post-progression survival rate of ovarian cancer patients receiving platinum or paclitaxel treatment ($P<0.05$) according to KM plotter. REG4 overexpression resulted in either cisplatin or paclitaxel resistance, and apoptosis resistance in ovarian cancer cells ($P<0.05$). REG4 transfectants showed a stronger migration and invasion of ovarian cancer cell treated with cisplatin or paclitaxel ($P<0.05$). Additionally, cisplatin or paclitaxel exposure led to the overexpression of p-PI3K, p-Akt, p-mTOR, GST- π , survivin and Bcl-2 in REG4 transfectants, compared with control ($P<0.05$).



Conclusion: The expression of REG4 was up-regulated in ovarian cancer, and associated with poor survival and chemotherapy resistance. REG4 promoted the occurrence, development and chemotherapy resistance of ovarian cancer by regulating cell proliferation, apoptosis, migration, invasion via PI3K/Akt/m-TOR signaling pathway.

Key words: REG4; ovarian cancer; chemoresistance

316. 血清标志物 HE4 和 CA125 在卵巢癌早期筛查中的价值

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目的: 探讨血清 HE4 和 CA125 在卵巢癌早期筛查中的临床价值。

资料与方法: 2.1 一般资料 选取在本院确诊为卵巢癌者 50 例为卵巢癌组, 同期妇科检查发现卵巢良性疾病 50 例为良性组, 妇科门诊健康体检者 50 例为对照组。采血时间均排除月经期。对照组 25~62 岁, 平均 41.63 ± 10.63 岁; 良性组 23~60 岁, 平均 40.52 ± 11.32 岁; 卵巢癌组 27~63 岁, 平均 42.15 ± 10.48 岁。浆液性卵巢癌 24 例, 黏液性卵巢癌 6 例, 子宫内膜样癌 8 例, 透明细胞癌 7 例, 不明类型 5 例; I~II 期 21 例, III~IV 期 29 例。本研究经过医院伦理委员会审核批准, 患者知情同意。2.2 方法 2.2.1 标本收集、测定 ①标本采集: 采 2ml 受试者清晨空腹静脉血, 3000r/min 离心 10 min, 取血清于 -40°C 冰箱内保存。②检测: 采用酶联免疫分析(EIA)试剂盒(购自瑞典 Can Ag 公司)检测血清 HE4 水平; 采用电化学发光免疫分析(ECLIA)试剂盒(购自德国罗氏公司)检测血清 CA125 水平。2.2.2 参考值及诊断标准 $\text{HE4} \geq 150 \text{ pmol/L}$ 为阳性, $\text{CA125} \geq 35 \text{ U/ml}$ 为阳性, 若两项指标有一项为阳性即为阳性, 两项均为阴性则为阴性。敏感性 = 真阳性 / (真阳性 + 假阴性), 特异性 = 真阴性 / (假阳性 + 真阴性)。2.3 统计学分析采用 SPSS20.0 软件进行数据处理, 计数资料用率(%)表示, 比较采用 χ^2 检验; 计量资料用均数 $\pm$ 标准差($\bar{x} \pm s$)表示, 采用 t 检验。 $P < 0.05$ 表示差异有统计学意义。

结果: 3.1 三组血清 HE4、CA125 水平比较 卵巢癌组血清 HE4、CA125 水平均高于良性组和对照组, 良性组均高于对照组, 差异具有统计学意义($P < 0.05$)。3.2 血清 HE4、CA125 水平对卵巢癌的诊断价值比较 联合检测血清 HE4、CA125 水平诊断卵巢癌的敏感性、特异性及诊断符合率值均高于单一检测, 差异具有统计学意义($P < 0.05$)。3.3 不同分期卵巢癌患者血清 HE4、CA125 水平比较 III~IV 期患者血清 HE4、CA125 水平均高于 I~II 期患者, 差异均具有统计学意义($P < 0.05$)。卵巢癌组血清 HE4、CA125 水平均高于良性组和对照组, 良性组高于对照组, 差异有统计学意义($P < 0.05$); 联合检测血清 HE4、CA125 水平对卵巢癌诊断的敏感性、特异性及诊断符合率均高于单一检测, 差异有统计学意义($P < 0.05$); III~IV 期患者血清 HE4、CA125 水平均高于 I~II 期, 差异有统计学意义($P < 0.05$)。**结论:** HE4、CA125 在卵巢癌患者血清中呈高水平状态, 联合检测其血清水平有利于卵巢癌的早期诊断, 可为临床个性化防治提供科学依据。

关键词: HE4; CA125; 卵巢癌; 早期筛查

317. 精氨酸缺乏对乳腺癌细胞的影响

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代谢组研究表明,肿瘤细胞的过度增殖导致其氨基酸的生物合成需求增加,肿瘤可以通过自噬自身老化及受损的蛋白质或者某些细胞器,借以实现细胞本身的代谢需求或者某些细胞器的更新。但自噬像一把“双刃剑”,基础自噬及过度自噬的发生对肿瘤细胞产生的影响各不相同;精氨酸是人体中非必须氨基酸,但它在多种代谢途径中起着至关重要的作用。本研究中,我们试图探讨不同浓度精氨酸对乳腺癌周期及细胞自噬的影响及相关机制,为精氨酸缺陷疗法的精细化提供理论依据。在本实验中,体外培养肿瘤细胞系 MCF-7,MDA-MB231,不同浓度的精氨酸处理,利用 CCK8, CFSE 标记, Annexin V-PE/7-AAD 双染法, PI 染色, 划痕实验, DAPI 染色, Western blotting, mRFP-GFP-LC3 病毒等方法综合分析不同浓度精氨酸对乳腺癌细胞 MCF-7,MDA-MB231 的影响并探讨相应可能机制。结果显示精氨酸缺乏可以诱导乳腺癌细胞死亡并影响细胞周期而对正常 HBE 细胞影响不大;这种死亡途径不是通过凋亡途径抑制细胞增殖而降低细胞活性的;精氨酸缺乏诱导乳腺癌细胞死亡是由自噬途径产生,并可诱导自噬溶酶体的聚集。我们的结果为精氨酸应用于临床治疗提供了潜在的理论依据,靶向自噬通路的药物研发或许会在将来为乳腺癌患者带来福音。

关键词: 精氨酸; 自噬; 乳腺癌细胞

318. Urine proteomic signatures predicting the progression of precancerous gastric lesions and risk of gastric cancer

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Background/aims: Gastric cancer (GC) is the third leading cause of cancer-related deaths worldwide. Most GC patients are diagnosed at the local advanced or advanced stages with unfavorable prognosis. Early detection remains challenging and molecular biomarkers aiding GC prevention and control are highly needed, particularly based on a non-invasive approach. In our study, we examined the urine proteomic signatures and identified protein biomarkers that predict the progression of gastric lesions and risk of GC.



Methods: Our study enrolled a total of 255 subjects from Linqi, a known high-risk area for GC, based on the National Upper Gastrointestinal Cancer Early Detection Program in China, including 88 with superficial gastritis (SG), 31 with chronic atrophic gastritis (CAG), 94 with intestinal metaplasia (IM), 10 with low grade intraepithelial neoplasia (LGIN), and 32 with GC (high-grade intraepithelial neoplasia or invasive GC). Among them, we prospectively followed 60 subjects with gastric lesions for 297 to 857 days. Proteomic profiling of urine samples was conducted using liquid chromatography-tandem mass spectrometry.

Results: A total of 3271 were identified with high reliability, of which 688 were detected in at least 50% of all samples. There was a clear distinction in urine proteomic profiles between subjects with precancerous gastric lesions and GC. We identified a total of 104 differentially expressed proteins ($P < 0.05$ & VIP score > 1), of which 80 were up-regulated and 24 were down-regulated in GC compared with mild gastric lesions (SG or CAG). Leveraging our prospective follow-up of subjects, 8 urine proteins, including ANXA11, ATIC, ATP6V1B1, ATP6V1B2, CDC42, NAPA, SLC25A4 and VDAC3 were further positively associated with the progression of gastric lesions. We found the risk of gastric lesion progression was increased by 2.47-fold (odds ratio[OR]=3.47, 95% CI:1.71-8.45) and the risk of GC was increased by 1.97-fold (odds ratio[OR]= 2.97, 95% CI: 1.90-5.03), per one SD increase of a risk score combining these 8 proteins. Integrating the urinary protein risk score with age, sex, and baseline gastric histology, prediction models showed outstanding performance in predicting the progression of gastric lesions (AUC=0.87, 95% CI: 0.78-0.97, $P=1.02 \times 10^{-14}$) and risk of GC (AUC=0.84, 95%CI: 0.76-0.93, $P=1.83 \times 10^{-15}$).

Conclusions: Our study revealed distinct urine proteomic profiles and a panel of protein biomarkers that may predict the progression of gastric lesions and risk of GC. These biomarkers based on a non-invasive approach may have translational significance by opening new avenues for defining high-risk populations of GC and its early detection, improving potential for targeted GC prevention.

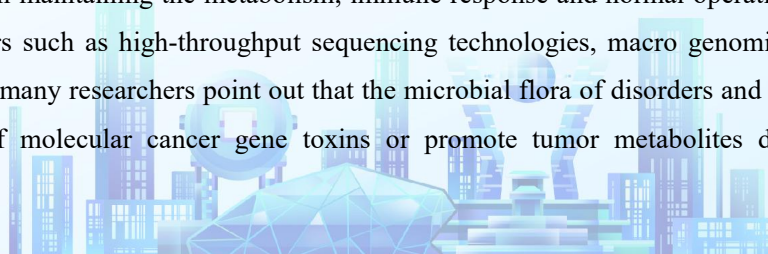
Key words: Gastric cancer; Gastric lesions; Proteomics; Differentially expressed protein; Urinary biomarkers; Progression

319. Intestinal and vaginal microflora and gynecological malignant tumor

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Liaoning Cancer Hospital

There are various microbes on the surface of the human body, intestines, vagina and other parts connected with the outside world. In healthy people, the same flora has certain similarity and stability, and they are involved in maintaining the metabolism, immune response and normal operation of relevant parts. In recent years such as high-throughput sequencing technologies, macro genomics technology rapid development, many researchers point out that the microbial flora of disorders and may change through the release of molecular cancer gene toxins or promote tumor metabolites directly increase the



incidence of gynecological malignant tumor or cause related to inflammation of department of gynaecology first, due to the inflammation has functions of promoting the development of the primary tumor and metastatic lesions in the tumor microenvironment of a series of bad effects, by increasing the incidence of gynecological malignancies. In addition, the detection of some iconic microorganisms such as vaginal vibrio, Porphyromonas, necrotic Clostridium, chlamydia trachomatis and so on plays an important role in the early screening of gynecological malignant tumors that are difficult to be detected. Early screening of gynecological malignancies, active intervention of human microbiota, and even the participation of probiotics such as Lactobacilli may be an effective treatment method associated with surgery, chemoradiotherapy in the future. This article reviews the relationship between intestinal and vaginal microflora and the pathogenic factors, early screening and treatment of cervical cancer, endometrial cancer and ovarian cancer.

Key words: Intestinal microflora; vaginal microflora; cervical cancer; endometrial cancer and ovarian cancer

320. Research progress of intestinal flora in patients with depression or depressive symptoms

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Depression is a chronic psychiatric disorders that have a devastating impact on Public health systems worldwide. Mental disorder results not only in substantial financial burden on individuals and society but also in leading cause of disability world-wide. The etiology of depression is complex and multifactorial. The risk of developing depression are influenced by genetic and environmental factors, and dietary habits. So various etiological hypotheses have also been developed. However, due to the complexity of the pathogenic factors, the pathogenesis has not yet been clarified, which seriously affects the development of clinical prevention and treatment technology. In recent years, the influence of intestinal flora on mental illness has become a hot spots in medical and biological research. The correlation between abnormalities in the gut microbiota - brain-gut axis and the incidence of depression has been demonstrated in many experiments. But the specific mechanism still needs to grope gradually. This review focuses on the etiological hypothesis of depression, the potential pathogenesis of depression, and the current progress in treatment of depression at home and abroad.

Key words: depression; intestinal flora; mechanisms

321. HDAC 9 通过调控 FOX O1 核转位促进浆液性卵巢癌细胞的迁移

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吉林大学

研究目的：组蛋白去乙酰化酶（HDAC）9 是 IIa 类组蛋白去乙酰化酶，被发现在多种肿瘤中作为癌基因发挥作用。在乳腺癌、非小细胞肺癌等肿瘤中异常表达的 HDAC 9 可以促进肿瘤增殖且与患者较差的预后相关。但其在卵巢癌中的作用尚不明确。

材料与方法：我们检测了 103 例卵巢癌患者肿瘤组织中 HDAC 9 的表达水平，通过评价患者生存期、肿瘤恶性程度等方面分析 HDAC 9 与卵巢癌患者预后的关系；基于浆液性卵巢癌 SKOV3 细胞以及子宫内膜样卵巢癌 A2780 细胞，克隆形成实验检测 HDAC 9 对细胞增殖能力的影响；细胞划痕实验及 Transwell 实验检测 HDAC 9 对细胞迁移能力的影响；免疫荧光、Western blot 实验分析 FOX O1 途径的活化情况。

结果：在浆液性卵巢癌患者中，HDAC 9 表达水平与患者预后呈负相关；与之相反，在非浆液性卵巢癌患者中，HDAC 9 表达水平与患者预后呈正相关。HDAC 9 对 A2780 及 SKOV3 细胞的增殖和凋亡水平没有明显影响。过表达 HDAC 9 可以促进 SKOV3 细胞的迁移，而在 A2780 细胞中敲除 HDAC 9 可以增强其迁移能力。进一步研究发现，在 SKOV3 细胞中上调 HDAC 9 可以增加 FOX O1 的细胞核定位，进而促进 EMT 相关蛋白及基质金属蛋白酶 MMP2、MMP9 的表达。但在 A2780 细胞中 HDAC 9 对 FOX O1 的亚细胞定位没有明显影响。

结论：本研究发现 HDAC 9 的表达水平与浆液性卵巢癌患者的预后呈负相关。相反，HDAC 9 的表达水平与非浆液性卵巢癌患者的预后呈正相关。在 SKOV3 细胞中，HDAC 9 通过影响 FOX O1 的细胞核定位上调 EMT 相关靶基因及基质金属蛋白酶 MMP2、MMP9 的表达进而促进细胞的迁移。HDAC 9 可能成为判断浆液性卵巢癌患者预后以及临床治疗的潜在靶点，同时为卵巢癌的精准医疗提供新的分子标记物。

关键词：HDAC9；FOXO1；卵巢癌

322. β -catenin/CBP 信号轴参与调节脓毒症炎症性肺损伤

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目的：观测 β -catenin 及 β -catenin/CBP 信号通路对脓毒症诱导的炎症性肺损伤的影响。

方法：通过盲肠结扎穿孔术（CLP）复制脓毒症模型，将 C57BL/6 小鼠分成以下 5 组：（1）sham 组；（2）CLP 组；（3） β -catenin knockout+CLP 组；（4）XAV-939+CLP 组；（5）ICG-001+CLP 组。XAV-939 和 ICG-001 在 CLP 术前连续注射一周，术后继续注射 2 天。CLP 术后 48h 观测每组小鼠的死亡率，肺组织病理学（HE 染色）特征和 β -catenin 的表达水平，血清细胞因子水平（TNF- α 、IL-10 和 IL-1 β ），肺髓过氧化物酶（myeloperoxidase, MPO）活性和肺组织凋亡细胞数量。



结果: 在脓毒症小鼠模型中, 抑制 β -catenin 的表达或通过 ICG-001 阻断 β -catenin/CBP 之间的相互作用均可以降低脓毒症小鼠的死亡率, 缓解肺组织病理学损伤, 同时降低血清 TNF- α , IL-10 和 IL-1 β 水平, 肺组织 MPO 活性和凋亡细胞数量。

结论: 抑制 β -catenin 的表达水平或者阻断 β -catenin/CBP 之间的相互作用, 可以缓解脓毒症炎症性肺损伤的症状。

关键词: β -catenin; 脓毒症; 炎症性肺损伤

323. 黄芩素对胃癌 HGC-27 细胞增殖, 凋亡, 周期及自噬的作用研究

段云霄*

延边大学肿瘤研究中心

目的: 探讨黄芩素 (Baicalein, BAI) 对胃癌 HGC-27 细胞增殖, 迁移, 凋亡及自噬的作用及其机制。

方法: 用不同浓度 BAI 处理胃癌 HGC-27 细胞后, 采用 MTT 比色法检测胃癌细胞的增殖; 平板克隆形成实验检测细胞的集落形成情况; 划痕愈合实验观察细胞横向迁移能力; Transwell 小室迁移实验检测细胞的纵向迁移能力; 细胞凋亡情况采用 Hoechst33342 染色观察细胞凋亡小体的形成, 采用 Annexin V-FITC/PI 双染流式细胞术检测细胞凋亡率; 免疫荧光实验观察细胞自噬情况; Western blot 实验检测 EMT 标志物蛋白, 凋亡及自噬相关蛋白的表达。

结果: 1. MTT 实验结果显示: 与对照组相比, 5, 15, 25 μ mol/L BAI 分别处理胃癌 HGC-27 细胞 24h, 48h, 72h, 均可显著抑制 HGC-27 细胞增殖, 并呈剂量和时间依赖性 ($P < 0.05$ 或 $P < 0.01$); 2. 平板克隆形成实验表明: 与对照组相比, 浓度为 5, 15, 25 μ mol/L 的 BAI 均可明显抑制胃癌 HGC-27 细胞的克隆形成 (均 $P < 0.05$); 3. 划痕愈合实验表明: 与对照组相比, 5, 15, 25 μ mol/L 的 BAI 处理胃癌 HGC-27 细胞 24h 和 48h 后, 细胞的横向迁移能力明显降低 ($P < 0.05$ 或 $P < 0.01$); 4. Transwell 小室迁移实验结果显示: 与对照组相比, 5, 15, 25 μ mol/L 的 BAI 处理胃癌 HGC-27 细胞 48h, 细胞的纵向迁移能力明显降低 ($P < 0.05$ 或 $P < 0.01$); 5. Hoechst33342 染色结果显示: 与对照组相比, 5, 15, 25 μ mol/L 浓度的 BAI 作用于胃癌 HGC-27 细胞后出现了亮蓝色凋亡小体, 凋亡小体数量随 BAI 浓度的增高而增多; 6. 流式细胞术检测细胞凋亡结果表明: 与对照组比较, 5, 15, 25 μ mol/L 的 BAI 处理组的胃癌 HGC-27 细胞的凋亡比率明显升高 ($P < 0.05$ 或 $P < 0.01$); 7. 免疫荧光实验结果表明: 与对照组比较, 5, 15, 25 μ mol/L 的 BAI 处理组的胃癌 HGC-27 细胞内 LC3B 阳性斑点增加; 8. Western blot 实验结果表明: 与对照组相比, BAI 可使胃癌 HGC-27 细胞凋亡有关的蛋白 Cleaved caspase-3 表达显著增加, Bcl-2 表达及 Bcl-2/Bax 明显下降 ($P < 0.05$ 或 $P < 0.01$), EMT 相关蛋白 E-cadherin 的表达水平上升, Vimentin



的表达水平下降 ($P < 0.05$ 或 $P < 0.01$), 自噬相关蛋白 ATG5, ATG16L1, Beclin1, LC3B 表达水平上升, p62 表达水平下降 ($P < 0.05$ 或 $P < 0.01$)。

结论: BAI 可有效抑制胃癌 HGC-27 细胞的增殖和迁移, 诱导凋亡和自噬体形成, 抑制自噬流过程。

关键词: 黄芩素; 胃癌细胞; 增殖; 迁移

324. 硼酸修饰磁性氮化碳对循环肿瘤细胞的捕获及无损释放

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研究目的: 循环肿瘤细胞 (Circulating tumor cells, CTCs) 是从原发肿瘤脱落进入血液循环系统的肿瘤细胞, 是导致肿瘤转移和复发的重要因素。对外周血中的 CTCs 进行分离和检测, 可获取肿瘤实时病变信息, 因而具有重要的临床应用价值。而通过高效、准确的分离富集方法从复杂的血液成分中获得高纯度、无损、活性的 CTC 细胞是进行下游分析的前提。因此, 建立特异性好, 捕获效率高、可无损释放的 CTCs 分离富集手段是目前 CTCs 检测领域的发展趋势。本工作中, 我们首次报道了硼酸修饰的磁性氮化碳用于 CTCs 的捕获与无损释放。

材料与方法: 首先采用直接热解双氰胺法制备石墨相氮化碳 ($g-C_3N_4$), 通过超声辅助剥离法将块状 $g-C_3N_4$ 剥离成 $g-C_3N_4$ 纳米片。再通过 HATU/DIEA 偶联反应, 使羧基苯硼酸的 $-COOH$ 与氮化碳固有的 $-NH_2$ 缩合形成酰胺键, 从而将硼酸修饰到 $g-C_3N_4$ 上, 制备成获得苯硼酸修饰的氮化碳纳米片 (BCNNS)。然后将 BCNNS 分散在 $FeCl_2$ 和 $FeCl_3$ 中, 利用水热法将 Fe_3O_4 负载到 BCNNS 表面, 从而得到负载 Fe_3O_4 颗粒的 BCNNS 纳米复合材料 (BCNNS/ Fe_3O_4)。最后基于硼酸与糖基之间的作用, 将亲和素-生物素修饰的适配体连接到硼酸修饰的磁性氮化碳纳米片上, 以实现 CTCs 的特异性捕获。

结果: 由于 B-N 作用, 硼酸配体与糖基的顺式二羟基在生理条件下即可形成环状硼酸酯, 而在弱酸性介质中发生解离, 基于此实现了弱酸性条件下联合果糖对 CTCs 的无损释放。利用该方法 CTCs 的捕获效率可达 98.1%, 释放效率可达 99.2%, 且释放后的细胞具有良好的活性, 可以实现后续 CTCs 的培养工作。

结论: 利用简单的化学合成方法对石墨相氮化碳改性, 使其带有磁性并利用硼酸与糖基之间的可逆作用, 实现了 CTCs 的特异性捕获以及无损释放, 方便了后续对细胞进行下游分析。

关键词: 石墨相氮化碳; 磁分离; 循环肿瘤细胞; 捕获; 无损释放

325. 识别可用于跨地区诊断肝硬化和肝癌的肠道微生物

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目的：肠道微生物的变化与肝脏疾病进展存在密切关系，其用于疾病诊断具有非侵入性的优点。然而，不同地域采集的同一疾病样本的肠道微生物组成存在显著差异。已有的大部分研究往往局限于一或两组数据集，所获得的肠道微生物标志难以在不同来源的数据集中得到验证。乙型肝炎病毒（Hepatitis B virus, HBV）持续性感染导致肝硬化和肝癌，其中肝癌的发生率和死亡率居中国癌症前列。因此，本研究拟识别可用于跨地区诊断肝硬化和肝癌的肠道微生物。

材料与方法：本研究收集了已发表的 4 组来自不同地区的粪便样本的 16S rRNA 基因测序数据集，共包括 122 例乙型肝炎,33 例肝硬化,70 例肝癌患者及 96 例正常对照。同时，本研究单独检测了一组由 21 例乙型肝炎，25 例肝硬化，21 例肝癌和 15 例正常对照组成的 16S rRNA 基因测序数据。使用 wilcoxon 秩和检验识别各阶段患者相对于正常患者跨地区变化的微生物群共同特征，利用随机森林方法构建用于肝硬化、肝癌诊断的分类器并采用 ROC 曲线评估诊断效能。

结果：本研究识别了 14 个在不同地区的肝硬化相对正常对照一致变化的微生物（ $P<0.05$ ）。与正常对照相比，Bacteroides 等 3 个属的相对丰度显著增加，Blautia, Butyrivibrio 等 11 个属的相对丰度显著减少，并且由这 14 个属构建的随机森林分类器对肝硬化具有良好的诊断效能（AUC=0.86）。同时，识别了 10 个在不同地区的肝癌相对正常对照中显著一致改变的微生物（ $P<0.05$ ）。与正常对照相比，Veillonella 等 6 个属的相对丰度显著增加，Lachnospiraceae UCG-008 等 4 个属的相对丰度显著减少，由这 10 个属构建的随机森林分类器对肝癌具有较高的分类效能（AUC=0.88）。进一步分析发现，Lachnospiraceae UCG-008, CAG-352 的相对丰度在乙型肝炎-肝硬化-肝癌的进程中逐渐减少。

结论：肠道微生物在不同地区 HBV 感染的肝硬化、肝癌中存在可重复的变化，可用于肝硬化、肝癌的早期诊断。

关键词：HBV 感染；肝硬化；肝癌；16S rRNA 基因测序；肠道微生物

326. 血清外泌体 miR-377-3p 和 miR-381-3p 作为结直肠癌的诊断生物标志物

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血清外泌体 microRNAs (ExmiRNAs) 为癌症诊断提供了一种理想的非侵入性方法。在这项研究中，我们评估了两种结直肠癌患者血清中的 ExmiRNAs 作为早期结直肠癌 (CRC) 的诊断工具。用 qNano, 透射电子显微镜和 Western blot 对外泌体进行了表征鉴定。用 RT-qPCR 方法检测 CRC 患者 (n=175) 和健康献血员 (n=172) 血清中差异表达的 miRNAs。通过受试者工作特性 (ROC) 分析测定其诊断值。结果表明，在结直肠癌患者中，ExmiR-377-3p 和 ExmiR-381-3p 的表达均显著降低。ExmiR-377-3p 和 ExmiR-381-3p 的 ROC 曲线下面积分别为 0.798 和 0.792。当这两个

ExmiRNA 联合在一起时, AUC 值增加到 0.807。ExmiR-377-3p 和 ExmiR-381-3p 均可用于区分早期结直肠癌(I 期和 II 期)和健康对照。ROC 曲线显示 AUC 分别为 0.794 和 0.805。当它们联合时, AUC 值增加到 0.814。另外, 用癌胚抗原(CEA)或糖链抗原 19-9(CA19-9)检测结直肠癌进展时, 发现 AUC 值分别为 0.739 和 0.707。综上所述, 循环血清外泌体 miR-377-3p 和 miR-381-3p 可作为结直肠癌早期诊断的有效、无创性生物标志物, 联合应用效果进一步提高。

关键词: 血清外泌体; miR-377-3p; miR-381-3p; 诊断标志物

327. 肿瘤标志物检测在肺癌诊断中的价值的 meta 分析

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目的: 肺癌是威胁人类生命安全的恶性肿瘤之一, 因在疾病发生早期缺乏明显的临床特征, 大部分患者发展至晚期才发现病变, 错失了最佳的治疗时机, 是一种高死亡率疾病。因此肺癌的早期诊断为临床研究重点。随着研究的深入, 发现肿瘤标志物检测对肿瘤早期诊断方面具有重要意义, 单一肿瘤标志物检验敏感性低, 但缺乏系统评价。文章以此系统评价肺癌诊断中应用肿瘤标志物检验的临床价值。

方法: 应用计算机检索中国知网 (CNKI), 维普数据库, 万方数据库, Pubmed, Web of science 中肿瘤标志物和肺癌诊断的相关 RCT。检索时间为 2011 年 1 月-2021 年 1 月。根据相关纳入与排除标准对文献进行筛选后提取相关资料, 并对纳入文献进行质量评价。采用 Stata14.2 软件进行 Meta 分析。纳入数据分为三组, 其中检验确诊的肺癌患者为 A 组, 良性肺部病变患者为 B 组, 健康者对照组为 C 组, 比较三组的血液标本中的肿瘤标志物 (癌胚抗原 (CEA), 糖类抗原 (CA125), 神经元特异性烯醇化酶 (NSE), 细胞角蛋白 19 片段抗原 21-1 (CYFRA21-1)) 的含量。

结果: Meta 分析结果显示: 三组的血液标本中四种肿瘤标志物的含量水平从高到低均依次为 A>B>C, 且 A 组与 B 组, C 组差异显著 ($P<0.05$), B 组与 C 组差异不显著 ($P>0.05$)。

结论: 癌胚抗原 (CEA), 糖类抗原 (CA125), 神经元特异性烯醇化酶 (NSE), 细胞角蛋白 19 片段抗原 21-1 (CYFRA21-1) 这四种肿瘤标志物可以作为肺癌的诊断指标, 具有临床应用价值。

关键词: 肿瘤标志物; 肺癌; 诊断; Meta 分析

328. 基于磁珠-M13 噬菌体-适配体体系用于捕获循环肿瘤细胞

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研究目的：循环肿瘤细胞的检测分析对癌症早期诊断,治疗具有重要的研究意义。由于患者血液中循环肿瘤细胞的数量极少,且具有异质性,这对循环肿瘤细胞的分离富集带来了很大的挑战。

本文构建了磁珠-M13 噬菌体-适配体体系,利用噬菌体的多个 P8 衣壳蛋白连接适配体, P3 蛋白连接磁球,形成多个适配体连接在 M13 噬菌体上,多个 M13 噬菌体连接磁球上的放大作用用于捕获 MCF-7 循环肿瘤细胞。

材料与方法：首先以 M13 噬菌体为载体,将 P8 衣壳蛋白表面的多个胺基基团利用酰胺反应修饰叠氮基。随后,将叠氮功能化的 M13 噬菌体通过点击反应与炔基功能化的适配体进行环加成反应,从而将适配体修饰在 M13 噬菌体上。M13 噬菌体的 P3 衣壳蛋白通过基因改性后展示的组氨酸与 IDA-Ni 功能化的磁珠连接,构建了磁球-M13-适配体的体系。以 MCF-7 细胞(MUC1 阳性表达细胞)作为模型细胞,对该体系的实验条件进行参数优化以探究最佳捕获效率。

结果：液相质谱分析结果表明 M13 噬菌体成功修饰上叠氮基。SDS-PAGE 电泳与荧光光谱结果显示 M13 噬菌体成功修饰适配体。基于单分子荧光显微分析表明成功构建了磁珠-M13 噬菌体-适配体体系。通过细胞的捕获效率的比较对体系的连接方式,点击反应时间,孵育时间,适配体浓度和连接噬菌体密度等进行优化,该体系对 MCF-7 细胞可以达到 92%以上的捕获效率。

结论：本工作以 M13 噬菌体为载体,成功构建了磁珠-M13 噬菌体-适配体体系。该体系对 MCF-7 循环肿瘤细胞良好的捕获性能,对癌细胞富集具有广阔的前景。

关键词： M13 噬菌体; 循环肿瘤细胞; 点击化学; 捕获

329. Plasma lipids associated with the progression of precancerous gastric lesions to gastric cancer: a prospective lipidomics study

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Background: Gastric cancer (GC), particularly of the intestinal subtype, is known to be preceded by a stepwise progression of precancerous gastric lesions, and its early detection and early management remain a major public health challenge. Robust biomarkers are urgently required to distinguish individuals of precancerous gastric lesions that have progression potential to GC. Lipids are involved in various key cellular processes that may be crucial for GC. Exploration of lipidomic profiles thus represents a biologically plausible approach to pursue promising biomarkers for early detection and diagnoses of GC. In a lipidomic study, we aimed to explore lipidomic fingerprints that may distinguish subjects with different gastric lesions and individuals that had a potential of progressing to GC.

Method: Our population-based cohort study included a total of 400 subjects in two stages, which was initiated in 2017 based on the National Upper Gastrointestinal Cancer Early Detection Program in Linqu County, Shandong Province of China, a recognized high-risk area for GC. The discovery stage

involved 200 participants with different gastric lesions (n=169) and GC (n=31). We then sought to validate the findings on the discovered lipidomic profiles and individual lipids based on an independent validation set of 200 participants, including 48 cases of GC and 152 cases of different gastric lesions, which were prospectively followed for the progression of gastric lesions by 118 to 1204 days. Of them, 76 subjects undertook three or more gastroendoscopy examinations during the follow-up. The plasma lipidomic profiling was conducted by using ultra high-performance liquid chromatography-mass spectrometry. We examined the lipidomic signatures associated with the risk of advanced gastric lesions and their progression to GC, leveraging the prospective follow-up of study subjects. The efficacy of lipids as potential biomarkers was evaluated by training extreme gradient boosting (XGBoost) models incorporated with latent feature extraction via a variational auto-encoder (VAE).

Result: Based on the two-stage study, 16 plasm lipids were significantly associated with the risk of GC comparing with mild (superficial gastritis or chronic atrophic gastritis) or advanced gastric lesions (intestinal metaplasia or low-grade intraepithelial neoplasia). Based on the prospective follow-up of 152 participants in the validation stage, 12 of the 16 lipids were further inversely associated with the risk of gastric lesion progression. Of them, additional longitudinal analysis based on the 76 participants with multiple endoscopy examinations during the follow-up substantiated the associations for 8 lipids, including PA32:1, LPI18:0, FFA20:4, FFA18:3, FFA18:0, LysoPC18:3, PC34:3, and LPI. These lipids were integrated as latent features to train XGBoost models, which significantly improved the ability to predict either the risk of GC (AUC: 0.94; 95% CI: 0.90-0.99) or the progression potential of precancerous gastric lesions (AUC: 0.82, 95% CI: 0.74-0.90), as compared to models only including age, sex, baseline gastric histopathology, and *H. pylori* infection (Delong's test $P = 7.5 \times 10^{-13}$ and 0.007 respectively).

Conclusion: Our study identified and validated lipidomic signatures that may be associated with the progression of precancerous gastric lesions and the risk of GC. Decreased plasm lipids levels show promise as noninvasive biomarkers for predicting the progression potential of gastric lesions to GC.

Key words: Gastric cancer; Biomarker; Lipidomics; Prospective study

330. 肿瘤突变负荷与肺癌临床病理特征的相关性及对术后辅助化疗预后预测价值

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目的: 探讨晚期肺癌中肿瘤突变负荷 (TMB) 与临床病理特征之间的相关性, 及分析术后肺腺癌患者样本, 通过单基因突变, 肿瘤突变负荷 (TMB), 拷贝数变异和 DNA 错配修复途径等评估肺癌术后辅助化疗的预后预测价值。



方法：来自河南省肿瘤医院 325 例肺癌患者组织样本，采用靶向二代测序技术检测其肿瘤组织标本的 TMB 水平，收集患者相关的临床信息、临床病理特征及随访资料。研究 TMB 与肺癌患者临床病理特征之间的关系。对 53 对匹配的术后肺腺癌患者 FFPE 样本（包括肿瘤组织和癌旁组织），通过 Cox 模型利用驱动基因突变、肿瘤突变负荷（TMB）、拷贝数变异和 DNA 损伤修复途径评估术后辅助化疗的无病生存期（PFS）和总生存期（OS）。

结果：TMB 在性别（ $P = 0.016$ ）、年龄（ $P = 0.012$ ）、吸烟史（ $P = 0.003$ ）、病理类型（ $P = 0.035$ ）、Ki67 的表达（ $P = 0.004$ ）和驱动基因（ $P < 0.01$ ）存在统计学差异。多元线性回归提示 TMB 与吸烟史密切相关。在 53 对匹配的术后肺腺癌患者 FFPE 样本中，本研究总结了肺腺癌的突变相关通路，主要集中在 RTK-RAS 通路（60%）、P53 通路（57%）和 Notch 通路（24%）。中位非同义 TMB 为 6.2 Muts/Mb（范围 0.78-17.77 Muts/Mb）。所有肿瘤样本基于 TMB 水平分为两类（低， ≤ 4 Muts/Mb；高， > 4 Muts/Mb）。单独使用驱动基因突变情况、TMB、拷贝数变异和 DNA 错配修复途径等单个指标并不适用评估术后辅助化疗的 PFS 和 OS。当 TMB 与 CNV 指标联合应用，在发生拷贝数变异时，低 TMB 组比高 TMB 组在 PFS 和 OS 上均可获益，但两者没有显著的统计学差异（PFS， $P = 0.067$ ；OS， $P = 0.054$ ）。在亚组分析时，拷贝数变异并且无驱动基因的条件下，与高 TMB 组相比较，低 TMB 组的预后较好，两者间有统计学差异（PFS， $P = 0.008$ ；OS， $P = 0.022$ ）。

结论：TMB 与吸烟史密切相关。利用拷贝数变异和 TMB 联合指标可以预测肺腺癌患者术后辅助化疗的预后。对于出现拷贝数变异并且低 TMB 患者，化疗辅助治疗的获益更为显著。

关键词：肿瘤突变负荷；肺癌；临床病理特征；疗效；预后

331. 基于微列阵技术 HRD 评分构建及临床应用研究

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背景：目前，卵巢癌在女性人群中仍较为高发，铂类药物是其一线化疗药物，但不同遗传状态病人对铂类化疗的应答不同，BRCA1/2 突变患者的 5 年生存率较非 BRCA 突变患者高（44%和 52% vs 36%），但仍有部分非 BRCA 突变患者对铂类化疗敏感，一系列后续研究通过同源重组修复（Homologous Recombination Repair, HRR）相关基因和同源重组缺陷（Homologous Recombination Deficient, HRD）状态等，对不同遗传状态患者的铂类化疗应答情况展开研究。

目的：本研究组通过计算 HRD 评分，寻找合适的 cutoff 值，区分不同 HRD 状态（低/高），以期可作为一种可用的评价指标，用于临床铂类化疗的预测。

方法：本研究采用 Affymetrix 基因芯片平台对不同 BRCA 突变状态的卵巢癌患者（BRCA 突变阴性和 BRCA 突变阳性）的 FFPE 样本提取 DNA 的全基因组拷贝数（Copy Number Variant, CNV）变化情况进行检测和分析，再通过本实验室自建的计算流程对 HRD-LOH（杂合性缺失）、HRD-TAI（端粒等位基因不平衡）和 HRD-LST（大片段迁移）进行计算，并得出 HRD 评分，通过组间比较，验证该方法用于铂类应答检测的有效性，并计算 cutoff 值。

结果：目前，我们对河南省肿瘤医院分子病理科 2016 年-2020 年接受 BRCA 基因突变检测的样本进行分析，筛选出 21 例 BRCA 突变阴性（BRCAwt）和 8 例 BRCA 突变阳性（BRCAmut）的卵巢癌患者，计算得到 BRCAwt 组和 BRCAmut 的 HRD-LOH、HRD-TAI 及 HRD-LST 平均值分别为 13.14、8.33、7.33 和 22.75、14.25、17，相应组的 HRD 评分分别为 28.81 和 54.00，统计分析可得 $t=2.508$, $df=24$, $P<0.05$ 。计算可得两组间 cutoff 值为 36.8。

结论：HRD 评分可作为一种评价指标用于卵巢癌的临床铂类化疗的预测，本研究组通过建立并验证的 HRD 评分方法，确定了其有效性，并进一步确定两组间的 cutoff 值为 36.8。

关键词：微阵列；HRD 评分；卵巢癌；铂敏感状态

332. 调节胆固醇代谢的 CETP 抑制剂 Evacetrapib 在结直肠癌中的作用与机制研究

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目的：内源性与外源性的胆固醇代谢重编程在肿瘤的发生发展中发挥着重要的作用，然而，抑制胆固醇酯转运蛋白（Cholesteryl Ester Transfer Protein, CETP）对肿瘤发生发展的影响尚不清楚。本研究旨在探讨 CETP 抑制剂 Evacetrapib 对结直肠癌发生发展的影响及作用机制。

方法：本研究利用 CCK8 以及克隆形成实验检测 Evacetrapib 对结直肠癌细胞增殖的影响；通过流式细胞术评价不同浓度 Evacetrapib 处理结直肠癌细胞后对其细胞周期及凋亡的作用，并对不同浓度 Evacetrapib 处理后的结直肠癌细胞中的细胞周期蛋白依赖性激酶抑制因子 P21 与 Caspase 家族、Bcl-2 家族及 IAP 家族相关蛋白进行 Western Blot 检测；在机制研究方面，利用双荧光素酶报告实验、RT-qPCR 以及 Western Blot 实验进一步探索 Evacetrapib 对结直肠癌细胞 Wnt- β -catenin 信号通路的影响。

结果：利用 CCK8 以及克隆形成实验发现 Evacetrapib 抑制结直肠癌细胞的增殖；通过流式细胞术以及 Western Blot 证明 Evacetrapib 可显著诱导结直肠癌细胞 G1/S 期阻滞及细胞凋亡；机制探索发现 Evacetrapib 通过抑制 Wnt- β -catenin 信号通路抑制结直肠癌细胞的增殖。



结论: Evacetrapib 通过抑制 Wnt- β -catenin 信号通路诱导结直肠癌细胞 G1/S 期阻滞及细胞凋亡, 从而进一步显著抑制结直肠癌细胞的增殖。

关键词: Evacetrapib; CETP 抑制剂; Wnt- β -catenin 信号通路; 结直肠癌

333. 肿瘤免疫治疗影响因素的研究进展

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在中国, 癌症已经成为主要的死亡原因, 近年来, 癌症死亡率的年龄标准化率大幅下降, 但一些癌症死亡率的年龄标准化率仍呈上升趋势 (例如: 肺癌, 结直肠癌和乳腺癌)。随着免疫检查点的发现, 例如: 细胞毒 T 淋巴细胞相关抗原 (CTLA-4), 程序性死亡蛋白 1 (PD-1), 程序性死亡配体 1 (PD-L1) 的抗体等, 针对免疫检查点抑制剂的抗肿瘤免疫治疗, 为多种类型的肿瘤患者提供了长久的临床获益率, 甚至是某些先前无法治疗的晚期疾病患者。尽管免疫疗法带来的临床数据都是正向的, 但是仅使小部分临床患者获益 (通过临床试验发现, 免疫治疗临床有效率仅为 20%)。另外, HDP (过度进展性疾病) 的出现, 患者的肿瘤发生率飞速进展, 同时肿瘤的体积快速增大, 导致患者存活率低, 生存期短, 更加降低了 ICI 临床有效率。由此可见并不是所有患者对免疫反应都有效, 有些患者还会产生严重的不良反应。目前迫切的工作就是找到影响免疫治疗有效率的多种因素, 例如肿瘤标志物 (TMB, MSI, PD-L1), 抗生素, 营养状况等, 用于筛选出潜在有效人群和剔除可能无效, 甚至会出现超进展的患者。本文将介绍肿瘤免疫抑制剂治疗疗效预测及耐药预测最新研究进展。

关键词: 肿瘤标志物; 疗效预测; 耐药预测

334. MiR-324-5P functions as a novel serum biomarker and modulates breast cancer malignant activity

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Background: Breast cancer (BC) is one of the most common cancer in women worldwide, and it is important to study the molecular mechanisms underlying its development. This study aimed to investigate the expression and effects of miR-324-5P in BC.

Methods: The expression of miR-324-5p was detected in the tissue and serum by quantitative real-time PCR. The diagnostic value of miR-324-5p was evaluated using a receiver operating characteristic (ROC) curve. Cell proliferation was assessed using the Cell Counting kit-8 (CCK-8) assay. Wound

healing and transwell assays were used to analyze migration and invasion abilities. Cell apoptosis was analyzed by flow cytometry. Bioinformatics tools were used to identify the potential targets of miR-324-5p.

Results: MiR-324-5P was upregulated in BC tissue and serum. Its expression was closely associated with tumor node metastasis and lymphatic metastasis. In addition, the serum miR-324-5P area under the ROC curve reached 0.79, with a sensitivity of 83% and specificity of 62%. MiR-324-5P promoted tumor cell proliferation and invasion and inhibited apoptosis. Bioinformatics analysis showed that the potential target genes of miR-324-5p in BC included CHIC1 and KLF7.

Conclusion: miR-324-5p may exert its oncogenic functions via CHIC1/KLF7 and that serum miR-324-5p can be used as a diagnostic biomarker of BC.

Key words: Breast cancer; miR-324-5p; diagnosis; biomarker

335. 结直肠癌的免疫治疗：现有成就及未来展望

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Following dramatic success in many types of advanced solid tumors, interest in immunotherapy for the treatment of colorectal cancer (CRC) is increasingly growing. Given the compelling long-term durable remission, two programmed cell death 1 (PD-1)-blocking antibodies, pembrolizumab and nivolumab (with or without Ipilizumab), have been approved for the treatment of patients with metastatic colorectal cancer (mCRC) that is mismatch-repair-deficient and microsatellite instability-high (dMMR-MSI-H). Practice-changing results of several randomized controlled trials to move immunotherapy into the first-line treatment for MSI-H metastasis cancer and earlier stage were reported successively in the past 2 years. Besides, new intriguing advances to expand the efficacy of immunotherapy to mCRC that is mismatch-repair-proficient and low microsatellite instability (pMMR-MSI-L) demonstrated the potential benefits for the vast majority of mCRC cases. Great attention is also paid to the advances in cancer vaccines and adoptive cell therapy (ACT). In this review, we summarize the above progresses, and also highlight the current predictive biomarkers of responsiveness in immunotherapy with broad clinical utility.

Key words: colorectal cancer; immunotherapy; immune checkpoint inhibitors; adoptive cell therapy; cancer vaccines; biomarkers

336. Expression and prognostic value of CENPI in patients with hepatocellular carcinoma

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Objective: To investigate the relationship between the expression of Centromere protein I(CENPI) and the occurrence, development and prognosis of hepatocellular carcinoma.

Methods: Using UALCAN and GEPIA database to analyze the expression of CENPI in HCC. RNA-sequencing and clinical data were acquired from The Cancer Genome Atlas database. The relationship between CENPI expression and clinical characteristics was analyzed by Kruskal-Wallis test and Logistic regression, and the influence of CENPI expression on the survival of patients with HCC was observed by Kaplan-Meier and Cox regression analysis. Finally, TIMER database was used to detect the correlation between CENPI and immune infiltration and its impact on patient survival.

Results: The results of UALCAN analysis showed that the median expression of CENPI mRNA in HCC (Median, M) was 0.22, which was significantly higher than the median value of normal liver tissue of 0.014 ($P<0.01$). TIMER analysis indicated that the infiltration level of CD8+T cells, B cells, dendritic cells, CD4+T cells, neutrophils and macrophages was significantly positively correlated with the expression level of CENPI. Cox analysis showed that CENPI high expression was a risk factor for overall survival (OS)(HR: 2.136, 95% CI: 1.549~2.946, $P<0.001$). And the mRNA expression of CENPI is positively correlated with HCC clinical stage.

Conclusion: The high expression of CENPI mRNA is closely related to the occurrence and development of HCC and demonstrate a poor prognosis of HCC.

Key words: CENPI; hepatocellular carcinoma; prognosis; bioinformatics

337. SPINK5 在皮肤恶性黑色素瘤中的表达及临床意义

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目的: 探讨 Kazal 型丝氨酸蛋白酶抑制因子 5 (SPINK5) 在皮肤恶性黑色素瘤临床组织样本中的表达情况,探讨其在皮肤恶性黑色素瘤发生或发展中的作用地位,以期发现皮肤黑色素瘤发生发展新的特异性治疗靶点,为云南地区皮肤恶性黑色素瘤的发病机制及其早期干预及预后提供重要的临床依据。

方法: 采用免疫组织化学 SP 法检测 SPINK5 在 47 例皮肤黑色素瘤与 56 例皮肤色素痣组织中的表达: 统计分析其与患者各临床参数间的相关性。

结果: SPINK5 在皮肤黑色素瘤组织中的表达水平低于皮肤色素痣组织,差异具有显著性 ($P<0.05$) 利用免疫组织化学方法,在 47 例皮肤黑色素瘤组织及 56 例良性皮肤色素痣组织中检测 SPINK5 的表达,结果发现,皮肤黑色素瘤组织中 SPINK5 阳性表达 16 例 (34.04%),阴性表达 31 例 (65.96%); 在良性皮肤色素痣组织中,阳性表达 39 例 (68.42%),阴性表达 18 例 (31.58%)。经统计分析后结果显示,二者表达差异具有统计学意义 ($P<0.05$)。提示: SPINK5 表达降低可能是促使皮肤恶性黑色素瘤发生的重要因素。SPINK5 在晚期皮肤黑色素瘤中的表达降低,但差



异未见显著性 ($P>0.05$) 临床亚组分析发现,在皮肤黑色素瘤组织中,SPINK5 的表达的阳性率随患者临床分期逐渐降低,但差异未见显著性; SPINK5 表达与患者的性别,年龄,病灶溃疡情况等均未见显著相关性 ($P>0.05$)。SPINK5 在发生转移的皮肤黑色素瘤中的表达高于未发生转移的皮肤黑色素瘤患者,且差异显著 ($P<0.05$) 令人感兴趣的是,结合患者随访信息结果显示,39 例具有随访信息的患者中,发生转移的患者 13 例,其中 SPINK5 阳性者 10 例; 未发生转移的患者 26 例,其中 SPINK5 阳性表达者有 7 例,阴性表达者 19 例。SPINK5 在转移性黑色素瘤患者中表达高于无转移的黑色素瘤患者,差异具有显著性 (76.92 vs 26.92, $P<0.05$)。

结论: SPINK5 在皮肤恶性黑色素瘤组织中的表达率显著低于皮肤色素痣组织,提示 SPINK5 表达降低可能在皮肤恶性黑色素瘤的发生过程中发挥重要作用。

关键词: SPINK5; 皮肤黑色素瘤; 良性色素痣; 临床相关性

338. DNA 修复基因 RAD52 miRNA 靶序列单核苷酸多态性与肝细胞癌术后总生存期的关系

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目的: 探讨 DNA 修复基因 RAD52 miRNA 靶序列上的单核苷酸多态性 (single nucleotide polymorphism, SNP) 对肝细胞癌 (hepatocellular carcinoma, HCC) 患者术后总生存期 (overall survival, OS) 的影响。

方法: 纳入 2007 年 1 月至 2011 年 4 月于广西医科大学附属肿瘤医院接受根治性手术治疗的 381 例 HCC 患者为研究对象, 采用 Cox 比例风险模型分析 RAD52 基因 3'-UTR 区域 miRNA 靶序列 SNP 与 HCC 患者术后 OS 的关系。

结果: 调整年龄,性别,吸烟史,饮酒史,乙型肝炎病毒 (hepatitis B virus, HBV) 感染,BCLC 分期,AFP,肝硬化,癌栓等因素后, Cox 比例风险回归分析结果均未发现 RAD52 基因 3'-UTR 区域 miRNA 结合位点上的 rs1051669 (C>T), rs1051672 (G>A), rs7301931 (T>C) 和 rs7310449 (A>G) 与 HCC 患者术后 OS 相关 (均 $P>0.05$)。SNP-SNP 之间的联合分析结果显示, 携带 1-3 个风险基因型 (风险基因型: rs1051669 CT/TT, rs1051672 GA/AA, rs7301931 TT 和 rs7310449 AA) 的高风险组患者比携带 0 个风险基因型患者的中位生存时间 (MST) 缩短, MST 分别是 33.8 和 41.1 个月。Cox 比例风险回归分析发现, 携带 1-3 个风险基因型的高风险组患者术后的死亡风险是携带 0 个风险基因型患者的 1.32 倍 ($HR = 1.32$, $95\%CI = 1.01-1.75$, $P = 0.043$)。进一步分层分析发现, 在年龄<50 岁,男性,AFP $\geq$ 400 及无癌栓的人群中, 携带 1-3 个风险基因型的患者较携带 0 个风险基因型患者术后死亡风险均显著升高 (年龄<50 岁: $HR = 2.12$, $95\%CI = 1.38-3.27$, $P < 0.001$; 男性: $HR = 1.43$, $95\%CI = 1.07-1.90$, $P = 0.015$; AFP $\geq$ 400: $HR = 1.65$,

95%CI =1.07-2.55, $P=0.022$; 无癌栓: HR =1.44, 95%CI =1.02-2.03, $P=0.038$)。利用 GTEx 数据库进行表达数量性状基因座分析,发现在肝脏组织中 rs1051669 T 等位基因,rs1051672 A 等位基因分别与 *RAD52* mRNA 较高的表达水平相关 (rs1051669: $P=0.003$; rs1051672: $P=0.007$)。

结论: *RAD52* 基因 3'-UTR 区域 miRNA 靶序列多态位点 rs1051669,rs1051672,rs7301931 和 rs7310449 的联合作用可能影响 HCC 患者术后的生存结局,携带 1-3 个风险基因型的高风险患者术后的死亡风险升高。

关键词: 肝细胞癌; *RAD52*; 单核苷酸多态性; 总生存期

339. Associations between tumor mutation burden and immune infiltration in colon cancer

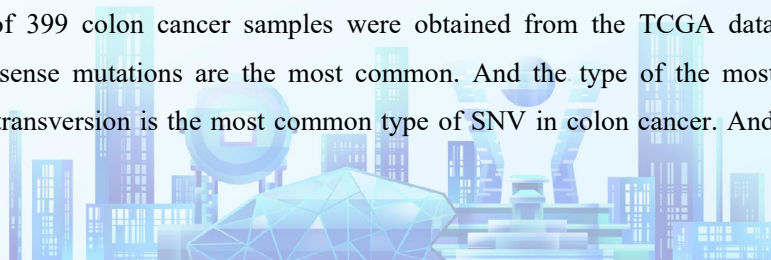
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Objective: China is one of the countries in the transitioning stage of cancer. According to Global cancer statistics 2020, colon cancer was the top five leading causes of death. It is reported that colon cancer incidence rates are about 3-fold higher in transitioned versus transitioning countries. Therefore, its the urge to seek the effective treatment of colon cancer. Immunotherapy is a vital component in cancer treatment. In several types of tumors, tumor mutation burden (TMB) and immune infiltration have been reported to predict the response to immunotherapy, although each has its limitations. In the current study, we aimed to explore the association of TMB with immune infiltration and prognosis in colon cancer.

Material and methods: Somatic mutation cases ($n=433$), transcriptome data ($n=514$), and their clinical information ($n=452$) of all Colon cancer samples were downloaded from The Cancer Genome Atlas (TCGA) database. The mutation data was visualized using the“maftools”R package. The mutations were further classified according to the variant effect predictor. For each sample, TMB was calculated as the number of variants per megabase. Based on K-M survival analysis, they were allocated into the high-TMB ($n=213$) and low-TMB ($n=201$) groups (the optimal cutoff was determined by the‘surv_cutpoint’algorithm of survival R package). Then, Gene Ontology (GO) and Gene Set Enrichment Analyses (GSEA) were performed, with immune-associated biological pathways found to be significantly enriched in the High-TMB group. CIBERSORT algorithm was used to calculate the fractions of infiltrating immune cells. At a threshold of $P<0.05$, the results of the inferred fractions of immune cell populations produced by CIBERSORT were considered accurate.

Results: A total of 399 colon cancer samples were obtained from the TCGA database. Among these mutation, missense mutations are the most common. And the type of the most common mutation is SNP. C>T,transversion is the most common type of SNV in colon cancer. And the top 10 mutated



genes are TTN (49%), APC (75%), MUC16 (27%), SYNE1 (29%), TP53 (55%), KRAS (43%), FAT4 (23%), RYR2 (21%), RIK3CA (28%), ZFHX4 (21%). Kaplan–Meier survival analysis revealed that patients with lower TMB had a higher 5-year survival rate. The CIBERSORT results shown that tumors with high TMB were significantly associated with high fractions of activated NK and Macrophages M1. In the low TMB group with a higher fraction of T cells regulatory (Tregs) and Macrophages M0.

Conclusion: This study indicated that patients with a lower TMB level experienced a favorable 5-year survival outcome. It may influence immune infiltration in colon cancer, which might be associated with a higher fraction of T cells regulatory (Tregs) and Macrophages M0.

Key words: tumor mutation burden; immune infiltration; colon cancer

340. 多发性骨髓瘤 RPMI-8226 细胞对 HUVEC 生物学行为的影响

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目的: 探讨多发性骨髓瘤 (multiple myeloma, MM) 细胞对人脐静脉内皮细胞 (human umbilical vein endothelial cells, HUVEC) 生物学行为的影响。

方法: 1. 无菌条件下使用 IMDM 完全培养基培养 RPMI-8226 细胞, 1640 完全培养基培养 HUVEC。

2. 当 MM 细胞与 HUVEC 达到指数生长期时, 分别收集两种细胞于 6 孔板中分组培养: MM 细胞与 HUVEC 细胞 1: 1 共培养组; HUVEC 细胞单独培养组。24h 后通过 CCK-8 检测细胞的增殖能力; Transwell 迁移和侵袭实验检测细胞的迁移和侵袭能力; 小管形成实验检测细胞的成管能力; qRT-PCR 检测肿瘤血管内皮细胞特异标志物 TEM5, TEM7 的表达, 联合鉴定诱导后的 HUVEC 是否具有肿瘤相关内皮细胞的特性。3. 收集处于指数生长期的 MM 细胞上清液, 与 1640 完全培养基配置成为 20% 上清液待用。细胞分组培养: 20% 上清液培养组, 正常对照组。24h 后通过 CCK-8 检测细胞的增殖能力; Transwell 迁移和侵袭实验检测细胞的迁移和侵袭能力; 小管形成实验检测细胞的成管能力; qRT-PCR 检测肿瘤血管内皮细胞特异标志物 TEM5, TEM7 的表达, 联合鉴定诱导后的 HUVEC 是否具有肿瘤相关内皮细胞的特性。

结果: 1. 与 MM 细胞共培养后, HUVEC 细胞的增殖, 迁移, 侵袭和成管能力显著增加, 肿瘤血管内皮细胞标志物 TEM5, TEM7 的表达水平显著升高。2. 与正常对照组相比, 20% 上清液诱导后, HUVEC 细胞的增殖, 迁移, 侵袭和成管能力显著增加, 肿瘤血管内皮细胞标志物 TEM5, TEM7 的表达水平显著升高。

结论: 多发性骨髓瘤 RPMI-8226 细胞能够通过分泌细胞因子将 HUVEC 诱导成为肿瘤相关内皮细胞。

关键词: 多发性骨髓瘤; 肿瘤相关内皮细胞

341. 血浆 SNORD84 作为诊断非小细胞肺癌的新型肿瘤标志物

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研究目的: 肺癌是世界上发病率最高的肿瘤, 每年大约会有 160 万人因肺癌死亡。根据组织类型, 肺癌可分为非小细胞肺癌 (NSCLC) 和小细胞肺癌 (SCLC), 其中非小细胞肺癌约占 85%。由于其早期无明显症状, 通常在晚期才被确诊。据报道, 接受有效治疗的 1 期非小细胞肺癌患者一年存活率为 83%, 而晚期非小细胞肺癌患者仅为 14%。因此, 揭示非小细胞肺癌发生发展的分子机制, 寻找新的可反映肿瘤早期发展的生物标志物尤其重要。小核仁 RNA(snoRNAs) 是一类广泛分布于真核生物细胞核仁的小分子非编码 RNA, 长度为 60~300 个核苷酸, 主要参与 rRNA 和其他小 RNA 转录后的成熟加工过程。snoRNAs 主要分为 C/D box snoRNAs 和 H/ACA box snoRNAs 两类, C/D box snoRNAs 主要介导 rRNA 特定位点的 2-O-甲基化, 而 H/ACA box snoRNAs 主要介导 rRNA 特定位点的假尿苷化, 二者均能与核糖核蛋白 (RNPs) 结合形成稳定的, 具有功能的 snoRNPs 复合体。近年来越来越多的证据表明 snoRNA 与肿瘤的发生、发展有关。此外, 在肿瘤细胞中部分 snoRNAs 的异常表达以及可在血液中长期稳定存在的特征, 也为其成为肿瘤诊断及其预后监测的生物标志物提供了可能。本研究旨在探索 SNORD84 是否可以作为诊断非小细胞肺癌的生物标志物。

研究方法: 1. TCGA 数据库筛选差异表达的 SNORNA 基因。2. 数据库及 24 对 FFPE 样本验证 SNORNA 的差异表达。3. 分析 snoRNA 在血浆中的表达特点。4. 收集 107 例肺癌血浆及 110 例健康人血浆样本分离提纯游离 RNA 并通过 RT-PCR 验证 snoRNA 差异表达。

结果: 1. SNORD84 在来自数据库配对癌组织与正常组织具有显著的差异表达 ($P < 0.0001$)。2. 数据库大样本及 FFPE 样本验证 SNORD84 在肺癌组织中的表达显著高于癌旁组织 ($P < 0.0001$)。3. SNORD84 在血浆中稳定存在。4. SNORD84 在 107 例肺癌血浆中表达显著高于在 110 例健康人血浆中的表达 ($P < 0.05$)。

结论: SNORD84 可作为非小细胞肺癌诊断的循环肿瘤标志物。

关键词: 非小细胞肺癌; 肿瘤标志物; SNORNA

342. 在缺氧条件下癌成纤维细胞对 MM 相关内皮细胞的生物学行为的影响



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目的: 通过多发性骨髓瘤 (MM) 细胞上清液诱导人脐静脉内皮细胞 (HUVEC) 成为 MM 相关内皮细胞, 观察癌相关成纤维细胞 (CAFs) 在缺氧条件下对 MM 相关内皮细胞的影响。

方法: MM 上清液作为条件培养基诱导 HUVEC 形成 MM 相关内皮细胞, 将不同比例的 CAFs 的上清液作为条件培养基培养 MM 相关内皮细胞; 再使用氯化钴进行化学缺氧, 二甲双胍抑制缺氧反应; 通过 CCK-8, 划痕实验, 迁移实验和血管形成实验进行功能实验检测; 再通过 Western blot, qRT-PCR 检测 VEGF 和 HIF-1 α 的 mRNA 和蛋白表达。

结果: 50%MM 上清液诱导 HUVEC 的 HIF-1 α 与 VEGF 蛋白表达量上升, 增殖, 迁移和血管形成能力增强, 100%CAFs 上清液诱导 MM 相关内皮细胞的 VEGF 蛋白表达量升高, 但并未对增殖产生影响; MM 条件培养基的诱导和缺氧环境均使 MM 相关内皮细胞的 HIF-1 α 表达量具有明显升高, 并且 HIF-1 α 和 VEGF 的蛋白表达量呈正相关。与对照组相比, 二甲双胍在缺氧条件下可以减弱 HIF-1 α 的表达, 这与常氧条件下的功能相反。

结论: CAFs 上清液通过 HIF-1 α /VEGF 途径促进 MM 相关内皮细胞的生物学行为, 并被缺氧条件所增强。

关键词: 癌成纤维细胞; 缺氧条件; MM 相关内皮细胞

343. 血浆外泌体 tRF-Trp-CCA-057 作为非小细胞肺癌的新型诊断标志物

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背景: 非小细胞肺癌 (NSCLC) 是世界上主要的死亡原因之一。非小细胞肺癌发病率高, 5 年生存率低。其中一个原因是, 大多数非小细胞肺癌患者在被发现时都处于中晚期。因此, 探索非小细胞肺癌的早期诊断标志物具有重要意义。目前缺乏有效的早期诊断标志物。为了提高诊断水平, 寻找新的生物学靶点。本研究旨在验证一种新的用于诊断非小细胞肺癌 (NSCLC) 的生物标志物。

材料与方法: 根据实验室非小细胞肺癌血浆外泌体 tRF 测序结果, 依据 $FC > 2$, 且 $P < 0.05$, 筛选出差异明显的 tRF 进行验证。实验纳入健康人 253 例及非小细胞肺癌患者 207 例, 对其血浆外泌体中的 tRF-Trp-CCA-057 表达量进行检测。ROC 曲线用于研究 tRF-Trp-CCA-057 作为非小细胞肺癌诊断标志物的诊断效能。



结果：我们利用 qPCR 对 253 例健康人及 207 例非小细胞肺癌患者血浆外泌体中的 tRF-Trp-CCA-057 表达量进行检测，结果表明，与健康人相比，在非小细胞肺癌患者血浆外泌体中的 tRF-Trp-CCA-057 的表达量明显减少（ $P < 0.0001$ ）。ROC 曲线显示血浆外泌体 tRF-Trp-CCA-057 诊断非小细胞肺癌的 AUC 为 0.62。这预示了血浆外泌体中的 tRF-Trp-CCA-057 可以作为非小细胞肺癌的一种新型诊断标志物。

结论：我们的研究结果表明，血浆外泌体中的 tRF-Trp-CCA-057 可能是 NSCLC 患者新的、有前景的诊断生物标志物，与 NSCLC 发生密切相关。

关键词：外泌体；NSCLC；tRF-Trp-CCA-057；生物标志物

344. 口腔鳞状细胞癌 TIGIT 表达及其对 T 细胞功能的研究

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目的：免疫检查点分子在肿瘤的发生发展中发挥重要作用。然而，不同肿瘤中的免疫检查点分子表达及功能并未一致。因此，我们通过比较口腔鳞状细胞癌患者 T 细胞上五种常见的负性免疫检查点分子的表达，研究其中发挥主要作用免疫检查点分子对 T 细胞的功能。

方法：通过收集就诊于中山大学附属口腔医院口腔颌面外科口腔鳞状细胞癌患者外周血及癌组织，以及健康人外周血。流式分析外周血 T 细胞以及肿瘤浸润性 T 细胞中免疫检查点分子表达。体外研究代表性免疫检查点分子对 T 细胞分化、增殖和效应功能的作用。采用 SPSS 和 GraphPad 软件进行统计分析， $P < 0.05$ 代表统计学意义。

结果：共收集口腔鳞状细胞癌患者外周血标本 45 例，癌组织 24 例，健康人外周血 20 例。与 PD-1、CTLA-4、LAG-3 和 TIM-3 比较发现，TIGIT 在口腔鳞癌患者循环 T 细胞及肿瘤浸润 T 细胞中的表达显著升高。CD4⁺ T 细胞 TIGIT 高表达组（>18.1%）与肿瘤 T 分期以及淋巴结转移密切相关；CD8⁺ T 细胞 TIGIT 高表达组（>34.9%）与肿瘤淋巴结转移密切相关。此外，在外周血和肿瘤中，TIGIT 主要表达在活化的 CD4⁺ T 和 CD8⁺ T 细胞表面。进一步分析发现，与 TIGIT-CD4⁺ T 及 TIGIT-CD8⁺ T 细胞比较发现，TIGIT+CD4⁺ T 及 TIGIT+CD8⁺ T 细胞表现为失功能表型（低增殖能力、低 IL-2、TNF- α 、IFN- γ 效应性细胞因子分泌能力），TIGIT+CD4⁺ T 细胞还表现出抑制性表型（Foxp3 表达增强以及 IL-10 分泌能力增加）。而且，TIGIT 单克隆抗体体外共培养可以增强 T 细胞的增殖能力以及 IL-2、TNF- α 和 IFN- γ 效应性细胞因子分泌能力。

结论：上述结果表明 TIGIT 在口腔鳞癌发展中发挥重要作用。TIGIT 可能是口腔鳞癌的潜在治疗靶点。

关键词：口腔癌；鳞状细胞癌；TIGIT；免疫检查点；T 细胞



345. 外泌体中 miR-let-7c 通过介导巨噬细胞极化促进多发性骨髓瘤血管生成

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目的: 探讨多发性骨髓瘤中骨髓间充质干细胞 (BMMSCs) 来源的外泌体中 miR-let-7c 对血管生成的影响。

方法: 1. 收集并原代培养多发性骨髓瘤患者的 BMMSCs, 并通过流式细胞仪检测其表面标记 STRO-1, CD105 及 CD90 对其鉴定。采用超高速离心法及试剂盒法两种方法提取培养上清的外泌体, 通过透射电子显微镜, 纳米颗粒跟踪分析仪及流式细胞仪方法检测表面标志物 CD63, CD81 对外泌体进行鉴定。2. 采用密度梯度离心法及 CD14 磁珠阳性分选法收集并筛选出外周血巨噬细胞, 与 BMMSCs 及外泌体分组培养后应用流式细胞仪检测 M2 型 TAMs 表面标志物 CD206 的表达情况, 采用 qRT-PCR 检测各组 MΦs 中 miR-let-7c 的表达情况。采用共聚焦显微镜观察外泌体被 MΦs 摄取的情况。3. 构建 miR-let-7c 过表达及抑制的稳定慢病毒感染细胞株, 采用 qRT-PCR 验证各组 MΦs 中 miR-let-7c 的过表达及抑制水平, 通过流式细胞仪检测感染前后 M2 型 TAMs 表面标志物 CD206 的水平变化。4. 分离并鉴定多发性骨髓瘤患者的骨髓瘤血管内皮细胞 (MVECs), 将细胞与极化后的 M2 细胞及巨噬细胞分组培养, 分别运用 CCK-8 试剂盒, 划痕实验, Transwell 迁移实验及小管形成实验检测共培养前后 MVECs 的增殖能力, 迁移能力及体外成环能力变化。

结果: 1. BMMSCs 来源的外泌体呈典型的双层膜茶托样结构, 其粒径中 20-200 nm 范围占 71.5%, CD63 和 CD81 表面蛋白均呈阳性表达 (分别为 81.1% 和 91.7%)。2. 外泌体共培养组 M2 特异性标志物 CD206 的水平明显升高 ($P < 0.01$), 且与外泌体共培养后细胞内 miR-let-7c 的水平明显上调 ($P < 0.01$)。在共聚焦显微镜下可见 PKH26 标记的外泌体向 DAPI 染色的巨噬细胞胞浆内聚集。3. miR-let-7c 过表达组极化为 M2 型 TAMs 比例较对照组明显增加 ($P < 0.05$) 而抑制组 M2 型 TAMs 比例则减少 ($P < 0.01$)。4. 运用 CCK-8 试剂盒检测结果显示, MVECs 与 M2 共培养 72 h 后, 细胞增殖能力出现明显增强 ($P < 0.05$)。通过划痕实验和 Transwell 迁移实验证实, MVECs 在与 M2 共培养 72 h 后细胞迁移能力明显增强 ($P < 0.01$), 小管形成实验结果显示, MVECs 在与 M2 共培养 72 h 后细胞体外成管能力明显增强 ($P < 0.01$)。

结论: BMMSCs 释放的外泌体中 miR-let-7c 可以诱导巨噬细胞极化为 M2 型, 从而在多发性骨髓瘤的血管生成起促进作用。

关键词: 多发性骨髓瘤; 外泌体; miR-let-7c; 血管生成



346. Characterization of metabolic reprogramming and immune infiltration in colorectal cancer

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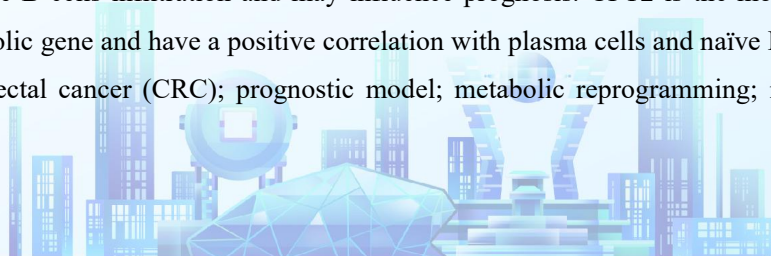
Purpose: To construct a metabolic-related gene prognostic index (MRGPI) for colorectal cancer(CRC) and make a full analysis of the relationship between metabolic reprogramming and immune infiltration in colorectal cancer.

Materials and methods: Based on The Cancer Genome Atlas (TCGA) dataset (COAD, n = 514), 5 survival-related metabolic genes were identified by the Cox regression analysis. Subsequently, MRGPI was constructed by the 5 survival-related metabolic genes and validated with the Gene Expression Omnibus(GEO) dataset (GSE39582, n = 585). Meanwhile, gene set variation analysis (GSVA) and cibersort analysis were used to comprehensively analyze the metabolic reprogramming and immune infiltration of colorectal cancer. CPT2 was selected by combining the 5 survival-related metabolic genes and metabolic reprogramming result. Afterwards, enrichment analysis, weighted gene coexpression network analysis (WGCNA) and immune infiltration analysis were performed to fully explore the function of CPT2.

Results: Five survival-related metabolic genes including ACOX1, ASNS, CPT2, FOLR1 and GCNT3 were selected by the Cox regression analysis and MRGPI was constructed by the 5 survival-related metabolic genes. In TCGA cohort, MRGPI-high patients had a better overall survival (OS) than MRGPI-low patients, consistent with the results in the GEO cohort. The metabolic reprogramming of colorectal cancer (CRC) showed that top 3 down-regulated pathways were Fatty Acids Oxidation(peroxisomal), Fatty Acids Oxidation (mitochondrial), Carnitine shuttle, and top 3 up-regulated pathways were Purine Biosynthesis, Pyrimidine Biosynthesis, Histone Methylation. Meanwhile, immune infiltration analysis suggested that Carnitine shuttle, Fatty Acids Oxidation(peroxisomal) and Fatty Acids Oxidation(mitochondrial) were positively correlated with plasma cells and naïve B cells. Purine Biosynthesis and Pyrimidine Biosynthesis were negatively correlated with plasma cells and naïve B cells. 5 survival-related metabolic genes and the most regulated metabolic reprogramming pathway genes have 2 same genes (CPT2, ACOX1). The 2 genes also have a positive correlation with plasma cells and naïve B cells, CPT2 is the protective factor with the most significant difference in survival analysis.

Conclusions: MRGPI is a promising biomarker to distinguish the prognosis of colorectal cancer (CRC). The most significant pathways for metabolic reprogramming are significantly associated with plasma cells and naïve B cells infiltration and may influence prognosis. CPT2 is the most obvious survival-related metabolic gene and have a positive correlation with plasma cells and naïve B cells.

Key words: colorectal cancer (CRC); prognostic model; metabolic reprogramming; immune infiltration; CPT2



347. 尿液 DNA 甲基化和突变在尿路上皮癌无创和精准诊断中的 前瞻性,多中心临床研究

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目的: 目前尿路上皮癌的诊断和复发监测方法主要通过侵入性的膀胱或输尿管镜检查, 无创尿液诊断技术如脱落细胞学, FISH 等肿瘤标志物在敏感性和/或特异性上难以满足临床需求。我们前期建立了尿液 DNA 甲基化诊断膀胱癌的技术, 已发表在 J Clin Invest 和 Clin Epigenetics 上。我们拟在全国的前瞻性大队列中进行 DNA 甲基化联合突变的技术优化和验证, 最终开发出高敏感性和特异性的尿液无创诊断技术。

方法: 我们在全中国 11 个大型三甲医院前瞻性收集了 1155 例患者尿液, 包含病例组膀胱和上尿路尿路上皮癌共 697 例, 其他泌尿系肿瘤共 113 例, 泌尿系良性疾病对照 345 例。基于 TCGA 和我国测序数据筛选和验证 15 个高频突变位点, 并建立检测 DNA 突变的 qPCR 检测方法, 结合前期已建立的 2 个位点的甲基化方法, 对上述样本进行检测, 并将本技术与目前临床常用的尿脱落细胞学和 FISH 进行诊断效能的比较分析。

结果: 对于上述入组病例, 目前我们已完成 449 例的 DNA 甲基化和突变检测, 发现 8 个突变位点在尿路上皮癌的尿液中突变率明显高于非肿瘤患者。在 NMIUC 占 75.7%, MIUC 占 21.4% 的病例组成下, 单用 DNA 甲基化和突变分别诊断尿路上皮癌的准确性 86.9% 和 86.3%, 敏感性为 84.1% 和 81.1%, 特异性为 88.9% 和 89.8%。联合甲基化和突变, 性能较前提高到准确性 88.6%, 敏感性为 86.8%, 特异性为 89.8%。无论是单用 DNA 甲基化或突变, 或者联合两者, 他们的敏感性显著高于尿脱落细胞学 (56.2%) 和 FISH (68.7%), 而特异性相近 (92.2% 和 86%)。而且尿液 DNA 甲基化联合突变, 在低分期肿瘤 (Ta-1), 低分级 (LG), 以及上尿



路尿路上皮癌(UTUC)展示出高的敏感性和准确性,显著优于脱落细胞学和 FISH。而且血尿,合并感染和结石等情况,无明显影响检测的特异性。

结论: 本研究是国内首个大样本的尿液 DNA 甲基化联合突变诊断尿路上皮癌的前瞻性,多中心临床研究,中期结果显示尿液 DNA 甲基化和突变检测是一种快速,高通量,无创,高诊断效能的方法,可减少不必要的有创检查和盲目的二次手术,为尿路上皮癌精准诊断提供高效新方法。

关键词: 尿路上皮癌;尿液无创诊断;DNA 甲基化;DNA 突变

348. 外泌体中 miR-let-7c 靶向结合 AGO1 调控多发性骨髓瘤血管生成过程

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目的: 探讨多发性骨髓瘤中骨髓间充质干细胞(BMMSCs)来源的外泌体中 miR-let-7c 靶向结合 AGO1 对 MM 血管生成的影响

方法: 1. 通过 LV3-miR-let-7c mimics,LV3-miR-let-7c inhibitor 的慢病毒载体分组感染骨髓瘤内皮细胞(MVECs),分别运用 CCK-8 试剂盒,划痕实验,Transwell 迁移实验及小管形成实验检测共培养前后 MVECs 的增殖能力,迁移能力及体外成环能力变化。收集各组 MVECs,并采用 Western blot 技术检测细胞中 HIF-1 α ,AGO1 及 VEGF 的蛋白表达;采用 qRT-PCR 技术检测各组细胞中 HIF-1 α ,AGO1 及 VEGF 的 mRNA 水平。2. 采用生物信息学软件 miRDB 和 Targetscan 预测筛选 miR-let-7c 对 AGO1 的靶向调控区。采用双荧光素酶报告系统验证 miR-let-7c 对 AGO1 的靶向调控作用。3. 构建小鼠 MM 模型:将 miR-let-7c mimics,inhibitor 及 NC 慢病毒感染的稳定细胞株分别注入小鼠腋背部皮下,采用免疫组织化学方法,以 CD31 标记血管内皮细胞,计算各组移植瘤组织 MVD 值;采用免疫组织化学检测各组移植瘤组织中 HIF-1 α ,AGO1 及 VEGF 的蛋白表达;采用 qRT-PCR 方法检测各组移植瘤组织中 HIF-1 α ,AGO1 及 VEGF 的 mRNA 水平。

结果: 1.过表达 miR-let-7c 后, MVECs 的细胞增殖能力,迁移能力及成管能力明显增加(均 $P < 0.01$),相反,抑制 miR-let-7c 表达后,血管内皮细胞的增殖能力,迁移能力及成管能力较对照组减弱(均 $P < 0.01$)。2. 生物信息学软件 miRDB 和 Targetscan 预测出 miR-let-7c 与 AGO1 存在与 3'UTR 结合的靶向调控区。双荧光素酶报告基因实验结果显示,与 LV3-NC+ AGO1 WT 组相比,miR-let-7c mimics+ AGO1 WT 组细胞中荧光素酶活性明显降低,差异具有统计学意义($P < 0.05$)。

3. 在小鼠 MM 移植瘤模型中,上调 miR-let-7c 水平后, MVD 值出现明显上升($P < 0.05$),血管生成增加;且 HIF-1 α ,VEGF 的 mRNA 及蛋白水平明显增加($P < 0.05$),而 AGO1 的 mRNA

及蛋白水平降低 ($P < 0.05$)。相反,在 miR-let-7c inhibitor 组移植瘤中 HIF-1 α , VEGF 的 mRNA 及蛋白水平明显降低 ($P < 0.05$),而 AGO1 的 mRNA 及蛋白水平升高 ($P < 0.05$)。

结论: BMMSCs 释放的外泌体中 miR-let-7c 可以靶向结合 AGO1 参与调控多发性骨髓瘤的血管生成。

关键词: 多发性骨髓瘤; 外泌体; miR-let-7c; AGO1; 血管生成

349. 仑伐替尼治疗晚期肝癌的作用价值

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目的: 分析仑伐替尼治疗晚期肝癌的作用价值。

方法: 选取 2020 年 1 月-2020 年 12 月收治的晚期肝癌患者 23 例为研究对象,按照患者的治疗意愿分为对照组 13 例,应用索拉非尼进行干预,观察组患者 10 例使用仑伐替尼治疗,分析两种治疗方式的效果。

结果: 观察组患者的客观缓解率及无进展生存期高于对照组,差异有统计学意义 ($P < 0.05$); 观察组患者不良反应的发生情况与对照组相比,差异无统计学意义 ($P > 0.05$)。

结论: 晚期肝癌患者采用仑伐替尼治疗时可有效提升整体治疗效果,且不增加不良反应的发生,有临床应用价值。

关键词: 仑伐替尼; 晚期肝癌

350. 线粒体分裂相关分子 Drp1 促进食管鳞癌转移的作用研究

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目的: 探究 Drp1 对食管癌细胞转移的影响及其相关机制。

方法: 通过免疫印迹法 (Western Blot), 荧光定量 PCR (qPCR) 等方法初步研究 Drp1 在食管癌组织中和细胞中的表达情况。利用公共数据库分析 Drp1 与食管癌病人预后相关性。采用克隆形成, Edu 方法研究 Drp1 过表达和干涉后对食管癌细胞体外增殖的影响。采用细胞划痕和 Transwell, Western Blot, 小鼠尾静脉注射检测 Drp1 异常表达对食管癌细胞体内外转移的影响。使用流式细胞仪检测 Drp1 异常表达对活性氧 (ROS) 的影响。通过 Western Blot 实验检测 Drp1 过表达对 ROS 相关的核因子 E2 相关因子 2 (NRF2) 途径的影响。

结果: 1, 通过 Western Blot, qPCR 等方法研究发现 Drp1 在食管癌细胞和组织中高表达, 且 Drp1 高表达患者预后较差。2, 克隆形成, Edu 实验结果提示 Drp1 显著促进食管癌细胞的增殖。3, 细胞划痕和 Transwell 实验检测到 Drp1 过表达时其迁移和侵袭能力增加。Western Blot 检测到 Drp1 过

表达细胞中 EMT 相关分子 E-cadherin,ZO-1 的表达下降, Vimentin,N-cadherin 的表达增加, Drp1 干涉后则表现出相反的结果。小鼠尾静脉注射食管癌细胞 8 周后出现肺转移。上述实验结果说明 Drp1 过表达促进食管癌的转移。4,流式细胞仪检测到 Drp1 过表达时, ROS 水平增加。Western Blot 显示 Drp1 过表达时 NRF2 表达也呈增加趋势, 使用 ROS 相关抑制剂 NAC 后, NRF2 表达降低, 并抑制了 Drp1 过表达时促进的食管癌转移。

结论: Drp1 促进食管癌细胞的增殖, 且可能通过 NRF2 途径促进食管癌的转移, 研究结果为食管癌的治疗提供新的靶点。

关键词: Drp1; 食管癌; 转移

351. 肺癌手术前后呼出气中挥发性有机化合物变化及其临床意义

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研究目的: 呼出气中挥发性有机化合物 (Volatile organic compounds, VOCs) 检测有望应用于肺癌早期诊断与监测随访。本研究通过对比肺癌患者手术切除前后呼出气中 VOCs 变化寻找肺癌特异性的 VOC 标志物。

材料与方法: 2020 年 9 月至 2020 年 12 月于北京大学人民医院胸外科前瞻性入组可疑肺癌患者 (ClinicalTrials.gov ID NCT04419207)。分别于术前 1 天及术后 4 周应用标准化采样流程收集呼出气样本。所有样本于 12 小时内经高压气相色谱-飞行时间质谱 (HPPI-TOFMS) 完成 VOC 成分分析。记录质核比 (m/z) 及相应谱峰峰强。通过 Wilcoxon 配对符号秩和检验寻找手术前后谱峰差异性 m/z 值。通过对照质谱文库确定 m/z 值对应的有机化合物即为潜在的肺癌特异性 VOC 标志物。

结果: 本研究共纳入 90 例可疑肺癌患者, 平均年龄为 55 ± 10 岁。术后病理确诊 84 例为肺癌 (病理分期 I/II/IIIA 分别为 75/2/7 例), 6 例为肺良性结节。所有患者均完成术前及术后 4 周呼出气标准化采集和 HPPI-TOFMS 检测分析。肺癌患者术后 4 周较术前呼出气中显著下降的 VOCs 包括乙烯, 异戊二烯, 己醛和庚醛 (所有 $P < 0.01$), 显著增加的 VOCs 包括乙醛, 丙醇和丁酸 (所有 $P < 0.01$)。良性结节患者术前术后对比中未发现上述 VOCs 变化; 特别地, 良性结节患者术后呼出气中乙醛和丙醇含量显著下降 (所有 $P < 0.05$)。

结论: 肺癌患者呼出气中乙烯, 异戊二烯, 己醛, 庚醛含量在手术切除后快速下降, 此类 VOCs 有望成为肺癌特异性呼出气标志物而应用于早期诊断和复发监测。

关键词: 肺癌; 呼出气检测; 挥发性有机化合物; 肿瘤诊断监测



352. PTRF 与胶质瘤研究的相关进展

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胶质瘤是中枢神经系统中最常见的恶性肿瘤，由于胶质瘤具有不正常的血管增生,可以明显破坏脑组织,可以产生耐药性等特点，使得胶质瘤患者即使经过手术,放化疗等治疗后与后仍然很差。

聚合酶I和转录释放因子（PTRF）在胶质瘤的发生发展中扮演着重要的作用，有可能成为胶质母细胞瘤的治疗靶点，在此对 PTRF 与胶质瘤的治疗做一综述

关键词：PTRF；胶质瘤

353. Analysis of stromal proteomes in colorectal cancer

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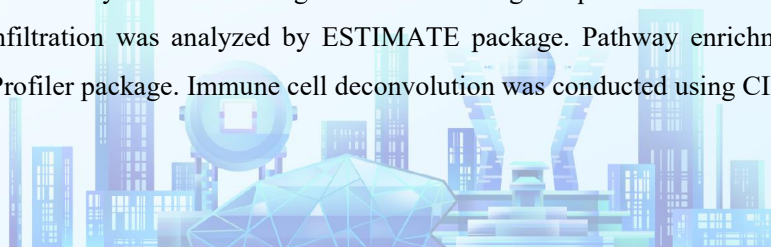
1. 深圳华大基因

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Introduction: It is well accepted that tumor microenvironment (TME) of colorectal cancer (CRC) plays a key regulator to CRC development and metastasis. during this course. Most cases of CRC occur malignancy of epithelial cells and undergo a process from normal, adenoma to carcinoma (N/A/C). There are many reports to explore the molecular mechanism of the CRC N/A/C process, however, is a few of study regarding the changes of stromal proteome during the process. Herein, the surgery tissues were carefully excised by laser capture microdissection (LCM) from 17 CRC patients. The proteomic analysis upon DIA aimed at assessment of the stromal proteome responses to adenoma and tumor in these patients.

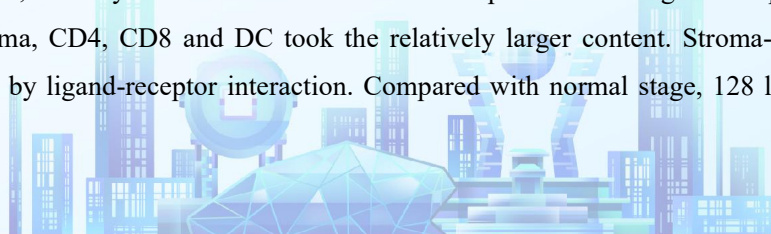
Material and method: A total of 52 colon tissues were obtained from Xijing Hospital from 17 CRC patients. The surgery samples were excised by LCM or general dissection, during which the LCM samples from a patient were obtained from adjacent, stroma and tumor, respectively. The corresponding proteins were extracted from either bulk or LCM samples followed by trypsin digestion. The digested peptides were delivered to a LC-MS/MS, equipped with Ultimate 3000 nanoLC connected with Orbitrap Fusion Lumos mass spectrometer. The ion library was first constructed at DDA mode, while the quantitative peptides were acquired at DIA mode. The MS/MS data acquired from DIA were analyzed with Spectronaut against the ion libraries generated by MaxQuant. The quantitative proteomes were normalized by MSstats package in R. Differential expressed proteins (DEP) were statistically evaluated using t-test with setting of q-value < 0.05 and fold-change > 2. Stroma cell infiltration was analyzed by ESTIMATE package. Pathway enrichment was performed using ClusterProfiler package. Immune cell deconvolution was conducted using CIBERSORTx.



Results: Upon DIA mode, more than 5000 proteins were identified in each type of bulk tissues, while averagely around 3600 and 2300 proteins were found in epithelial and stromal samples with LCM preparation. As regards the overlapped proteins in both bulk and LCM preparation in the same patient, the majority of the proteins from LCM was counted in the list of the identified proteins from bulk. The correlation coefficients of all the samples both bulk and LCM were above 0.7 with medians over 0.8, suggesting a close correlation of the samples in a group and a reasonable comparison of gene expression among groups. PCA analysis was applied to evaluated samples similarity among the tissue types. For bulk preparation, a considerable segregation was shown between carcinoma and adjacent samples, whereas the adenoma samples were partially overlapped either carcinoma or adjacent samples. For the LCM epithelial samples, the three groups, adjacent, adenoma and tumor, were well separated, indicating that sample difference during N/A/C transition were more obviously at cell level than that in bulk. By integrated of differential expression analysis and WGCNA, the proteins identified in bulk and LCM epithelial were evaluated. A total of 132 proteins from the WGCNA modules were selected, 70, 14 and 48 as carcinoma-, adenoma- and carcinoma-/adenoma-related proteins, respectively. Many of them were reported by others as the colorectal abnormality at protein or mRNA level. The discovery gained from the proteomics data on the bulk and LCM preparation to the colorectal tissues was in a great agreement with the previous study and was enlightening for exploring novel protein biomarkers of CRC.

Molecular differences among bulk, epithelia and stroma were further compared. Infiltration analysis by ESTIMATE indicated more stromal cell infiltration in stroma than epithelia and bulk, implying that the stromal samples collected by LCM were typically represented by the specific features of stromal proteins. Comparison of the proteins identified in epithelia and stroma under different circumstances unraveled that most identified proteins in stroma were co-existed in epithelia regardless of which circumstance. The DEPs between stoma and epithelia were evaluated from functional enrichment, the shared pathways with higher protein counts related to the functions of focal adhesion, ECM-receptor interaction, protein digestion and absorption and complement related pathways.

The identified proteins in stroma from adjacent, adenoma and tumor were quite flexible, ones in adjacent significantly lower than that in the other tissues. PCA analysis with combining qualitative and quantitative proteomics demonstrated a good separation of principle features in the adjacent stroma from that in the adenoma or carcinoma, nevertheless, a poor segregation between the adenoma and carcinoma stroma. Since the adenoma stromal proteomes were comparable with the carcinoma stromal ones, the two sets of proteomic data were treated as one group, termed as AC. Using CIBERSORTx, the immune cell fractions in each stroma were estimated, in which nine distinct immune cell types were found based on the proteomics data. Although the immune cell compositions were varied sample to sample, some typical changes in the compositions between adjacent and AC were obvious. In most adjacent stroma, monocytes and natural killer cells occupied relative higher composition, whereas in most AC stroma, CD4, CD8 and DC took the relatively larger content. Stroma-epithelia interaction were depicted by ligand-receptor interaction. Compared with normal stage, 128 ligand-receptor pairs



were up-regulated, while 65 pairs down-regulated, suggesting more tight interaction in tumor and tumor associated microenvironment.

Conclusions : Compared with bulk preparation, LCM can provide more specific molecular features of tumor in response to the N/A/C stages, with more clearly separation among normal, adenoma and carcinoma. Proteomic landscape in stroma was different with epithelia, with more microenvironment-related functions enriched, indicating stromal samples were truly reflect microenvironment features in all stages. The stromal proteins in adenoma and carcinoma showed same pattern, implying a very similar microenvironment in these two stages. Compared with normal stroma, the proportion of CD4, CD8 and DC were significantly increased, indicating a strong immune response happened in disease microenvironment. More ligand-receptor pairs were up-regulated compared with normal stage, revealing a stronger interaction between stroma and tumor cells.

Key words: colon cancer; proteomics

354. 宫颈癌细胞中 EphA7 基因转录调控因子的鉴定

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目的: 宫颈癌是女性常见的恶性肿瘤,发病率居妇科肿瘤第四位。研究显示 EphA7 与肿瘤的发生发展及预后相关,课题组前期亦证实 EphA7 基因在宫颈癌组织中呈现高甲基化低表达现象,因此本课题将深入探讨宫颈癌细胞中 EphA7 基因差异表达的机制。

方法: 采用特异性的 CRISPR 甲基化干扰系统(dCas9-Tet1/Dnmt3a)对 EphA7 基因的甲基化进行双向调控,采用 RT-PCR 及 pyrosequencing 证实 DNA 甲基化直接参与 EphA7 基因的转录表达;同时,基于在线数据平台对 EphA7 基因启动子的转录因子进行筛选,并采用特异性的原位捕获技术,鉴定其基因启动子区域的转录因子。

结果: CRISPR 甲基化干扰系统可以有效调控 EphA7 基因的转录表达,在宫颈癌细胞系中可提高其 mRNA 表达水平达 6.20, 7.51 倍等($P<0.05$),同样在正常 EphA7 非甲基化细胞系,其转录水平可下调 72.75%。另外,在宫颈癌细胞系中也初步鉴定 SP1 和 MAZ 与 EphA7 基因结合,调控其表达。

结论: CRISPR 甲基化干扰系统可以特异性的作用于 EphA7 基因甲基化的调控,原位捕获技术可特异性的捕获结合与靶位点的调控元件,为下一步机制的深入研究及后续的宫颈癌治疗及预后的监测奠定了良好的基础。

关键词: 宫颈癌; EphA7; 甲基化



355. Visfatin 活化癌相关成纤维细胞促进结直肠癌转移

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研究目的: 结直肠癌是我国常见的癌症之一, 其治疗的难点之一就是肿瘤的转移, 肿瘤相关成纤维细胞的活化与肿瘤转移密切相关, 研究发现肿瘤相关成纤维细胞(Cancer-associated fibroblast, CAFs)的活化是促进结直肠癌转移的重要因素, 炎症因子对 CAFs 的活化有重要作用, 胞外内脂素(Visfatin/Nampt) 作为促炎性细胞因子是否参与 CAFs 活化促进结直肠癌转移的影响尚不清楚。因此探讨胞外 Visfatin 活化 CAFs 促进结直肠癌转移的分子机制, 有助于探索干预 Visfatin 调节肿瘤微环境稳态抑制结直肠癌转移的治疗策略, 为治疗结直肠癌提供新思路。

材料与方法: ① 从人结直肠癌组织分离 CAFs 并采用流式细胞仪和免疫荧光进行标志物鉴定后, 采用 visfatin 处理 CAFs, 蛋白印迹检测其活化情况, 并对活化后的 CAFs 进行炎症因子检测。② 将 CAFs 与结直肠癌细胞共培养, 并设置结直肠癌细胞单独培养作为对照, 通过 Transwell 迁移实验, 检测加入 visfatin 前后细胞的迁移能力的变化, 探讨 visfatin 对结直肠癌转移的影响。③对 visfatin 处理的 CAFs 进行基因测序,GO 富集分析寻找与之相关的富集通路基因, 采用蛋白印迹和免疫荧光分析 Visfatin 活化 CAFs 的分子机制。

结果: 1. Visfatin 增加炎症因子的分泌活化 CAFs: 1.1 CAFs 的分离与鉴定: 从人结直肠癌组织中分离出 CAFs, 采用免疫荧光法检测波形蛋白 Vimentin, 所有细胞呈现绿色荧光; 流式细胞术检测 CAFs 标志蛋白 α -平滑肌肌动蛋白(α -Smooth muscle actin, α -SMA)和血小板衍生生长因子受体 β (Platelet-derived growth factor receptor β , PDGFR β), 阳性率均达 95%以上, 分离出的细胞为 CAFs, 可用于后续实验研究。1.2 Visfatin 活化 CAFs: Visfatin 处理 CAFs 后, α -SMA 和 PDGFR 表达升高, 炎症芯片检测发现 β -NGF, 白介素-11(Interleukin-11, IL-11)等炎症因子分泌增加。

2. Visfatin 活化 CAFs 促进结直肠癌转移: Transwell 迁移实验结果表明, 与 SW480 细胞组, Visfatin 处理 SW480 组, CAFs 与 SW480 细胞共培养组相比, Visfatin 处理后的 CAFs 与 SW480 共培养组的 SW480 细胞转移数量显著升高。

3. Visfatin 活化 CAFs 的分子机制: 基因测序和 GO 富集分析结果表明, visfatin 处理后的 CAFs 应激活炎症信号通路显著激活, 蛋白印迹和免疫荧光检测发现, visfatin 增加 JAK2 和 STAT3 的磷酸化水平, 且细胞核内的 STAT3 含量增加, 而加入 JAK2 特异性抑制剂 AG490 后, 共培养体系中 SW480 细胞转移数量降低。

结论: Visfatin 通过 JAK2-STAT3 信号通路增加 β -NGF 和 IL-11 等炎症因子的分泌, 使得 CAFs 活化从而促进结直肠癌的转移。

关键词: 结直肠癌; 癌相关成纤维细胞; 内脂素; 转移



356. 基于 EP9-A3 评价两种方法学检测神经元特异性烯醇化酶结果的一致性

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目的: 肺癌是我国死亡率最高的恶性肿瘤。由于肺癌患者早期没有特异性临床表现,容易忽视病情病程,导致出现明显症状后治愈极为困难。肺癌及早发现,诊断,治疗有助于降低患者死亡率,提升患者预后判断效果,肺癌的早期筛查十分重要。在肺癌中,小细胞肺癌(SCLC, Small Cell Lung Cancer)的发病隐匿性更高,病情进展更为迅速,恶性程度更高,导致患者预后较差,但 SCLC 对放化疗度敏感高,如早期发现并进行有效治疗,可明显提升五年生存率。神经元特异性烯醇化酶(NSE, Neuron Specific Enolase)作为 SCLC 的最敏感最特异性的肿瘤标志物之一,且在 SCLC I期患者中的灵敏度明显高于其它肿瘤标志物, NSE 是 SCLC 早期筛查的良好指标。有研究表明,血清中 NSE 的水平对辅助肺癌病理类型预测,临床分期判断和预后评估有着重要临床意义。因此,本文针对两种不同的免疫学检测系统检测血清中 NSE 结果的一致性进行方法学比对,评估磁微粒化学发光法检测 NSE 的临床适用性能。

方法: 收集肿瘤专科医院 232 份患者临床样本进行了方法学检测,比较一致性,以罗氏神经元特异性烯醇化酶测定试剂盒(电化学发光法)为参考方法,安图神经元特异性烯醇化酶检测试剂盒(磁微粒化学发光法)为待评价方法进行分析,根据美国临床和实验室标准协会(CLSI, Clinical and Laboratory Standards Institute)第三版《使用患者样本进行方法比对及偏倚评估》指南(EP9-A3, *Measurement Procedure Comparison and Bias Estimation Using Patient Samples, 3rd Edition*)的文件要求,对两种检测方法进行 NSE 方法学比对和偏倚评估。

结果: 在 5.08-290ng/ml 范围内,两种方法学的 NSE 检测结果具有较好的相关性,相关系数 $r=0.9967$,截距-0.2337。

结论: 安图神经元特异性烯醇化酶检测试剂盒(磁微粒化学发光法)和罗氏神经元特异性烯醇化酶测定试剂盒(电化学发光法)检测 NSE 结果具有可比性。

关键词: 方法学比对;神经元特异性烯醇化酶;小细胞肺癌;肺癌;

357. 米诺环素通过 STAT3 通路抑制结肠癌细胞迁移与侵袭

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目的: 通过探讨米诺环素抑制结肠癌细胞迁移与侵袭的机制,促进米诺环素在结肠癌肿瘤治疗与应用。



材料与方法：1.米诺环素对结直肠癌细胞迁移与侵袭的影响①通过MTT和细胞克隆形成实验，探讨米诺环素是否影响结直肠癌细胞增殖。②细胞划痕实验,Transwell迁移和基质胶侵袭试验确定米诺环素是否影响结直肠癌细胞迁移与侵袭。③构建BALB/c小鼠鼠源性结直肠癌CT-26细胞肺转移模型，以在动物水平上确定米诺环素抑制结直肠癌细胞的转移。

2.米诺环素抑制结直肠癌迁移与侵袭的分子机制①使用免疫印迹探究米诺环素对结直肠癌细胞上皮-间质转化(EMT)相关蛋白表达的影响。②使用免疫印迹探究米诺环素对结直肠癌细胞EMT相关转录因子表达的影响。

3.米诺环素抑制结直肠癌细胞STAT3信号通路①用米诺环素处理SW480和SW620细胞，检测STAT3的磷酸化水平。②p-STAT3的临床相关性分析，分析在60个与患者匹配的结直肠癌样本的组织芯片微阵列中结肠癌组织与癌旁组织的p-STAT3水平。

结果：1.米诺环素对结直肠癌细胞迁移与侵袭的影响①米诺环素是否影响结直肠癌细胞增殖。米诺环素处理结直肠癌SW480,SW620细胞48小时后，较低浓度下细胞存活率无明显变化但随着药物浓度的增加，细胞存活率与药物浓度呈反比。通过结合米诺环素处理正常的结直肠细胞NCM-460细胞存活结果，终选用4 μmol/L和8 μmol/L的米诺环素用于后续实验。细胞克隆形成实验表明，与对照组细胞相比，4 μmol/L和8 μmol/L的米诺环素处理结直肠癌SW480,SW620细胞，细胞克隆数无明显差异，统计分析表明不具有统计学意义。②米诺环素是否影响结直肠癌细胞迁移与侵袭。米诺环素处理结直肠癌SW480,SW620细胞后，划痕实验表明米诺环素抑制结直肠癌细胞划痕愈合能力。Transwell迁移和基质胶侵袭试验显示，与对照组相比，米诺环素处理导致SW480,SW620细胞侵袭到下室的细胞数量明显减少，且呈明显浓度依赖性。③构建BALB/c小鼠鼠源性结直肠癌CT-26细胞肺转移模型。米诺环素处理BALB/c小鼠结直肠癌CT-26细胞转移瘤模型后，小鼠肿瘤数目和肺重量明显降低。

2.米诺环素抑制结直肠癌迁移与侵袭的分子机制①米诺环素对结直肠癌细胞EMT的相关蛋白表达影响。用米诺环素处理结直肠癌SW480,SW620细胞后，EMT标志蛋白N-钙黏蛋白(N-Cadherin),波形蛋白(Vimentin)的表达降低，E-钙黏蛋白(E-Cadherin)的表达明显增加。②米诺环素对结直肠癌细胞EMT相关转录因子表达的影响。米诺环素处理结直肠癌SW480,SW620细胞后，Snail,Slug,ZEB1的表达量明显减少，证明米诺环素能通过抑制EMT调控相关转录因子抑制结直肠癌细胞EMT过程。

3.米诺环素抑制结直肠癌细胞STAT3信号通路①用米诺环素处理SW480和SW620细胞，STAT3的磷酸化水平降低。②p-STAT3的临床相关性分析，在60个与患者匹配的结直肠癌样本的组织芯片微阵列中结肠癌组织的p-STAT3水平明显高于癌旁组织

结论：米诺环素作用结直肠癌细胞后，抑制STAT3信号传导途径，抑制EMT相关转录因子的表达，从而抑制EMT，导致抑制结直肠癌细胞迁移与侵袭。为促进米诺环素的临床应用提供了新的证据。

关键词：米诺环素；结直肠癌；STAT3；EMT



358. Development of Prognostic Indicator Based on RNA-binding proteins related lncRNAs in bladder urothelial carcinoma

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Background: Numerous evidences have shown RNA-binding proteins (RBPs) were closely related to tumor survival, suggesting that RBPs might be used as prognostic predictors, while lncRNAs had been known as powerful biomarker in predicting the prognosis of cancer. Bladder urothelial cancer (BLCA) shown a high recurrence risk that approximately 70% in non-muscle-invasive type and roughly up to 21% with high-risk disease will progress to muscle invasive bladder cancer, which leads to a poor prognosis. Regrettably, so far, no ideal markers were found to monitor the prognostic survival of BLCA. Besides, the construction of prognostic markers based on RBPs-related lncRNAs has not been reported in BLCA yet. To address these challenging issues, we aim to develop a prognostic indicator to predict BLCA patient prognostic survival based on RBPs-related lncRNAs.

Methods: This study was based on tissue transcriptome data obtain from The Cancer Genome Atlas (TCGA) database (<https://portal.gdc.cancer.gov/>). After inclusion and exclusion criteria, a total of 396 pairs of BLCA patients' tumor tissues and normal tissues were enrolled in our final analyses. The Cox proportional hazards regression and least absolute shrinkage and selection operator (LASSO) regression were used to screen RBPs-related lncRNAs based on differentially expressed lncRNAs (DELs) between BLCA and normal control to construct a risk score and build an independent prognostic model. Using the median risk score as cut-off, the patients were classified into two groups: high-risk and low-risk groups. Nomogram was utilized to predict survival for the patients. Moreover, the index of concordance (C-index), calibration curves, and receiver operating characteristic (ROC) curves were applied to explore the accuracy of the model. The TIMER, CIBERSORT, CIBERSORT-ABS, QUANTISEQ, MCPOUNTER, XCELL and EPIC algorithms were used to assess cellular components or cell immune responses between high- and low-risk groups based on RBPS-related lncRNAs signature. Furthermore, single-sample gene set enrichment analysis (ssGSEA) was used to quantify the tumor-infiltrating immune cell subgroups, as well as to assess their immune function.

Results: A total of 2305 differentially expressed lncRNAs were identified between BLCA and normal control. Correlation test was performed on RBP genes and lncRNAs in BLCA, and 603 RBPs-related lncRNAs ($|R_2| > 0.3$ and $P < 0.001$) were obtained. A total of 23 RBPs-related lncRNAs were identified in LASSO regression. Then, multivariate Cox proportional hazards regression found that 14 lncRNAs were independently prognostic factors (Table 1). The risk score was significantly related to

the survival time of BLCA patients, as well as the overall survival time of the high-risk group was significantly lower than that of the low-risk group ($P < 0.001$, log-rank test). As the risk score increases, the mortality rate of patients also increased (Figure 1A – B). After adjusting age, gender and TMN stage, the risk score remained an independent prognostic indicator in multivariate Cox proportional hazards regression analysis (HR = 1.308, 95% CI = 1.212– 1.412, $P < 0.001$, Figure 1C). When evaluating the predictive performance of the model, the areas under the ROC curve corresponding to 1 year, 3 years, 5 years and 10 years of survival were 0.773, 0.768, 0.799 and 0.838, respectively (Figure 1D). Meanwhile, the C-index of the prognostic model was 0.746 (95% CI: 0.725–0.767). The AUC of survival rate for the risk score have reached 0.828, even was higher than the traditional TMN stage in predicting the prognosis of BLCA (Figure 2B). Moreover, the net benefit of risk scores was also higher than age, gender, and TMN stage, except the integration of all clinical information achieves the maximum net benefit (Figure 2C). Correlation analysis between immune cell subpopulations and related functions revealed that APC-co-inhibition, APC-co-stimulation, and CCR were significantly different between the low- and high-risk groups (Figure 3B). We further compared the differences in immune checkpoints between high- and low- risk groups. Besides, the expression of CD80 and CD86, as the ligand of CTLA-4, was significantly higher in the high-risk group (Figure3C).

Conclusion: A novel RBPS-related lncRNAs signature shows the ability to predict the prognosis of BLCA, which exhibited superior performance than the TMN staging system that has been widely used clinically. Our results might be of great significance in providing evidence that CTLA-4 blockade might be a more beneficial immunotherapy target for the high-risk BLCA patients.

Key words: prognostic; indicator; BLCA; immunity

359. 基因 DCAF8 在多发性骨髓瘤中的临床意义

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目的: 通过对多发性骨髓瘤 (Multiple Myeloma, MM) 基因芯片数据集的深入挖掘, 寻找 MM 的潜在致病基因, 疾病诊断和预后相关因子, 治疗靶点并阐明其作用机制。

方法: 获取基因芯片数据集 GSE13591 和 Zhan Myeloma 并使用 R 语言进行基因差异表达分析。对共同高表达基因进行 Meta 分析, 得到 p 值中位秩次 TOP10 基因。利用 CCLE 数据库分析 TOP10 基因在各种肿瘤细胞系中的 mRNA 表达情况, 筛选出蛋白酶体通路相关基因 DCAF8。在 cBioPortal 数据库中分析 DCAF8 基因在各种肿瘤细胞系的突变率。随后, Western Blot 检测 DCAF8 蛋白在骨髓瘤细胞系中的表达情况。利用 SPSS 和 GraphPad 软件分析 DCAF8 表达量和 MM 病人临床特征之间的相关性, 进行受试者工作特征曲线 (ROC 曲线) 绘制和生存分析。最后, 使用 R 语言 clusterProfiler Package 和 Metascape 数据库对 DCAF8 互作蛋白基因和共表达基因进行 GO 和 KEGG 功能富集分析。



结果：数据集 GSE13591 和 Zhan Myeloma 的上调基因取交集得到 477 个共同高表达基因。在合并数据集中对上述基因进行 Meta 分析，得到 p 值中位秩次 TOP10 基因。TOP10 基因中只有 DCAF8 在 MM 细胞系中的平均表达水平位于所有肿瘤细胞系之首。DCAF8 基因在浆细胞骨髓瘤中的突变率位于各肿瘤细胞系的第一位。与人胚肾细胞系 293T 对照比较，DCAF8 蛋白在多种 MM 细胞系中的表达量显著升高。DCAF8 表达量与 MM 病人的肿瘤负荷显著正相关，1q21 扩增阳性组的 DCAF8 的表达量显著高于 1q21 阴性组。ROC 曲线显示曲线下面积（AUC）均>0.8， $P<0.01$ ，说明 DCAF8 的表达水平可以很好地区分 MM 病人和正常人。生存分析结果表明 DCAF8 高表达组比 DCAF8 低表达组中位生存时间显著缩短。蛋白互作网络显示 DCAF8 可与 XPO1 蛋白直接相互作用。对 DCAF8 互作蛋白基因和共表达基因进行 GO 和 KEGG 功能富集分析，DCAF8 与蛋白酶体功能,剪切体活性,组蛋白乙酰化酶活性,RNA 转运等功能相关。

结论：DCAF8 在多发性骨髓瘤中显著高表达，其表达水平可以很好地区分 MM 病人和正常人，其高表达与 MM 病人的生存预后显著负相关，而且与 1q21 扩增和 XPO1 蛋白相关。因此，DCAF8 可作为 MM 的诊断和预后评估生物标志物，并有望为 MM 的精准诊疗和克服 MM 病人的耐药性提供新的靶点信息。

关键词：多发性骨髓瘤；DCAF8；泛素-蛋白酶体通路；XPO1 蛋白。

360. 结肠癌组织中 COL21A1 的表达水平及与免疫细胞浸润的关系

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背景：COL21A1 是具有间断螺旋的原纤维相关胶原家族的一员。生理状态下，COL21A1 对于维持细胞外基质的完整性具有重要作用；其在恶性肿瘤发生发展过程中所起的作用尚不明确。本研究对 COL21A1 在结肠癌组织中的表达水平及其与组织中免疫细胞浸润和免疫调节因子表达的相关性进行初步探讨。

方法：使用基因表达谱交互分析（GEPIA）和肿瘤免疫评估资源网站（TIMER）分析不同类型肿瘤和人体组织中 COL21A1 的表达情况，基于肿瘤基因组图谱数据库（TCGA）分析 COL21A1 在结肠癌中的表达情况；LinkedOmics 数据库分析结肠癌组织中与 COL21A1 相关的差异基因，基因本体论分析(GO)和 KEGG 通路分析分析了 COL21A1 的表达与分子机制的关系以及相关通路，肿瘤免疫评估资源网站（TIMER）和 TISIDB 数据分析研究了 COL21A1 与免疫浸润的相关性。



结果：COL21A1 在结肠癌组织中的表达显著低于在癌旁正常组织中的表达。与 COL21A1 共表达的基因中，前 50 个正相关基因中成为结肠癌低风险标志物的概率很高。GO 分析显示，COL21A1 主要参与细胞外结构的组织构建,信号转导的细胞外调节,环核苷酸代谢等过程。KEGG 通路分析显示，COL21A1 与细胞外基质-受体相互作用通路和蛋白质消化吸收通路显著相关。COL21A1 的表达水平与肥大细胞,巨噬细胞,树突状细胞,中性粒细胞和调节性 T 细胞等免疫细胞的浸润程度呈正相关。此外，COL21A1 与 TGFB1,CCL11,CX3CR1,CXCL14,CCL14,CCR4,CD28 等抑癌性免疫调节分子的表达呈正相关；与 CCL5,CCL15 等促癌性免疫调节分子的表达呈负相关。

结论：COL21A1 在结肠癌组织中呈显著的低表达，其表达水平与结肠癌组织中免疫细胞浸润和免疫调节分子的含量有关，值得深入研究其在结肠癌免疫治疗中的价值。

关键词：COL21A1；结肠癌；免疫浸润；预后；TCGA；生物信息学

361. 基于高通量转录组测序技术寻找多发性骨髓瘤诊断和预后评估的新靶点

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目的：基于高通量转录组测序结果筛选参与 MM 发生发展的关键基因，以获得可能用于 MM 诊断、治疗及预后判断的相关分子标志物。

方法：对 23 例初诊高危，15 例初诊标危和 36 例复发的 MM 患者及 3 例正常人进行高通量基因表达谱分析。使用 R 语言 DESeq2 package 筛选差异基因。对 GSE13591 和 Zhan Myeloma 进行荟萃分析，对我们的差异基因结果进行验证。使用 DAVID 进行差异基因的功能富集分析。使用 STRING 和 Cytoscape 制作蛋白质互作网络（PPI）并用 MCC 算法筛选出 hub 基因，制作 ROC 曲线评估 hub 基因的诊断价值。使用 GSE2658,GSE4452 和 GSE9782 构建 Cox 风险比例回归模型，绘制 Kaplan-Meier 曲线来评估 hub 基因的预后价值。

结果：1.初诊和正常人比较，根据 $|\log FC| \geq 1$ 和 $FDR < 0.05$ 选出 1396 个 DEGs。生存分析显示 788 个基因与病人预后不良相关。对 GSE13591 和 Zhan Myeloma 进行荟萃分析，筛选出 477 个高表达与病人预后不良相关的基因。绘制 Venn 图找出我们与公共数据交集的 39 个基因。功能富集显示其与蛋白酶体通路最相关。构建 PPI 并筛选出评分 >100 的 hub 基因为 PSMB3,PSMD4,COPS6,PSMB7,PSMB4,VHL。制作 ROC 曲线评估这 6 个基因的诊断价值， P 值全部 <0.05 。2.初诊高危与标危患者比较，筛出 1032 个 DEGs。DEGs 通路分析显示与 MAPK 信号通路,cAMP 信号通路等相关。270 个基因与病人预后不良相关,其中 84 个基因高表达与病人预后不良相关。构建 PPI 并筛选出前 10 位的 hub 基因为



EGFR,ITGA5,NTRK2,MYCN,ANXA1,COL5A1,MMP14,ABCB1,PTPRC,GHRHR。绘制 Kaplan-Meier 曲线, P 值全部 <0.05 。3.初诊与复发患者比较, 筛出 1462 个 DEGs, 其在 1 号染色体上分布最多(9%)。DEGs 功能富集分析显示其与 PD-1 信号通路,T 细胞分化等免疫通路显著相关。其中 131 个基因高表达与病人预后不良相关。构建 PPI 并筛选出前 10 位的 hub 基因为 KIF23,KIF2C,NEK2,CASC5,CENPF,MKI67,ASPM,TRIP13,PLK1,TPX2。绘制 Kaplan-Meier 曲线, P 值全部 <0.05 。

结论: 本研究所鉴定的 Hub 基因可作为多发性骨髓瘤分子标志物,为 MM 诊断和治疗新靶点的选择及预后判断提供参考。

关键词: 多发性骨髓瘤; 分子标志物; 高通量测序

362. tRNA-based signature derived from salivary exosomes: tumor-growth modulator and prognostic biomarker in human esophageal carcinoma

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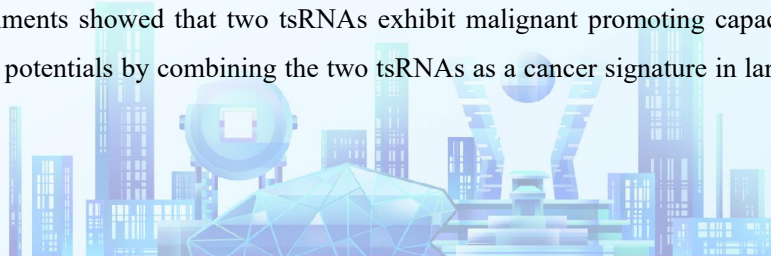
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Background: Transfer RNA-derived small RNAs (tsRNAs) is emerging as cancer signature with translational potential. Esophageal squamous cell carcinoma (ESCC) is ranked seventh for cancer morbidity and sixth for cancer mortality worldwide. Patients often present at an advantage stage with lymph node metastasis at the time of diagnosis, which leads to a 5-year survival rate of approximately 20%. To discover cancer-specific tsRNAs with diagnostic and prognostic potentials for ESCC, we performed RNA sequencing of salivary exosomes from patients with ESCC, and evaluated the discovered tsRNAs for their potent function in cancer pathogenesis and their potentials as liquid-biopsy biomarker in human ESCC.

Methods: Small-RNA transcriptome sequencing was performed using salivary exosomal RNA collected from ESCC patients vs. healthy controls. The top changed tsRNAs were validated and screened using qRT-PCR in salivary exosomes and tissues specimens of a discovery cohort of ESCC patients, as well as in relevant ESCC cell lines. The in vitro and in vivo models were used to examine the potent functions of tsRNAs in ESCC pathogenesis. Large cohorts of ESCC patients were further measured by RT-qPCR and analyzed for diagnosis, assessment of treatment response, and prediction of prognosis.

Results: RNA sequencing and validation studies demonstrated that two tsRNAs were specifically enriched in salivary exosomes and tissues of ESCC patients, as well as in human ESCC cell lines. In vitro and in vivo experiments showed that two tsRNAs exhibit malignant promoting capacities. We evaluated the diagnostic potentials by combining the two tsRNAs as a cancer signature in large cohorts of ESCC



patients vs. healthy controls. Analysis of the data indicates that the tsRNA signature provides a reliable approach for diagnosis, treatment prediction and prognostic indicator for human ESCC.

Conclusion: RNA sequencing of salivary exosomes following validation revealed a tsRNA signature for human ESCC. The tsRNAs are functions of malignant modulation in ESCC, with diagnostic, prognostic, and therapy predictive values for ESCC. Given that there is no clinically applicable ESCC biomarker currently, our findings possess a great translational potential as a non-invasive and convenient biomarker for this malignancy.

Key words: transfer RNA; transfer RNA-derived small RNA; salivary extracellular vesicles; liquid biopsy

363. DEK 对 HER-2(+)胃癌转移和血管形成的作用及机制研究

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目的: 探究 DEK 在 HER-2(+)胃癌转移和血管形成过程中的作用及分子机制。

材料与方法: 应用 TCGA, Oncomine, GEPIA 和 Kaplan Meier Plotter 数据库分析 DEK 在胃癌中的表达情况及与患者预后的相关性; 应用慢病毒转染技术构建差异表达 DEK 细胞株 NCI-N87-shCON/NCI-N87-shDEK (HER-2 阳性胃癌细胞) 和 AGS-Vector/DEK (HER-2 阴性胃癌细胞) 后, 通过 Western blot 实验检测 DEK 与 HER-2 蛋白表达的一致性; CCK-8 实验和平板克隆实验检测 DEK 对胃癌细胞活性和克隆形成能力的影响; 划痕实验和 Migration 检测 DEK 对胃癌细胞迁移能力的影响; 微管形成实验和鸡胚尿囊膜模型检测 DEK 对血管形成的影响; Western blot 实验检测 MMPs 家族和 HIF1a/VEGF 通路的相关标志物; 应用 PPI 和富集分析明确 DEK 与 HER-2 之间的互作关系并应用 CoIP 实验和免疫荧光实验进行验证。

结果: DEK 在胃癌组织中显著高表达于癌旁正常组织 ($P < 0.05$), 且其高表达与 HER-2(+)胃癌患者的不良预后密切相关; DEK 与 HER-2 的蛋白表达具有一致性。沉默 DEK 可显著抑制 NCI-N87 细胞的细胞活性, 克隆形成能力, 迁移能力和血管形成能力; 下调 MMP-2, MMP-9, HIF1a 和 VEGF 的蛋白表达水平。高表达 DEK 可显著增强 AGS 细胞的细胞活性, 克隆形成能力, 迁移能力和血管形成能力; 上调 MMP-2, MMP-9, HIF1a 和 VEGF 的蛋白表达水平。

结论: DEK 对 HER-2(+)胃癌的转移和血管形成具有正性调控作用, 其机制可能与 MMPs 家族和 HIF1a/VEGF 信号通路的抑制有关。

关键词: DEK; HER-2 阳性胃癌; 转移; 血管形成

364. 一条参与结合 NR2E1 的 LSD1 多肽对脑癌干细胞的抑制

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研究目的: 脑癌干细胞因为其对化疗和放疗具有抗性, 与脑癌复发快和预后极差密切相关。因此, 我们的研究靶向脑癌干细胞, 通过研究脑癌干细胞的增殖机制, 有针对性地设计多肽干扰相关机制, 以实现抑制脑癌干细胞生长的目的, 从而为脑癌的治疗提供新的策略。

材料和方法: 采用从 Nestin-TV-a mice 小鼠分离出来的脑癌干细胞, 我们通过基因敲除联合肿瘤干细胞成球实验, 细胞增殖实验, 免疫共沉淀实验和染色质免疫沉淀实验, 研究了调控脑癌干细胞增殖的机制。通过 Hydrogen/Deuterium Exchange and Mass Spectrometry (HDX-MS) 实验, 我们研究了调控脑癌干细胞增殖的两个蛋白的结合多肽。进一步通过上述细胞实验和从病人分离的脑癌干细胞所构建的脑癌动物模型, 我们研究了相关多肽对脑癌的作用。

结果: 我们发现在小鼠脑癌干细胞中孤儿核受体 NR2E1 招募赖氨酸特异性组蛋白去甲基化酶 LSD1 到抑癌基因 Pten 的启动子区域, 通过对其组蛋白 H3K4me 和 H3K4me2 去甲基化而抑制 Pten 的表达, 从此促进脑癌干细胞的增殖。一条位于 LSD1 蛋白 SWIRM 结构域多肽主要参与 NR2E1 和 LSD1 的结合, 并形成 LSD1 蛋白 SWIRM 结构域特异的蛋白结合口袋。在小鼠脑癌干细胞中过表达这条多肽能够干扰 NR2E1 和 LSD1 所促进的脑癌干细胞增殖, 但不会影响 NR2E1 和 LSD1 都高表达的 293T 细胞的增殖。进一步在人脑癌干细胞中诱导该多肽的表达, 我们发现该多肽能够有效抑制人脑癌干细胞在体外增殖和体内成瘤。

结论: 我们的研究揭示 NR2E1 和 LSD1 协同促进脑癌干细胞增殖。针对 NR2E1 和 LSD1 的结合, 我们发现了一条有效抑制脑癌干细胞增殖的多肽。这条多肽有可能成为脑癌多肽药物开发的先导肽。

关键词: 脑癌干细胞; NR2E1; LSD1; 多肽

365. The establishment and mechanism of core transcriptional regulatory circuitry in regulating blast transformation of chronic myelogenous leukemia

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Aims: Chronic myelogenous leukemia (CML) is a typical multistep progression malignancy, including chronic phase (CP), accelerated phase (AP), and blastic phase (BP). The characterization of CML-CP is the excessive proliferation of myeloid cells, while CML-AP/BP is the cell differentiation arrest and an increased proportion of blast cells. According to the report, the survival period of CP patients with TKI treatment is for decades, but only a few months after the blast onset. Therefore, it is important to

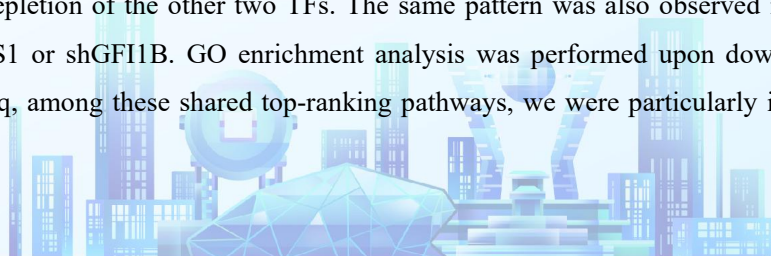
explore new biomarker and therapeutic target for predicting and curing CML-BP through elucidating the mechanism of blast transformation.

This study compared super-enhancer landscape of the peripheral blood mononuclear cells (PBMCs) in normal, CML-CP, and CML-BP, to identify CML-BP specific super-enhancers. We try to reveal the mechanism of super-enhancer driven transcriptional regulation abnormalities in CML-BP for searching the new biomarker and therapy target. The main objectives including: 1) Screening and verifying the core transcription factors (TFs) and the core transcriptional regulatory circuitry (CRC) driven by CML-BP specific super enhancers. 2) To elucidate the biological functions and related molecular mechanisms of CRC transcription factors (CRC-TFs) and their downstream target genes in CML-BP, and to estimate the significance of these genes in the prediction and treatment of CML-BP. 3) To explore the potential application of blocking super enhancer driven transcriptional activation program in the treatment of CML-BP.

Methods: Chip-seq was performed on PBMCs of normal, CML-CP, and CML-BP samples by H3K27ac antibody, to characterize the specific super-enhancer landscape in CML-BP. Firstly, we sought to identify mathematically core TFs with high inter-connectivity through binding to their super-enhancers by motif scanning using our established method. The CRC-map algorithm was used to calculate the core TFs with mutual regulation as candidates for CRC-TFs. Next, to verify the CRC TFs, we detect the inter-connectivity of the candidates by WB and RT-qPCR. Using MTS assay and flow cytometry to determine the proliferation and differentiation after knockdown CRC-TF in CML-BP cell lines (K562, KBM5, KU-812). RNA-Seq was performed in K562 with lentiviral vectors expressing shRNAs targeting CRC-TF. Chip-seq was performed on K562 and KBM5 cells by CRC-TF antibodies.

Results: Chip-seq was performed on PBMCs of normal (n=3), CML-CP (n=8), and CML-BP (n=3) samples by H3K27ac antibody, we identified nine candidates CML-BP specific super-enhancer driven CRC-TFs, also the nine CRC-TFs were expressed higher in CML-BP than CP which verified by the public RNA-Seq data in GEO. As a parallel analysis, Pearson correlation coefficient of the mRNA levels of these nine candidates was determined, considering the co-regulatory relationship between CRC members. Notably, FLI1, MEIS1, and GFI1B displayed strong positive correlations with each other on CML-BP but not on CML-CP. Also, we verified the co-regulatory relationship between these three CRC-TFs in mRNA and protein level by silencing three CRC-TFs individually. Therefore, we consider that FLI1, MEIS1, and GFI1B constitute a specific CRC in CML-BP.

Lentivirus infection used to construct CRC-TF stabilized knockdown in K562, KBM5, and KU812 cell lines, then we found that silencing the three CRC-TFs inhibited cell proliferation and granulocyte, erythrocyte, as well as megakaryocyte differentiation. RNA-Seq assay of shFLI1, shMEIS1, and shGFI1B in K562 were performed, gene set enrichment analyses (GSEA) showed that the genes decreased following silencing of FLI1 were strongly and significantly enriched in the downregulated genes upon depletion of the other two TFs. The same pattern was also observed in RNA-Seq data of either shMEIS1 or shGFI1B. GO enrichment analysis was performed upon downregulated genes in each RNA-Seq, among these shared top-ranking pathways, we were particularly interested in the cell



differentiation, since cell differentiation arrest is the main pathological features of CML-BP. To elucidate the mechanisms of CRC TFs regulate cell differentiation in CML-BP, we performed the Chip-Seq of three CRC-TFs in K562 to analyze the 29 genes, which downregulated by depleted CRC-TFs and enriched in cell differentiation pathway, found that 18 genes were co-binding by three CRC-TFs. The seven genes (ETV6, DOCK2, VAV1, FEV, EVI2B, ITGAM, TYROBP) that highly related to hemopoietic differentiation according to the reports were selected to further verify. The result illustrated that the mRNA level of seven genes is downregulated after silencing each CRC-TFs in K562 and KU812. Moreover, CYPYY, the inhibitor of DOCK2, showed significant cell viability suppression in CML-BP cell lines.

To explore the significance of super-enhancer driven transcriptional regulation abnormality in CML-BP, the BRD4 and CDK7 inhibitor ARV825 and THZ1 have been used to treat CML-BP cell lines and PBMCs of CML-BP patients, the result shown that ARV825 and THZ1 were obviously impaired cell viability and induced cell apoptosis in CML-BP.

Conclusion: The landscape of CML-BP specific super-enhancer was identified by Chip-Seq using H3K27ac antibody on the collected CML samples, three super-enhancer driven TFs (FLI1, MEIS1, GFI1B) were clarified to constitute the CRC in CML-BP. Their co-regulated relationship was illuminated by WB and RT-qPCR. Furthermore, depleting the four CRC-TFs individually inhibits the cell proliferation and differentiation of CML-BP cells. The GSEA analyses of three CRC-TFs' RNA-Seq data demonstrated the high similarity of their regulated genes. Moreover, the three CRC-TFs co-regulated cell differentiation pathway to facilitate blast transformation. ARV-825 and THZ1, the inhibitor of BRD4 and CDK7, significantly suppressed cell viability and induced cell apoptosis in CML-BP.

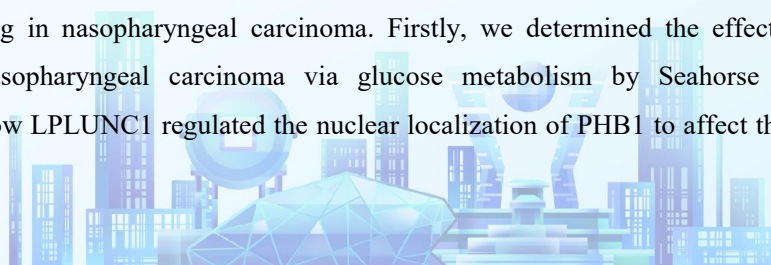
Key words: chronic myelogenous leukemia (CML); blast transformation; super-enhancer; transcriptional regulation

366. LPLUNC1 regulates glucose metabolism reprogramming via affecting PHB1 nuclear localization and activating PHB1-p53/c-Myc axis in nasopharyngeal carcinoma

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Cancer glucose metabolism reprogramming is an important feature of tumor cells. As the suppressor genes, LPLUNC1 play important anti-cancer effect in nasopharyngeal carcinoma via regulating PHB in our pervious study. This study explored the effect and mechanism of LPLUNC1 on glucose metabolism reprogramming in nasopharyngeal carcinoma. Firstly, we determined the effects of LPLUNC1 and PHB1 on nasopharyngeal carcinoma via glucose metabolism by Seahorse assay. We further determined how LPLUNC1 regulated the nuclear localization of PHB1 to affect the expression of p53



and c-Myc via co-immunoprecipitation, immunofluorescence and other assays. We found that LPLUNC1 and PHB1 inhibited aerobic glycolysis and promoted oxidative phosphorylation. LPLUNC1 not only up-regulated the expression of PHB1, also regulated the nuclear localization of PHB1 via 14-3-3 σ to regulate the expression and distribution of some nuclear transcription factors, such as p53 and c-Myc. Evidently, activation of the LPLUNC1-PHB1-p53/c-Myc axis inhibited the aerobic glycolysis and promoted oxidative phosphorylation. ATRA can induce the activation of LPLUNC1-PHB1-p53/c-Myc axis in nasopharyngeal carcinoma cells, regulate the reprogramming of glucose metabolism and inhibit the proliferation of nasopharyngeal carcinoma. Our study indicate that the LPLUNC1-PHB1-p53/c-Myc axis inhibit the progression by inhibiting aerobic glycolysis and promoted oxidative phosphorylation and uncover that new therapeutic targets of ATRA in nasopharyngeal carcinoma.

Key words: LPLUNC1; PHB1; glucose metabolism reprogramming; nasopharyngeal carcinoma; nuclear localization

367. Promoter Hypomethylation and Increased Expression of Syncytin-1 in Non-small Cell Lung Cancer

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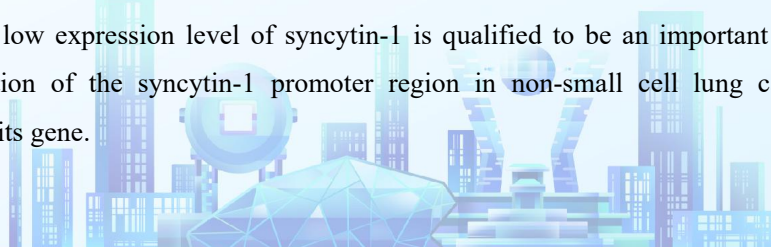
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Purpose: In this study, fluctuation of syncytin-1 expression in non-small cell lung cancer (NSCLC) and relative para-cancerous tissues during its prognosis as a plausible pathological mechanism of NSCLC is discussed by statistical analysis of syncytin-1 gene methylation and expression levels.

Methods: Syncytin-1 expressions in NSCLC and its relative para-cancerous tissues were verified by immunohistochemistry method. Differentiation of between 5-year survival and death group was analyzed. Survival ratio was calculated by Kaplan-Meier survival curve. Death risk assessment was executed by Cox risk regression model. 5-LTR methylation level of syncytin-1 promoter was detected by EpiTYPER method.

Results: Syncytin-1 expression in NSCLC tissue is higher rather than para-cancerous tissues in significant differences with $P < 0.01$ and in 5-year survival group is lower than death in significant difference with $P < 0.01$ respectively. Based on the average survival period of higher syncytin-1 expression group is significantly lower than the lower one with $P < 0.01$, clinical stage and syncytin-1 positive ratio were considered as top risk factors according to Cox ratio risk regression model analysis. The total methylation ratio of NSCLC tissues is lower than para-carcinoma tissues with no significant difference but the CpG-2 site methylation ratio of NSCLC tissue is lower than para-carcinoma tissues in significant difference with $P < 0.05$.

Conclusions: The low expression level of syncytin-1 is qualified to be an important prognosis standard. Hypomethylation of the syncytin-1 promoter region in non-small cell lung cancer promotes the expression of its gene.



Key words: Non-small cell lung cancer; Syncytin-1; expression level; prognosis; methylation

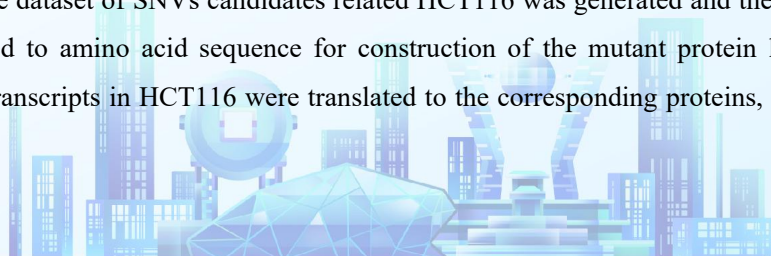
368. Exploration towards the mutated proteins in a cell line of colorectal cancer

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BGI

Objective: The Cancer Genome Atlas (TCGA) to colorectal cancer (CRC) has demonstrated approximately 93% of mutations derived from single-base changes, whereas most of these mutations identified by next generation of sequencing (NGS) are not verified at translational level yet. It is a logical deduction following the principle of central dogma that the mutations on a genome should be transcribed to message RNAs and be finally translated to the mutated proteins, while the molecular mechanisms of cancer on etiology and pharmaceutics are just hypothesized upon the theoretical base. A primary question is naturally raised why the mutated proteins (peptides) are rarely detected by the current technology, leading to next inquiry which approach is reasonable and convincing to measure the delivery of mutational messages from genome to proteome. Herein, we postulated an integrated strategy that combines the current RNA-seq and MS techniques and aims at accurate identification of the mutated transcripts and proteins in a colorectal cancer cell line.

Materials and Methods: Cancer mutation is typical diverse with cancer type-, individual- and anatomic position- dependent, we selected a CRC cell line, HCT116, as a material in this study to avoid other possible interferences. Due to some theoretical and experimental difficulties on identification of single nucleotide variates (SNVs) on transcriptional level using NGS, a core hypothesis herein was that a promise for identification of mutated proteins was building of a solid dataset of mutated transcripts. To obtain SNVs with high quality, thus we designed a combination strategy at either RNA-seq technologies and SNV analysis algorithms. In RNA-sequencing, three approaches were adopted, NGS, single tube Long Fragment Read (stLFR), and PacBio for full-length transcripts, respectively, while at SNV analysis, three software were conducted, GATK, SAMTOOLS and DeepVariant were used at the same time to identify SNVs. Based upon an accepted SNV dataset, we implemented two proteomic approaches to identify the mutated peptides, profiling and target using OrbiTrap-based mass spectrometer. In experiment, first of all, the genomic DNAs, total of RNAs and proteins were extracted from the same cultured batch of HCT116. The genomic DNAs were sequenced by NGS followed by genome mapping with BWA and SNVs calling with GATK. The corresponding RNAs were sequenced by three techniques and the sequenced data was treated with three algorithms to call SNVs. Through integration of the SNVs from different sequencing technologies and SNV calling algorithms, the dataset of SNVs candidates related HCT116 was generated and the missense mutations were translated to amino acid sequence for construction of the mutant protein library. To verify if these muted transcripts in HCT116 were translated to the corresponding proteins, we acquired the MS



signals at DDA mode of OrbiTrap , and analyzed the mutated peptides with MaxQuant searching against the mutation library. Besides, a target approach was adopted at PRM mode of OrbiTrap for specifically look for the mutated peptides.

Results: There was a diverse result of SNVs called from different algorithms, 88% of SNVs overlapped in genome among GATK, SAMTOOLS and DeepVariant, whereas around 30% of overlapped SNVs in transcriptome called by the three algorithms. Although the overlap ratios for transcriptomic SNVs were slightly improved by setting more strict filtrations in GATK, the lower ratios from the other two were still poor. Moreover, the SNVs acquired from different sequencing technologies but called with the same algorithm were overlapped approximately 4%. Our results were well agreed with other observations regarding the SNV calling at transcriptome, however, with carefully checking at the overlapped SNVs elicited from different sequencing methods and algorithms, such SNVs were come from the solid evidence supported by more sequencing reads. More importantly, once adoption of co-calling strategy for SNVs with different algorithms, the SNVs derived from NGS were almost covered that from stLFR and PacBio. We, therefore, took a filtration strategy to selected SNVs based upon the NGS data, and defined an accepted SNV at transcriptome as co-called by three algorithms.

These accepted SNVs were further searched against the dbSNP database, and a set of the missense mutations in HCT116 was generated from removal of SNPs. A total of 1218 missense mutations at genome were found in HCT116, while 202 missense mutations at transcriptome were verified by the co-calling strategy, indicating about 17% transcriptional ratio of mutated information. These mutated transcripts were added into a SwissProt dataset. Using shotgun strategy of proteomics, 39 peptides corresponding to the mutated transcripts were identified with about 19% translational ratio. Alternatively, the MS/MS signals search against a library of COSMIC, 25 corresponding to 202 missense mutation were identified (12.3% of translational ratio). Thus we came to a conclusion that the improved dataset of mutated transcripts would benefit to exploration of mutated proteins (peptides).

Key words : SNVs callers; mutations; multi-omics; sequencing technologies

369. 环状核糖核酸调节肾透明细胞癌生物学行为的研究进展

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肾细胞癌 (renal cell carcinoma, RCC) 是最常见的肾脏肿瘤, 起源于肾小管上皮细胞, 占成人肾脏恶性肿瘤的 85%~90%。据估计, 2020 年美国将有 73750 例新发肾细胞癌病例。肾透明细胞癌 (clear cell renal cell carcinoma, ccRCC) 占 RCC 的 70-75%。非编码核糖核酸 (non coding RNA, ncRNAs) 是一种调节性核糖核酸。环状核糖核酸 (cyclic ribonucleic acid, Circ RNAs) 是 ncRNAs 的亚型, 含共价单链闭环结构。Circ RNAs 是一种转录产物, 由外显子反向剪接及选择性剪接形成。Circ RNAs 由基因的内含子、外显子、非翻译区或基因间区编码产生, 包括外显

子环状核糖核酸,外显子-内含子环状核糖核酸(exon intron cyclic ribonucleic acid, EIciRNAs)和环状内含子核糖核酸(cyclic intron RNA, ciRNAs)。与线性 RNA 相比, Circ RNAs 可抵消核酸外切酶活性而维持稳定, 并通过与 ceRNA 的竞争来调节基因表达与转录[3]。越来越多的证据表明, Circ RNAs 在人类疾病发病机制中起着至关重要的作用, 特别是在恶性肿瘤中, 如三阴性乳腺癌,肺腺癌,结肠癌,肝细胞癌,膀胱癌及 ccRCC[3]。近期研究发现, Circ RNAs 在调节 ccRCC 细胞增殖,凋亡,迁移和侵袭中起关键作用[4]。因此, 阐明 Circ RNAs 调节 ccRCC 生物学行为的有关机制及临床相关性, 为 ccRCC 的诊断,预后和选择性治疗提供线索或信息。

关键词: 环状核糖核酸; 肾透明细胞癌; 生物学行为

370. Comprehensive Analysis of the Expression and Prognosis for HDACs in Glioma

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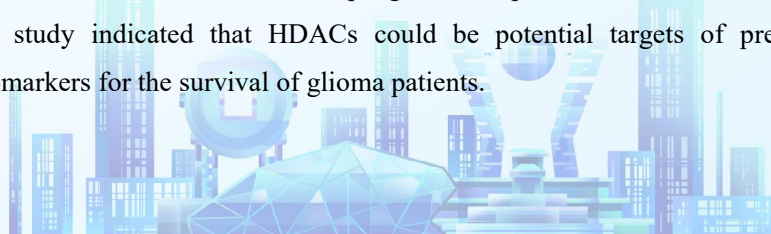
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Objective: Gliomas are the most frequent and aggressive malignancies of the central nervous system. Histone deacetylases (HDACs) have emerged as important targets for cancer treatment and implicated in regulating complex cellular mechanisms to influence tumor biology and immunogenicity in various types of cancer. However, little is known about the function of distinct HDACs proteins in glioma.

Methods: Oncomine, Human Protein Atlas, Gene Expression Profiling Interactive Analysis (GEPIA), Broad Institute Cancer Cell Line Encyclopedia (CCLE), Chinese Glioma Genome Atlas (CGGA), OmicShare, cBioPortal, GeneMANIA, String and TIMER were utilized to analyze differential expression, prognostic value, genetic alteration and immune cell infiltration of HDACs in glioma patients.

Results: The expression levels of HDAC1/2 were significantly elevated in glioma tissues, whereas the expression level of HDAC11 was lower in cancer tissues. HDAC1/2/3/4/5/7/8/11 were significantly correlated with the clinical cancer stage in glioma patients. HDAC1/2/3/10 are highly expressed in them by exploring the expression of HDACs in 11 glioma cell lines. Besides, the high HDCA1/3/7 mRNA levels and the low HDAC4/5/11 mRNA levels were significantly associated with the overall survival (OS) and disease progression survival (DFS). HDAC1/2/3/4/5/7/9/10/11 Could be exploited as useful biomarkers for prediction of glioma patients' survival. The functions of HDACs and 50 neighbor genes were primarily related to Transcriptional dysregulation in cancers, Notch signaling pathway, cGMP - PKG signaling pathway, Thyroid hormone signaling pathway. The expression of HDACs were significantly correlated with the infiltration of diverse immune cells, including six types of B cells, CD4⁺ T cells, CD8⁺ T cells, macrophages, neutrophils, and dendritic cells in glioma.

Conclusions: Our study indicated that HDACs could be potential targets of precision therapy and prognostic biomarkers for the survival of glioma patients.



Key words: bioinformatics analysis; HDACs; immune infiltration; biomarker; glioma

371. Human Oral–nasopharynx Microbiome as Risk Screening Tool of Nasopharyngeal Carcinoma

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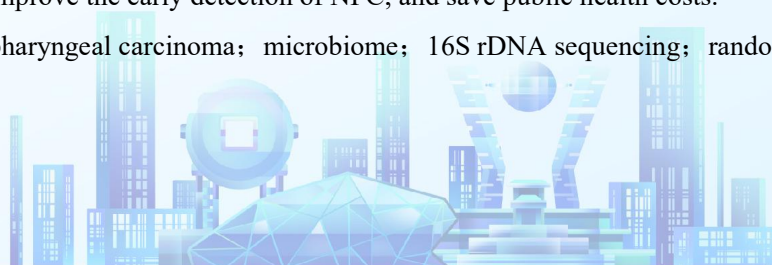
Introduction: Nasopharyngeal carcinoma (NPC) is a common head and neck cancer, and the prognosis of NPC patients with locally advanced or distant metastasis is poor, which accounts for 80%. Thus, finding a simple and convenient screening tool for early detection and risk screening of NPC is an urgent problem to be solved in clinic.

Methods: A total of 139 microbial samples were collected from 79 volunteers, including 40 and 39 oral microbial samples, 8 and 27 nasal cavity microbial samples, 9 and 16 nasopharyngeal microbial samples from 40 healthy people and 39 patients with nasopharyngeal biopsy, respectively. Based the 16S rDNA sequencing and random forest, a risk screening tool for NPC was constructed, of which the accuracy rates were evaluated by cross-validation method.

Results: We found a significantly lower microbial diversities of nasal cavity and nasopharynx in patients with nasopharyngeal biopsy when comparing with healthy people. There was a significant difference of oral microbiome based on beta diversity. There was no difference of microbial community composition in oral, nasal cavity and nasopharyngeal between nasopharyngitis group and NPC. The screening tools of NPC were established with oral microbiome and nasopharyngeal microbiome, and the accuracy rates were 77.2% and 88%, respectively. Patients with nasopharyngeal biopsy had significantly higher abundance of *Granulicatella* in oral cavity, and significantly lower abundance of *Pseudomonas* and *Acinetobacter* in the nasopharynx than healthy people.

Conclusion: This study establishes the non-invasive, simple, no radiation and low-cost NPC screening tools based on microbiome. It is beneficial to guide people at high risk of NPC for further examination which could improve the early detection of NPC, and save public health costs.

Key words: Nasopharyngeal carcinoma; microbiome; 16S rDNA sequencing; random forest



372. Pan-cancer analysis of the oncogenic role of PLCG2 gene in human tumors

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Objective: Angiogenesis is present in most solid tumors. IP3/calcineurin signaling pathway is an important pathway involved in angiogenesis, development and function, and PLCG2 is an important signal transduction molecule. We explored the possible functional mechanism of PLCG2 in tumor angiogenesis and carcinogenesis by studying the oncogenic effect of PLCG2 in various cancers. To lay the theoretical foundation for the follow-up research.

Methods: Data mining of PLCG2 gene was performed by Timer2, Ualcan, GepiA2, Cbioportal and other online tools to explore its gene/protein expression, mutation, modification and cancer prognosis in different tumors.

Results: Through analysis, PLCG2 was differentially expressed in 17 tumors such as SKCM, and its low expression had a significant impact on the survival of 4 tumors such as TGCT, and its expression was significantly different in different stages of Kirc and Luda. Mutation analysis showed that the mutation rate was the highest in SKCM, and PLGC2G1035D and PLGC2G1035D had the highest missense mutation frequency. Correlation survival analysis showed that PLCG2 mutation had a significant impact on the overall survival rate and disease-free survival rate of SKCM.

Conclusion: PLCG2 all show lower expression state among many kinds of cancer, the expression of cut often affect survival, and as the tumor progression present gradually cut phenomenon, its missense mutation can affect the function of the corresponding protein, to a certain extent affect patients overall survival and disease-free survival, treatment and prognosis of tumor and survival prediction has important value.

Key words: PLCG2; carcinogenesis; clinical prediction

373. 铁死亡相关抑制基因在胶质瘤免疫和临床预后意义的综合分析

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目的: 胶质母细胞瘤(GBM)是最具侵袭性的神经胶质瘤, 并且占有所有神经胶质瘤的 50%。已知铁死亡是细胞死亡的铁依赖性机制。在调节细胞死亡中的作用, 铁死亡可能在肿瘤发生和发展中起重要作用, 然而对于铁死亡相关靶标在胶质瘤中的作用研究仍然较少。

方法: 本研究使用 FerrDb, Oncomine, TCGA, cBioPortal, STRING, Gene-MANIA 和 Metascape 数据库评估了其在胶质瘤中 10 个铁死亡相关抑制标记基因的表达差异, 预后价值和免疫细胞浸润情况。

结果: 在胶质瘤患者中 SLC7A11, SESN2, SLC3A2, CBS, ATF4, FTH1, SLC40A1, GPX4, HSPB1, NFE2L2 的 mRNA 表达水平显著上调并且均与 WHO 分级显著相关 ($P < 0.001$)。除 ATF4 的 mRNA 的表达与 1p/19q 缺失不相关 ($P > 0.05$)。SESN2, SLC3A2, CBS, FTH1, SLC40A1, GPX4, HSPB1, NFE2L2 在胶质瘤中 mRNA 的表达增高与 IDH 突变, 1p/19q 缺失相关 ($P < 0.05$)。生存分析中, CBS, SLC7A11 低表达的胶质瘤病人总生存期(OS)较差 ($P < 0.01$), 其余基因则在高表达组 OS 预后生存差 ($P < 0.01$)。铁死亡相关抑制基因主要遗传突变分别是 DNA 拷贝数扩增和 DNA 深度缺失, 与改变组相比, 未突变分组的 OS 预后差 ($P < 0.05$)。单因素分析显示: 铁死亡抑制基因的表达, WHO 分级, 1p/19q 缺失, IDH 突变和年龄与 OS 显著相关 ($P < 0.01$)。多因素 Cox 回归分析显示: CBS, HSPB1, NFE2L2 的 mRNA 表达 ($P < 0.05$), WHO 分级 ($P < 0.001$), IDH 突变 ($P < 0.001$), 和年龄 ($P < 0.001$) 是影响 OS 的独立预后因素。构建 ROC 曲线得出, 铁死亡抑制基因均有一定的准确性 ($AUC > 0.5$)。成功构建了铁死亡相关抑制基因与 50 个相关基因网络与功能 PPI。基于 CBS, HSPB1, NFE2L2 基因建立临床预后模型, HR 值为 0.15, 曲线下面积(AUC)为 0.84 (1 年), 0.89 (3 年), 0.83 (5 年)。GO 和 KEGG 分析显示: 铁死亡抑制基因及其共表达的 50 个基因参与氧化应激反应, TGF- β 信号通路及 NRF2 通路。并且与凋亡信号通路的负调控, 氧化应激反应, 一碳代谢及相关途径, 通过 CYP2E1 乙醇代谢产生 ROS, 神经元死亡的正调控密切相关。通过免疫分析得出, 预测模型的风险评分与 B 细胞及 CD4+ T 细胞成显著负相关 ($r > 0.4$, $P < 0.01$), 巨噬细胞和 NK 细胞成显著正相关 ($r > 0.4$, $P < 0.01$)。

结论: 铁死亡相关抑制基因可能是胶质瘤患者精确治疗的潜在靶点和预后生物标志物。

关键词: 铁死亡; 胶质瘤; 生存预后; 肿瘤标志物; 预测模型

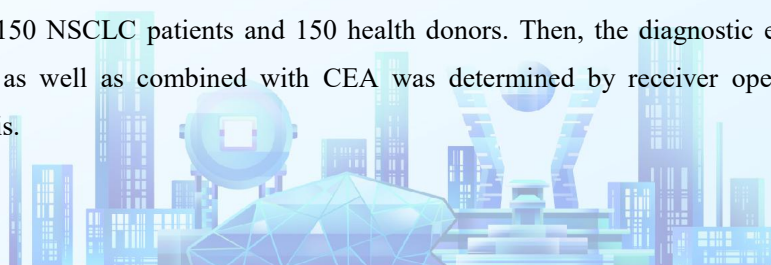
374. Plasma SNORD83A as a potential biomarker for early diagnosis of non-small cell lung cancer

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Background: Despite decades of efforts, non-small-cell lung cancer (NSCLC) remains the leading cause of global cancer mortality primarily due to the challenge in early detection of the cancer. The present study aimed to validate plasma snoRNAs as biomarkers for diagnosing early-stage NSCLC.

Materials and Methods: Differential levels of snoRNAs were screened and validated in NSCLC tissues and normal tissues by TCGA and snoRNAs databases, then SNORD83A was selected and further verified in FFPE samples including 48 NSCLC tissues and 48 adjacent normal tissues, as well as in plasma from 150 NSCLC patients and 150 health donors. Then, the diagnostic efficiency of plasma SNORD83A, as well as combined with CEA was determined by receiver operating characteristic (ROC) analysis.



Results: SNORD83A was significantly upregulated in tissues and plasma samples of NSCLC patients, as well as early-stage NSCLC patients compared to those of healthy donors. Plasma SNORD83A was capable to act as the promising diagnostic biomarker for NSCLC and early-stage NSCLC. The combination of CEA and SNORD83A provided a more accurate diagnostic efficiency than CEA alone for early-stage NSCLC. The expression levels of plasma SNORD83A was significantly decreased postoperatively.

Conclusions: SNORD83A is significantly upregulated in NSCLC patients, and can serve as the promising and non-invasive diagnostic biomarker for NSCLC and early-stage NSCLC.

Key words: SnoRNAs; SNORD83A; biomarker; NSCLC; diagnosis

375. Predictive Protein Biomarkers for Response to Neoadjuvant Chemoradiation in Locally Advanced Rectal Cancer

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Background: Colorectal cancer is the third most common and the fourth most lethal cancer in the world. In the majority of cases, patients are diagnosed at an advanced stage or even metastatic, thus explaining the high mortality. The standard treatment for patients with locally advanced rectal cancer (LARC) is neoadjuvant chemoradiotherapy (nCRT) with 5-fluorouracil (5-FU) followed by surgery. Most patients with LARC present incomplete pathological response to nCRT, the resistance rate to this treatment remains high with approximately 30% of non-responders. Despite the efforts to predict treatment response using tumor-molecular features, as differentially expressed genes, no molecule has been proved to be a strong biomarker. The tumor proteomic analysis is a promising strategy for biomarkers identification, which can be used to identify a predictive model to forecast treatment response outcomes and figured out response relevant proteins in nCRT.

Methods: We performed LC-MS/MS-based proteomic analysis to select potentially proteins and then used in silico approach to further validate the differential proteins screened out from our training cohort. 42 patients diagnosed with LARC and treated with 5-FU based nCRT between 2010-2018 at Chinese PLA General Hospital were enrolled in the study. All of these cases had available paired pre-treatment formalin-fixed paraffin-embedded (FFPE) biopsies and post-CRT FFPE surgical specimens from the same patients and histologically confirmed adenocarcinoma. According to Tumor Regression Grade (TRG), patients were divided into three treatment response groups: poor-responders (PR, AJCC TRG2+3), moderate responders (MR, AJCC TRG1) and total responders (TR, AJCC TRG0), and to compare the proteomes of these different groups. From 42 paired FFPE biopsies and surgical specimens, we extracted and analysed the tumor proteome of these patients.

Results: Comparing TR and PR group, we have identified 91 differentially abundant proteins between biopsies, 165 between surgical specimens of two groups. Next, comparing biopsies and surgical specimens of each group through paired t-test, we screened out 1467 and 771 proteins changed after

nCRT in TR and PR group, respectively. 848 proteins with different change directions (from biopsies to surgical specimens) in TR and PR group were defined as response relevant proteins which might provide some indications to explain different response in TR and PR group. Then, 129 proteins were figured out in intersections between differentially expressed proteins and response relevant proteins, which might play a role in tumor resistant to nCRT and predict the patient response to the therapy. Among these proteins, we have identified 43 genes expressed significantly different in rectal cancer tissue and normal tissue using GEPIA2 database (mainly involved in TFIID-class transcription factor complex binding, ATPase binding, RNA polymerase II transcription factor binding, etc), and there were 11 genes related to the overall survival of rectal cancer patients (favorable: SF3B6, NUP153, ARGLU1, GNL3, MTHFD1L, PTCO3, SLC27A2; unfavorable: SPTB, TMOD1, CD63, S100A13). A set of 16 proteins(over-expressed in PR group: PLEKHA6, CHMP4B, VWA1, LMNA; over-expressed in TR group: PTPN6, SF3B3, HDAC2, NDUFA5, PHGDH, TIMM44, AHS1, GNL3, POLR2A, MTHFD1L, PTP4A1, NUP35) was independently validated in a gene expression dataset for chemoradiosensitivity of colorectal cancer cells from GSE20298 to be related to nCRT resistance, enrichment analysis found that these 16 proteins were related to nuclear envelope (NE) reassembly, nucleus organization, and generation of precursor metabolites and energy.

Conclusions: From this retrospective study, protein differences between different response groups to nCRT in LARC patients were highlighted using FFPE proteomic analysis, they might be the novel biomarkers for diagnosis and guiding therapeutic strategies of rectal cancer. These results will pave the way for a larger cohort for better sensitivity and specificity of the signature to guide decisions in the choice of treatment. Furthermore, the findings will provide an insight about the proteins and molecular pathways involved in the response to treatment of LARC patients.

Key words: locally advanced rectal cancer; neoadjuvant chemoradiotherapy; 5-Fluorouracil; proteomics; therapy response

376. 口腔癌中三级淋巴结构和肿瘤浸润淋巴细胞的表达及其预后关系探讨

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目的: 通过检测口腔鳞状细胞癌 (Oral squamous cell carcinoma) 组织中三级淋巴结构 (Tertiary lymphoid structures, TLS) 及肿瘤浸润淋巴细胞 (Tumor infiltrating lymphocyte, TIL) 的表达及其特征,探究 TLS,TIL 与 OSCC 预后的关系。

研究方法: 收集 168 例 OSCC 的组织标本并制备石蜡切片。利用免疫组化技术对 TLS 相关标志物包括 CD20,PNAd,CD3, TIL 成分细胞毒性 T 细胞标志物 CD8,NK 细胞标志物 CD56 进行染色,并根据染色结果进行定量分析。利用 Kaplan-Meier 进行对总生存率(Overall survival, OS)和无复



发生存率（Recurrence free survival, RFS）进行分析。采用 Cox 比例风险回归模型分析 OSCC 患者 OS 及 RFS 的影响因素。利用 ROC 曲线评价 TLS 和 TIL 及两者联合对 OSCC 预后的诊断效能。

结果： TLS 表达与 OSCC 的预后显著相关。相比 TLS 阴性患者，TLS 阳性患者 5 年 OS ($P<0.001$) 和 RFS ($P=0.002$) 更高。COX 回归模型显示 TLS 是 OSCC 5 年 OS ($P=0.005$) 和 RFS ($P=0.014$) 的独立阳性预后因素。与 TLS-OSCC 相比，TLS+OSCC 中浸润更多的 CD8⁺ T 细胞和 CD57⁺ NK 细胞 ($P<0.001$)。TLS 的 ROC 曲线下面积 (AUC) 值为 0.641, TLS 联合 CD8⁺ T 细胞和 CD57⁺ NK 细胞的 AUC 值为 0.730。

结论： TLS 是 OSCC 的独立阳性预后因素。TLS 结合 TIL 可更准确预测 OSCC 患者的 5 年 OS。

关键词： 三级淋巴结构；肿瘤浸润淋巴细胞；OSCC；预后

377. Super-enhancers drive the core transcriptional regulatory circuitry to regulate abiraterone resistance in castration-resistant prostate cancer

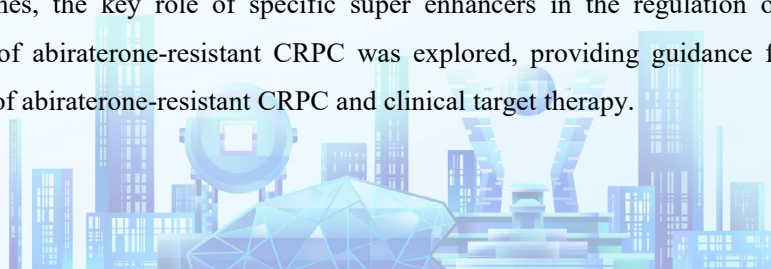
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Objective: Prostate cancer is the most common malignancy of male genitourinary system. Castration refractory prostate cancer (CRPC) is the leading cause of cancer-related death in men in the United States. Due to the relative lack of treatment options, almost all patients with CRPC eventually develop androgen treatment-resistant CRPC as the disease progresses. The potential mechanism of androgen therapy resistance to CRPC is still unknown. Therefore, it is vital to identify new carcinogenic pathways for the treatment of androgen treatment-resistant CRPC, and more efficient drugs are urgently needed because of the lack of valid chemotherapies that can provide satisfactory clinical outcomes for androgen treatment-resistant CRPC patients.

Super-enhancers (SEs) are large clusters of transcriptional enhancers, including populations of transcription factors (TFs), cofactors, chromatin regulators, and transcription apparatus occupying super-enhancers, which drive the expression of genes that define cell identity. Tumor cells assemble their own specific SEs to form a core transcriptional regulation circuits (CRCs), which significantly promotes the expression of multiple oncogenes, thereby enhances the ability of tumor cell proliferation, invasion and metastasis.

In this study, by comparing the transcription profiles of super enhancers in abiraterone-resistant/sensitive CRPC cell lines, the key role of specific super enhancers in the regulation of CRCs during the development of abiraterone-resistant CRPC was explored, providing guidance for the delay of the development of abiraterone-resistant CRPC and clinical target therapy.



Methods: Super enhancer regulatory profiles and transcriptional expression levels of abiraterone resistant/sensitive cell lines and tumor specimens were obtained by chromatin immunoprecipitation sequencing (ChIP-seq) and RNA sequencing (RNA-seq), and transcriptional factor regulatory profiles were obtained by TF ChIP sequencing. Through “ROSE”, “CRC_mapper” and other bioinformatics analysis, the possibility composition of the CRCs were analyzed. Small interfering RNA (SiRNA) or shRNA knock-down core transcription factors were detected, and qPCR and Western Blot were used to detect changes in transcription and translation levels of other TFs within the CRCs. MTS, transwell and plate cloning formation methods were used to observe the effect of TF on the malignant phenotype of drug-resistant cell lines.

Results: We first examined the effect of abiraterone on the viability of abiraterone-resistant/sensitive CRPC cell lines, and found that the IC₅₀ of abiraterone-resistant C42B (C42B_AbiR) was more than 30 times that of abiraterone sensitive C42B cell line. Based on targeting H3K27ac ChIP-seq and RNA-seq results of C42B abiraterone-resistant/sensitive cell lines, we found ALF3, NTF1, IAF1, PAX4, FOSL1, NRAT1, JUNB, RORC, EHF, NFKB, PBX, ZKSCAN1, NFKB2, ZTBT1, 14 transcription factor regulated by SEs and highly expressed in C42B_AbiR cell line. Based on Pearson correlation analysis, it was found that in the RNA-seq public data of CRPC patients tumor tissues, there were two large clusters of significant correlations among 14 TFs. There are ALF3, NTF1, IAF1, PAX4, and JUNB, RORC, EHF, NFKB, ZKSCAN1. Meanwhile, based on ChIP-seq data targeting H3K27ac in CRPC tumor tissue (n=9) collected at our hospital and similar ChIP-seq data of PDX model of CRPC patients, the peak intensity of RORC, EHF, NFKB and ZKSCAN1 were the highest in CRPC group, followed by localized PC group and the lowest in paracancer group. The mRNA and protein level shown a mutual regulation relationship between EHF, NFKB and ZKSCAN1, but not include RORC, when individually knockdown four TFs. This implies that EHF, NFKB and ZKSCAN1 may form a CRCs regulated by each other. The RNA-seq data of knockdown each CRCs TF also demonstrates this. Subsequent functional enrichment analysis found that the CRCs composed of 3TFs promoted the development of abiraterone resistance in CRPC by influencing downstream lipid metabolism and signaling pathways.

Conclusion: CRPC drives the formation of CRCs regulated by EHF, NFKB and ZKSCAN1 by assembling tissue-specific SEs. This CRCs then promotes the development of abiraterone resistance in CRPC by influencing lipid metabolism and signaling pathways.

Key words: CRPC; Abiraterone; Super enhancer; Core transcriptional regulation circuits; CRC

378. The molecular mechanism of b-AP15 involved in inhibiting malignant phenotypes of colorectal cancer cells and reversing 5-FU resistance

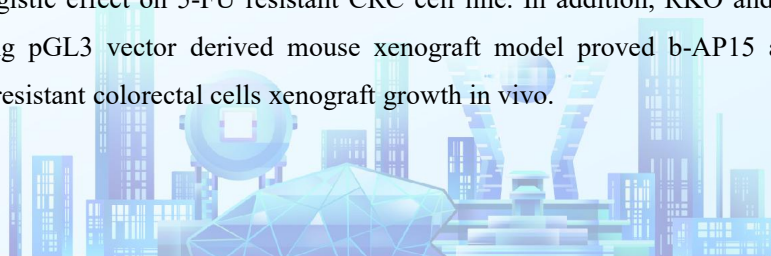
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Aims: Colorectal cancer is one of the most common malignant tumor of digestive tract. 5-Fluorouracil (5-Fu) is the first line therapy for patients with colorectal cancer (CRC). However, acquired resistance limits the application of 5-Fu in clinical. NF- κ B pathway activation, deubiquitinase mediated chemoresistance and redox homeostasis damage are responsible for 5-FU resist. Yet the specific mechanism of drug resistance is still unclear. To improve CRC patients survival, it's urgently needed to identify novel drug targets and effective therapeutic agent. b-AP15 is an alternative molecular inhibitor targeting 19S deubiquitinase USP14 and UCHL5, showing efficacy in several other cancer types. This assay first reports the cytotoxicity effect and its mechanism of b-AP15 in 5-FU sensitive and resistant CRC.

Method: Cell lines including two pairs of CRC and its 5-FU resist cell lines (RKO/RKO 5-FU-R, HCT 15/HCT 15 5-FU-R) were used in the current study. Cell viability was measured by MTS assay. Flow cytometry with Annexin V-fluoroisothiocyanate (FITC)/ PI double staining were applied to test apoptosis level of b-AP15 treated CRC and 5-FU resist CRC cell lines. Cell proliferation was evaluated by plate clone formation assay and EdU incorporation assay. The mitochondrial membrane potential of b-AP15 treated or untreated cells were evaluated by mitochondrial membrane potential kit. Protein and message RNA (mRNA) level were detected by Western Blot and RT-qPCR respectively. Transwell were used to detect cell migration and invasiveness. DCF-DA kit was used to measure total reactive oxygen species (ROS). ELISA was applied to evaluate cell ATP content of b-AP15 treated CRC cells with D-fluorescein potassium salt. Nuclear translocation was observed by immunofluorescence. Mouse xenograft models of Luciferase- RKO and Luciferase-RKO 5-FU-R cells were used to determine in vivo effects of b-AP15 in CRC tumors.

Results: Compared to non-resistant cell, the expression of mRNA and protein level of USP14 were higher in 5-FU resistant CRC cells, while there was no difference of UCHL5. Cell proliferation was evidently inhibited after knocking down USP14 while not significant after knocking down UCHL5. b-AP15 caused reduction of USP14 protein and increase of ubiquitinated proteins. Moreover, b-AP15 effectively inhibited malignant phenotype including cell growth, proliferation, metastasis, invasiveness and dose-dependent, time-dependent apoptosis in both 5-FU sensitive and resistant CRC cell lines. By detecting mitochondrial membrane potential, content of ATP generation and molecular of apoptosis pathway, we found that b-AP15 resulted in apoptosis of both CRC 5-FU sensitive and 5-FU resistant cells by damaging mitochondria. To reverse 5-FU resist, b-AP15 suppressed NF- κ B pathway through restraining activity of p-IKK α / β , degrading I κ B α and nuclear translocation of p65. Furthermore, after being treated by b-AP15, reductase was downregulated and ROS in mitochondrial, cytoplasm were upregulated correspondingly in 5-FU resistant CRC cells. Antioxidant could partially reverse cell apoptosis and upregulated ROS caused by b-AP15. Then we found that b-AP15 and 5-FU combination showed synergistic effect on 5-FU resistant CRC cell line. In addition, RKO and RKO 5-FU-R cells which carrying pGL3 vector derived mouse xenograft model proved b-AP15 restricted both 5-FU sensitive and resistant colorectal cells xenograft growth in vivo.



Conclusion: High expression of USP14 in CRC is involved in 5-FU resistance of colorectal cancer. Targeted inhibition of 19S deubiquitinase USP14 by b-AP15 can inhibit the cell growth and malignant phenotypes, induce cell apoptosis and ROS production in both 5-FU sensitive and resistant CRC cells. b-AP15 can overcome 5-FU resistance by inhibiting the degradation of I κ B α , blocking p65 nuclear translocation, and inhibiting the activation of NF- κ B signaling pathway. we found that b-AP15 can disrupt the intracellular redox homeostasis in 5-FU-resistant cells, further increase the production of ROS in intracellular and mitochondria to reverse 5-FU resistance. Furthermore, b-AP15 combined with 5-FU produce a synergistic effect on 5-FU sensitive and resistant CRC cells. Additionally, b-AP15 inhibits both 5-FU sensitive and resistant CRC cells xenograft growth in vivo model.

Key words: b-AP15; Colorectal cancer; Chemoresistance; NF- κ B; ROS; apoptosis

379. C1QTNF6 inhibits tumorigenesis and progression regulated by miR-29a-3p in stage I lung adenocarcinoma

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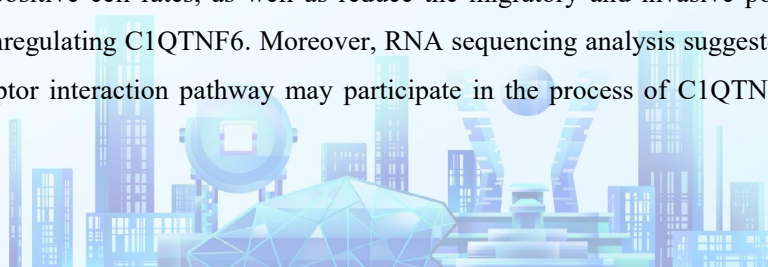
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Objective: Non-small cell lung cancer (NSCLC) is a major type of lung cancer with high morbidity and high mortality. Currently, there is a lack of valuable predictors for the recurrence and progression of early-stage lung adenocarcinoma (LUAD). The present study focused on C1QTNF6 to explore its potential function and underlying mechanism in the tumorigenesis and progression of stage I LUAD.

Methods: We detected mRNA and protein expression levels of C1QTNF6 via RT-qPCR and western blot, respectively. RNA interference and overexpression of C1QTNF6 was constructed to determine the biological role of C1QTNF6 in regulating cell proliferation, migration and invasion. Next, we applied dual-luciferase reporter assay to identify the interaction between C1QTNF6 and miR-29a-3p. Moreover, RNA sequencing analysis of C1QTNF6 knockdown was performed to identify its potential regulatory pathways.

Results: C1QTNF6 was upregulated in stage I LUAD tissues compared with adjacent non-cancerous tissues. Concurrently, C1QTNF6 knockdown could inhibit cell proliferation, migratory and invasive abilities, while overexpress of C1QTNF6 presented opposite results. Additionally, miR-29a-3p could act as an upstream regulator of C1QTNF6, whose overexpression could reduce the expression of C1QTNF6. Subsequent experiments showed that miR-29a-3p could decrease the cell viability and proliferation positive cell rates, as well as reduce the migratory and invasive possibilities in LUAD cells via downregulating C1QTNF6. Moreover, RNA sequencing analysis suggested that the cytokine-cytokine receptor interaction pathway may participate in the process of C1QTNF6 regulating tumor progression.



Conclusion: Our study first demonstrated that downregulation of C1QTNF6 could inhibit tumorigenesis and progression in LUAD cells negatively regulated by miR-29a-3p. These findings could enhance our understanding of the underlying mechanisms and provide a novel and promising therapeutic target for LUAD.

Key words: C1QTNF6; lung adenocarcinoma; miR-29a-3p; cytokine-cytokine receptor interaction pathway

380. HSPs+肿瘤相关巨噬细胞促进肝细胞癌细胞增殖,迁移与侵袭的机制探索

潘静*

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研究目的: 结合单细胞 RNA 测序数据, 在体外构建热休克蛋白阳性肿瘤相关巨噬细胞模型, 分析相关的生物学功能, 以及对肿瘤细胞的作用, 为以巨噬细胞为靶向的免疫治疗提供理论依据。

材料与方法: 采集肝细胞癌 (HCC) 患者的肿瘤组织, 使用冰冻切片机切片, 通过 HE 染色观察组织的形态结构, 通过免疫组织化学染色观察肿瘤相关巨噬细胞在肿瘤组织中的分布, 通过免疫荧光共定位 CD68 与 HSP90 α 验证热休克蛋白阳性肿瘤相关巨噬细胞在 HCC 肿瘤组织中是否存在; 使用饥饿、缺氧、炎症的方式上调单核来源的巨噬细胞 (THP-1) 中热休克蛋白的水平, 通过 qPCR 检测热各种休克蛋白 HSPA1A, HSPA1B, DNAJB1, HSP90AA1, HSPH1 和细胞因子 TNF- α , IL-1 β , CCL4, TGF- β 1 的相对表达量; 使用热休克蛋白上调的巨噬细胞培养液处理 HCC 细胞系 HepG2, Hep3B, Huh7, 通过 CCK-8 检测细胞增殖, 通过划痕实验检测细胞迁移, 通过 Transwell 实验检测细胞侵袭, 并通过 Western Blot 检测 K-ras, P53, PI3K 等探索机制。

结果: ①通过 HE 染色发现在肿瘤组织中存在大量炎性巨噬细胞浸润, 通过免疫组织化学染色发现肿瘤组织中存在 CD163 阳性肿瘤相关巨噬细胞, 通过免疫荧光共定位发现在肿瘤组织中存在热休克蛋白阳性肿瘤相关巨噬细胞。②饥饿、缺氧和炎症刺激上调巨噬细胞中热休克蛋白 HSPA1A, HSPA1B, DNAJB1, HSP90AA1, HSPH1 的相对表达量, 促进肿瘤细胞增殖的细胞因子 TGF- β 1 相对表达量升高。③CCK8 结果表明热休克蛋白上调的巨噬细胞培养液促进 HCC 细胞增殖, 预计可以促进 HCC 细胞迁移和侵袭, 且预计 HCC 细胞的 K-ras, P53, PI3K 存在差异。

结论: 热休克蛋白阳性的肿瘤相关巨噬细胞促进了肝细胞癌细胞的增殖、迁移与侵袭。

关键词: 肝细胞癌; 巨噬细胞; 热休克蛋白

381. ASCancer Atlas: a knowledgebase of aberrant alternative splicing in human cancers

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Abstract: Different isoforms of a gene produced by alternative splicing (AS) could play diverse roles in human cancers. Dysregulated alternative splicing performs important function in tumorigenesis and progression. In recent years, a growing number of studies have reported that aberrant alternative splicing is closely related to human cancers. There are many AS-related databases that focus on human cancers. They can be divided into two major categories - one is based on data reanalysis and annotation in TCGA (The Cancer Genome Atlas), such as TCGASpliceSeq, CancerSplicingQTL and ExonSkipDB; and the other is based on data from public resources (e.g., LncAS2Cancer). No resource, however, is available to collect and integrate tumor-specific splicing variants, which have been experimentally confirmed and frequently reported in multiple publications. Here we present ASCancer Atlas (<https://ngdc.cnbc.ac.cn/ascancer/home>), a public knowledgebase of alternative splicing variants in human cancers by curating a large number of literatures and mining data of TCGA. Unlike existing data-oriented databases, ASCancer Atlas dedicates to collecting, integrating and visualizing tumor-specific alternative splicing variants and normalizes their experimentally proven function. ASCancer Atlas currently houses 385 manually curated publications from January 2010 to June 2021, involving 77 cancer subtypes, 203 genes and 407 splice variant entries. It covers six alternative splicing events, including exon skipped (ES), alternative 5' splice site (A5SS), alternative 3' splice site (A3SS), mutually exclusive exons (MEX), intron retained (IR) and complex events. Meanwhile, ASCancer Atlas illustrates related regulatory mechanism, biological function, signaling pathway and potential clinical application of splicing variants. ASCancer Atlas provides a comprehensive overview of splicing dysregulation in human cancers, which attribute to better understand the role of aberrant alternative splicing in human cancers. As more and more splice variants were found to be cancer therapeutic targets, ASCancer Atlas will be a value-added resource for global cancer researchers.

Key words: Alternative splicing; Splicing variants; Human cancer; Knowledgebase

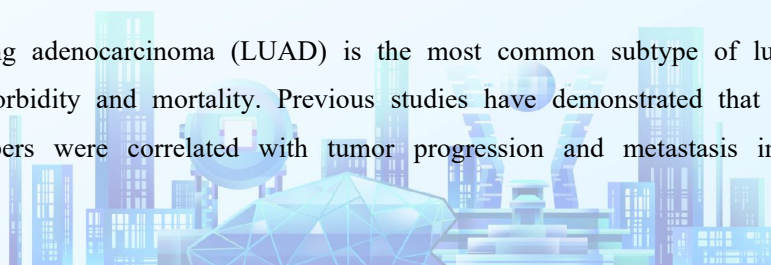
382. Comprehensive analysis of aquaporin superfamily in lung adenocarcinoma

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Background: Lung adenocarcinoma (LUAD) is the most common subtype of lung cancer with an increasing morbidity and mortality. Previous studies have demonstrated that aquaporins (AQPs) family members were correlated with tumor progression and metastasis in several kinds of



malignancies. However, their biological behaviors and prognostic values in LUAD have not been comprehensively elucidated.

Methods: RNA sequencing and real-time polymerase chain reaction (RT-PCR) were used to assess AQP1/3/4/5 genes expressions in LUAD patients using GEPIA, UALCAN database. And then, Kaplan-Meier analysis, cBioPortal, GeneMANIA, Metascape, TISIDB and TIMER were utilized to determine the prognostic value, genetic alteration and immune cell infiltration of AQPs family members in LUAD.

Results: We found that AQP3 expression was significantly elevated and AQP1 expression was obviously reduced in LUAD patients, whereas the expression levels of AQP4 and AQP5 exhibited no significant changes. The Kaplan-Meier survival analysis indicated that the higher expressions of AQP1/4/5 were related to longer overall survival (OS). Of interest, AQP3 was significantly correlated with the clinical tumor stage and lower AQP3 expression showed favorable prognosis in LUAD patients, which suggested that AQP3 may be a potential prognostic biomarker for the survival of patients. Through functional enrichment analysis, the functions of these four AQPs genes were mainly involved in the passive transport by aquaporins, water homeostasis and protein tetramerization. Moreover, AQP1/3/4/5 expression were strongly associated with tumor-infiltrating lymphocytes (TILs) in LUAD.

Conclusion: AQP3 can be used as a prognosis and survival biomarker for LUAD. These findings may provide novel insights into developing molecular targeted therapies in LUAD.

Key words: Lung adenocarcinoma; aquaporins family; prognosis; bioinformatics analysis

383. Value of circulating fibrinogen-to-pre-albumin ratio in predicting survival and benefit from chemotherapy in colorectal cancer

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Background: To evaluate the prognostic role of circulating fibrinogen-to-pre-albumin (FPR) in colorectal cancer (CRC) with different tumor locations and its involvement in chemosensitivity and chemoresistance.

Patients and methods: A total of 2917 eligible CRC patients from multiple centers were enrolled in this prospective study, and three years follow-up was carried out to obtain the outcome of these patients. Circulating fibrinogen (Fib), pre-albumin (pAlb), carcinoembryonic antigen (CEA), and carbohydrate antigen 19-9 (CA19-9) were detected, and we calculated FPR according to the detected results. Kaplan-Meier curves, Cox proportional regression, time-dependent receiver operating characteristic curves, Harrell concordance index, calibration, and decision curves were used to investigate the role of FPR in predicting chemotherapy efficacy and prognosis of CRC patients.



Results: Our results showed that cancer bulk, its infiltrating depth, and distal metastasis status of CRC determined circulating FPR level. High FPR was associated with a significantly inferior prognosis, and the outcomes of right-sided patients with stage III and IV CRC were worse than the left-sided cases. However, only FPR was found to be a reliable and independent prognostic factor for each stage of CRC. Moreover, the prognostic FPR-contained nomograms were superior to the non-FPR nomograms and FPR in predicting the outcomes in both localized and metastatic CRC patients. Additionally, circulating FPR was significantly associated with chemotherapy efficacy in stage III and IV CRC patients. Specifically, low-grade ($FPR < 15$) and medium-grade ($15 \leq FPR < 20$) FPR patients exhibited a complete response to chemotherapy and attenuated chemosensitivity, respectively, whereas high-grade inflammation ($FPR \geq 20$) conferred resistance to the treatment.

Conclusion: Circulating FPR is a robust and independent prognostic factor and a simple and economically friendly predictor of chemotherapy efficacy within localized and metastatic CRC. FPR-contained nomograms are more effective in predicting the prognosis of these patients. FPR and the nomogram can be recommended for evaluation of chemotherapy efficacy, and decision-making in the management of these patients.

Key words: fibrinogen to pre-albumin ratio; biomarkers; cancer-related inflammation; colorectal cancer; chemotherapy

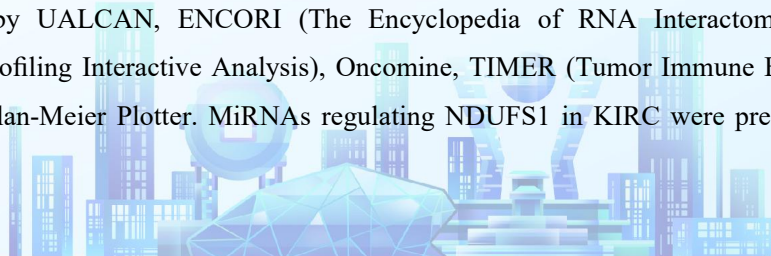
384. The combination of NDUFS1 with immune infiltration predicts favorable prognosis in kidney renal clear cell carcinoma

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Purpose: Kidney renal clear cell carcinoma (KIRC), the most common malignant tumor of the urinary system, is an immunogenic tumor, and KIRC patients therapeutic response and prognosis are relevant to immune infiltration. NDUFS1, the core subunit of mitochondria complex I (CI) in the respiratory chain, participating in the procedure of electron transport has been reported to be associated with the occurrence and development of tumors and be down-regulated in KIRC and associated with poor prognosis. However, the upstream regulator for NDUFS1 and their correlations with immune infiltration or patients survival remain unclear. Here, we tried to elucidate the immunological mechanism and clinical significance of NDUFS genes in KIRC.

Methods: The expression of NDUFS genes in KIRC and their influences on patients survival were investigated by UALCAN, ENCORI (The Encyclopedia of RNA Interactomes), GEPIA (Gene Expression Profiling Interactive Analysis), Oncomine, TIMER (Tumor Immune Estimation Resource site) and Kaplan-Meier Plotter. MiRNAs regulating NDUFS1 in KIRC were predicted and analyzed



by TargetScan and ENCORI. The correlations between NDUFS1 or miRNAs expression with immune cell infiltration or gene marker sets of immune infiltrates were analyzed via TIMER. The overall survival curves in high/low NDUFS1 or high/low hsa-miR-320b expressed KIRC patients based on immune infiltration were analyzed via Kaplan-Meier Plotter.

Results: From comprehensive bioinformatic analysis through digging into public online databases, we consistently found that in NDUFS gene family, NDUFS1 was significantly down-regulated in KIRC, high expression of NDUFS1, NDUFS4 predict good overall survival (OS) prognosis, and high expression of NDUFS1, NDUFS2, and NDUFS4 are correlated with good disease-free survival (DFS) prognosis. Moreover, the expression of NDUFS1 negatively correlates with advanced tumor grades and individual cancer stages, demonstrating that NDUFS1 may serve as a tumor suppressor gene in KIRC. NDUFS1 expression was positively correlated with infiltration of neutrophil and CD4⁺ T cells but negatively with NKT cell infiltrations. Furthermore, low NDUFS1 expression had a favorable survival in KIRC patients with enriched CD4⁺ T and neutrophil cell infiltration. In addition, 6 conserved miRNAs, including hsa-miR-599, hsa-miR-320a, hsa-miR-320b, hsa-miR-320c, hsa-miR-320d and hsa-miR-4429, were predicted to bind to the 3' UTR region of NDUFS1 mRNA, among which only hsa-miR-320b was highly expressed in KIRC and predicted poor survival. Hence, hsa-miR-320b act as a possible negative regulator of NDUFS1. Most importantly, low NDUFS1 or high hsa-miR-320b consistently correlated to unfavorable outcomes in KIRC patients with decreased CD4⁺ T cell infiltration.

Conclusion: Based on the comprehensive analysis of NDUFS genes expression in KIRC and their influence on prognosis, we found that NDUFS1 could be served as prognostic biomarkers for KIRC as reported previously. In addition, from the view of immunology and epigenetics, we have obtained a preliminary understanding of the possible functions and upstream regulator of NDUFS1 in KIRC. NDUFS1, a core protein of mitochondrial complex I, is negatively correlated with its down-regulator hsa-miR-320b in KIRC. Both low NDUFS1 and high hsa-miR-320b were connected with decreased CD4⁺T cell infiltration, and further with KIRC patients unfavorable outcomes. Our findings revealed that miRNA- mitochondrial signatures could be a potential biomarkers for the optimal selection of patients with KIRC to immunotherapy.

Key words: kidney renal clear cell carcinoma; NDUFS1; survival; expression; immune infiltration; hsa-miR-320b

385. Chemotherapy plus bevacizumab as an optimal first-line therapeutic treatment for patient with right-sided metastatic colon cancer: a meta-analysis of first-line clinical trials

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Background: Inhibitors of epidermal growth factor receptor (EGFR) have been recommended as first-line therapy for left-sided metastatic colorectal cancer (mCRC) patients with wild-type RAS. The effect of tumor laterality on anti-vascular endothelial growth factor (anti-VEGF) antibody and how to optimize targeted therapies for right-sided cases remain controversial.

Patients and Methods: A comprehensive meta-analysis including 16 first-line clinical trials (4574 mCRC patients) was carried out to evaluate the efficacy of chemotherapy alone, chemotherapy plus targeted therapies for mCRC patients with the right primary site.

Results: Here, we found that progression-free survival (PFS) (Ph=0.28, combined HR=1.30, 95%CI=1.17-1.44) and overall survival (OS) (Ph=0.83, combined HR=1.46, 95%CI=1.32-1.62) of the right-sided patients were significantly inferior to the left-sided individuals treated with chemotherapy alone, regardless of race status. Prognosis of left-sided mCRC patients receiving chemotherapy plus bevacizumab was superior to the right-sided individuals (Ph<0.01, combined MSR=1.23, 95%CI= 1.08-1.39 for OS), especially for wild-type RAS and mixed population. Moreover, the right-sided patients benefited from chemotherapy in combination with bevacizumab (Ph=0.009, combined MSR=1.40, 95%CI=1.15-1.71 for PFS; Ph=0.658, combined MSR=1.21, 95%CI=1.11-1.31 for OS) compared to chemotherapy alone. Importantly, the right-sided patients with wild-type RAS achieved longer survival from chemotherapy plus bevacizumab in comparison to chemotherapy-associated with anti-EGFR agents (Ph=0.552, combined HR=0.67, 95%CI=0.52-0.88 for PFS; and Ph=0.966, combined HR=0.74, 95%CI=0.56-0.98 for OS).

Conclusions: Right-sided mCRC patients show impaired chemosensitivity, coupling chemotherapy with bevacizumab can be an optimal first-line therapeutic regimen for wild-type RAS patients.

Key words: primary tumor location; bevacizumab; prognosis; colorectal cancer

386. Identification of a ZC3H12D-regulated competing endogenous RNA network for prognosis of lung adenocarcinoma at single-cell level

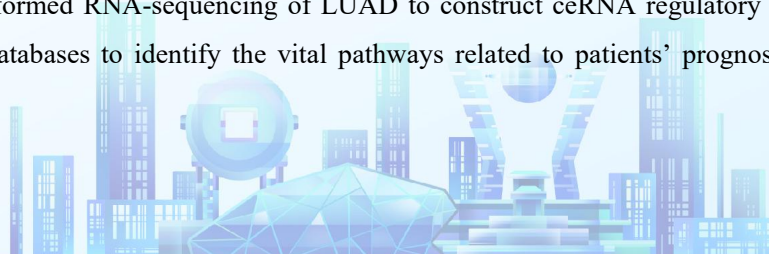
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Objective: To identify hub genes from the competing endogenous RNA (ceRNA) network of lung adenocarcinoma (LUAD) and to explore their potential function on prognosis of patients from a single-cell perspective.

Methods: We performed RNA-sequencing of LUAD to construct ceRNA regulatory network, integrating with public databases to identify the vital pathways related to patients' prognosis and to reveal the



expression level of hub genes under different conditions, the functional enrichment of co-expressed genes and their potential immune-related mechanisms.

Results: ZC3H12D-hsa-miR-4443-ENST00000630242 axis was found to be related with LUAD. Lower ZC3H12D expression was significantly associated with shorter overall survival (OS) of patients (HR=2.007, $P<0.05$), and its expression was higher in early-stage patients, including T1 ($P<0.05$) and N0 ($P<0.05$). Additionally, ZC3H12D expression was higher in immune cells displayed by single-cell RNA-sequencing data, especially in Treg cells of lung cancer and CD8 T cells, B cells and CD4 T cells of LUAD. In the brain metastasized, the expression of ZC3H12D in macrophages was relatively abundant. The functional enrichment analysis showed that the co-expressed genes mainly played a role in lymphocyte activation and cytokine-cytokine receptor interaction. In addition, ZC3H12D was associated with multiple immune cells and immune molecules, including immune checkpoints CTLA4, CD96 and TIGIT.

Conclusion: ZC3H12D-hsa-miR-4443-ENST00000630242 ceRNA network was identified in LUAD. ZC3H12D could affect the survival and prognosis of patients by regulating mRNA, miRNA, lncRNA, immune cells and immune molecules. Therefore, it may serve as a vital predictive marker and could be regarded as a potential therapeutic target for LUAD in the future.

Key words: zinc finger CCCH-type containing 12D (ZC3H12D); competitive endogenous RNA; single-cell RNA sequencing; lung adenocarcinoma; immunomics

387. Eight synthetic oleanolic acid derivatives inhibit breast cancer cells by induction of apoptosis and autophagy

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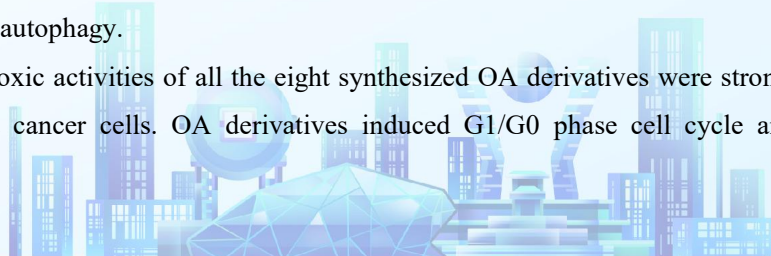
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Background: Oleanolic acid (OA) possesses various pharmacological activities, such as antitumor and anti-inflammation. however, its clinical applications are limited by its relatively weak activities and low bioavailability. In this study, we evaluated the cytotoxic activity of eight novels OA derivatives, and anticancer effect of the on breast cancer cells and action mechanisms were investigated.

Methods: The viability of OA and eight synthesized derivatives treating breast cancer cells was detected using MTT. The effect of cell cycle was identified by PI staining assay. The cellular apoptosis was tested by annexin V/PI. The cellular morphological changes and ultrastructural structures were observed and imaged through inverted phase contrast microscope and transmission electron microscopy. Western blotting was performed to explore the expression of proteins associated with apoptosis and autophagy.

Results: The cytotoxic activities of all the eight synthesized OA derivatives were stronger than that of OA against breast cancer cells. OA derivatives induced G1/G0 phase cell cycle arrest, apoptosis and



autophagy in breast cancer cells. Caspase-dependent apoptosis was confirmed to be associated with upregulation of Bax and downregulation of Bcl-2 and Bcl-xL, while upregulation of Beclin 1 and ATG 5 was inferred to be involved in autophagy.

Conclusions: The cytotoxic activities of eight OA derivatives were generally stronger than that of OA and would be promising chemotherapeutic agents for the treatment of breast cancer.

Key words: Oleanolic acid; Breast cancer; Apoptosis; Autophagy

388. 胃癌组织中 TOP II α 的表达及临床病理特征 Meta 分析

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目的: Meta 分析 TOP II α 的在胃癌组织中的表达及临床病理特征。

方法: 检索多个数据库: CNKI, WanFang Data, Web of Science, CBM, The Cochrane Library 及 PubMed, 搜集国内外关于 TOP II α 与胃癌 (Gastric Cancer, GC) 相关的病例—对照研究, 检索时限均为建库至 2021 年 6 月。由两位研究者按纳入和排除标准独立筛选相关文献, 提取资料并进行质量评价后采用 Stata 12.0 软件对纳入文献进行 Meta 分析。

结果: 最终共有 17 篇文献纳入对照研究, 共计 3628 例研究对象。Meta 分析结果显示, 胃癌组的 TOP II α 表达水平显著高于癌旁正常胃组织, 差异有统计学意义 [OR=0.23, 95%CI(0.14, 0.37), $P<0.00001$]; TOP II α 在胃癌伴淋巴结转移组的表达明显高于无淋巴结转移组, 差异有统计学意义 [OR=0.16, 95%CI(0.12, 0.23), $P<0.00001$]; TOP II α 的表达在不同年龄和性别胃癌患者的癌组织中无明显差异。

结论: TOP II α 的表达与胃癌及其不同临床病理特征高度相关, 可以作为新的作用靶点, 具有较高的研究价值。

关键词: 胃癌; TOP II α ; Meta 分析

389. 免疫治疗 EGFR 突变晚期非小细胞肺癌

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肺癌是全球癌症相关死亡的主要原因。免疫检查点抑制剂的出现, 包括抗程序性死亡-1 (PD-1) 和程序性死亡配体-1 (PD-L1) 的单克隆抗体, 已经显著改善了晚期非小细胞肺癌 (NSCLC) 患者的生存和生活质量。多种预测生物标志物用于选择可能受益于免疫检查点抑制剂的患者。表皮生长因子受体 (EGFR) 突变 NSCLC 是亚洲肺癌患者中最普遍的分子亚型。然而, EGFR 突变 NSCLC 患者对抗 PD-1/PD-L1 治疗反应不佳。虽然小分子 EGFR 酪氨酸激酶抑制剂 (TKIs) 是晚期 EGFR 突变 NSCLC 的首选治疗方法, 但获得性耐药严重限制了其长期疗效。除了传统化疗,

目前尚无进一步有效的治疗方案。初步研究显示, EGFR 突变 NSCLC PD-L1 表达较低, TMB 较低。在 EGFR-TKI 之前或同时使用 PD-1/PD-L1 拮抗剂会增加肺毒性的风险。新的证据表明, PD-1/PD-L1 阻断在非小细胞肺癌患者中可导致病情高度进展, 预后不佳。因此, 迫切需要新的生物标志物来预测 EGFR 突变 NSCLC 患者使用 PD-1/PD-L1 免疫治疗相关的反应和毒性。最近, 一些有前景的数据表明, 抗血管生成药物和其他一些新型治疗药物可以增强抗 PD-1/PDL1 单克隆抗体的疗效。本文对抗 PD-1/PD-L1 治疗晚期 EGFR 突变 NSCLC 的新策略进行综述。

关键词: 肺肿瘤; 表皮生长因子; 基因突变; 免疫治疗

390. 体外骨髓瘤血管内皮细胞中 RhoC 的表达对骨髓瘤 RPMI8226 细胞的影响

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目的: 探讨 RhoC 在骨髓瘤血管内皮细胞 (MVECs) 中表达对骨髓瘤细胞增殖、侵袭能力的影响及可能机制。

方法: 构建 RhoC shRNA 慢病毒载体并分组转染 MVECs 和人脐静脉内皮细胞 (HUVECs), 以血管内皮细胞上清液作为条件培养基培养 RPMI8226 细胞, 分别采用 CCK8 试剂盒、流式细胞仪、Transwell 实验检测条件培养基对骨髓瘤 RPMI8226 细胞增殖、细胞周期和侵袭能力的影响; Western blot 检测 RhoC、CDK、CyclinD1、MMP2、MMP9、PI3K、AKT 等蛋白表达。

结果: 下调 MVECs 和 HUVECs 中 RhoC 表达, 实验组 (S 组) 骨髓瘤 RPMI8226 细胞增殖和侵袭能力均较阴性对照组 (NC 组) 降低, 细胞周期阻滞在 G0/G1 期; 骨髓瘤 RPMI8226 细胞 S 组 RhoC、CDK、CyclinD1、MMP2、MMP9、PI3K、AKT 等蛋白表达均较 NC 组表达降低。

结论: RhoC 在 MVECs 中表达, 对骨髓瘤 RPMI8226 细胞增殖和侵袭能力具有调节作用; 其机制可能与 PI3K、AKT、CDK、CyclinD1、MMP2、MMP9 等参与有关。

关键词: RhoC; 多发性骨髓瘤; 血管内皮细胞; 慢病毒载体;

391. 基于免疫相关基因的预后模型预测乙肝携带肝癌患者的生存整体分析

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背景: 肝癌 (HCC) 是一种发病率高,预后差的疾病。越来越多的证据表明,免疫系统在肝癌的生物学过程中起着关键作用,如肿瘤发生发展,复发和转移。一些人已经讨论将免疫作为对抗各种癌症的武器。然而,免疫相关基因 (IRG) 对乙肝病毒携带者 (HBV) 的肝癌预后的影响仍不清楚。

方法: 基于癌症基因图谱 (TCGA) 和免疫学数据库分析门户 (ImmPort) 数据集,我们整合了 105 名携带乙肝病毒的肝癌患者的核糖核酸 (mRNA) 测序资料和临床资料,计算出与免疫相关的差异表达基因 (IRGs)。功能分析表明,IRGs 在细胞生长相关,代谢相关和免疫相关的途径中富集最为显著,表明携带 HBV 的 HCC 的癌变机制较为复杂。基于基因组学和临床病理数据,我们将携带 HBV 的肝癌患者的免疫相关基因分成高风险和低风险组。构建了一个生存分析模型来预测携带 HBV 的 HCC 患者的预后。接下来,我们评估了风险评分和免疫细胞浸润之间的相关性。最后,我们在 GEO 数据库 GSE25599 数据集中验证了该模型的预后性能。

结果: 共有 113 个免疫相关基因与携带 HBV 的 HCC 患者的临床结果显著相关。我们对这些基因进行了单变量和多变量回归分析和选择运算符 (Lasso) 回归分析。筛选出了 10 个免疫预后相关基因 (FABP6, RBP2, MAPT, BIRC5, CSPG5, ATAD2, FIGL1, IL17D, SPP1, STC2), 根据风险评分的中值,整个 TCGA 队列被分为高风险组和低风险组。而低风险组有更好的总生存率 (OS)。并据此构建预后模型,根据与 TNM 等临床分期相比,其预后性能更好。为了预测肝癌的总生存率,我们建立了一个与基因和临床因素相关的列线图。接受者操作特征 (ROC) 曲线,一致性指数 (Cindex) 和校准曲线显示,该模型具有较好的准确性。并且该预后模型可以为后期患者治疗提供更多信息。筛选出来的免疫基因和六种常见的免疫细胞浸润之间的相关性风险评分分析表明,ATAD2 可作为携带 HBV 肝癌患者免疫治疗的新靶点,为携带乙肝病毒的肝癌患者的免疫治疗提供新方向。

结论: 最后,我们在携带 HBV 的肝癌患者中发现了一个新的 ATAD2 (ATPase family, AAA domain containing 2) 免疫治疗相关靶点。并系统的阐述了携带乙肝病毒的肝癌患者发病的分子机制。

我们的 IRG 预后模型被证明在监测,治疗和预后评估方面具有价值。

关键词: 肝细胞癌; 乙肝病毒; 免疫相关基因; 预后模型; 免疫浸润。

392. SZC014, a novel oleanolic acid derivative, induces apoptosis and autophagy in human breast cancer cells

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Oleanolic acid (OA) possesses various pharmacological activities, such as antitumor and anti-inflammation. however, its clinical applications are limited by its relatively weak activities and low bioavailability. In

this study, we elucidated the anticancer effect of SZC014, a novel OA derivative and identified the mechanisms by which SZC014 induces MCF-7 cell death. We found that SZC014 decreased the cell viability of breast cancer cells. Mechanisms underlying the inhibition of cell viability are apoptosis, autophagy and cell cycle phase arrest. SZC014 treatment suppressed the levels of Akt, phosphorylated-Akt (p-Akt), total p53 and in addition to p-p53 in breast cancer cells. Furthermore, the inhibition of p53 nuclear translocation was confirmed by immunofluorescence staining. Cell viability was increased after pretreatment with chloroquine, an inhibitor of autophagy. A concentration-dependent increase in the intracellular ROS level was observed with the treatment of SZC014 in breast cancer cells. Additionally, pretreatment with N-acetyl-L-cysteine (NAC), a ROS scavenger, increased cell viability. These data show that SZC014 is an effectively selective anticancer agent against breast cancer cells, highlighting the potential use of this derivative as a breast cancer therapeutic agent.

Key words: Oleanolic acid; Breast cancer; Apoptosis; Autophagy

393. The dual induction of apoptosis and autophagy by SZC013, a synthetic oleanolic acid derivative, in gastric cancer cells

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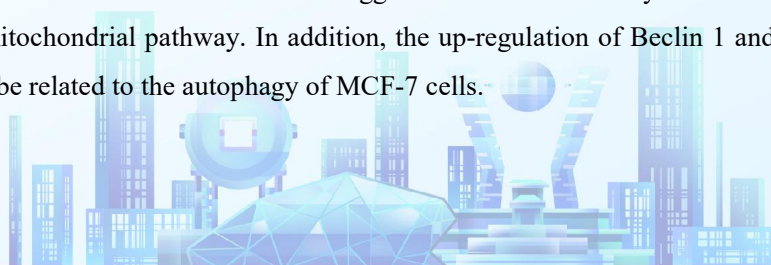
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Background: Oleanolic acid (OA) has a variety of pharmacological effects, such as liver protection, anti-inflammatory, anti-oxidation and anti-tumor. However, its relatively weak activity and low bioavailability limit its clinical application. In this study, we synthesized a new OA derivative-SZC013, and the anti-tumor effect in breast cancer cells and the mechanism of action are investigated.

Methods: The MTT method was used to determine the survival rate of breast cancer cells treated with different concentrations of OA and SZC013. PI staining flow cytometry was used to determine the effect of SZC013 on the cell cycle. Changes in cell morphology and ultrastructure after SZC013 treatment were observed with an inverted phase-contrast microscope and a transmission electron microscope. Western blot was used to determine the changes in the expression of apoptosis-related proteins and autophagy-related proteins after SZC013 treatment.

Results: The MTT experiment proved that SZC013 can inhibit the proliferation of breast cancer cells, and its growth inhibitory effect is stronger than that of OA. PI staining flow cytometry proved that SZC013 induced MCF-7 cell cycle arrest in G2/M phase. Inverted phase contrast microscope and transmission electron microscope proved that apoptosis and autophagy were found in MCF-7 cells treated with SZC013. Western blot results suggested that SZC014 may induce MCF-7 cell apoptosis through the mitochondrial pathway. In addition, the up-regulation of Beclin 1 and ATG 5 induced by SZC013 may be related to the autophagy of MCF-7 cells.



Conclusion: SZC013, as a new OA derivative, shows stronger anti-breast cancer activity than OA, and this anti-tumor effect may be related to apoptosis and autophagy.

Key words: Oleanolic acid; Breast cancer; apoptosis; autophagy

394. LncRNA MALAT1 与肿瘤血管生成关系的研究进展

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近年来, 随着对长链非编码 RNA (long non-coding RNA, lncRNA) 的研究, 发现 lncRNA 在肿瘤的发生发展过程中扮演着重要角色。作为 lncRNA 家族中的重要成员之一, 肺腺癌转移相关转录本 1 (metastasis-associated lung adenocarcinoma transcript 1, MALAT1) 不仅参与肿瘤细胞的增殖、凋亡、迁移、侵袭等生物学行为, 在肿瘤血管生成的调节中也起着重要作用。肿瘤的发生和发展离不开肿瘤血管生成, 而 MALAT1 参与调节肿瘤血管生成的具体机制有待进一步阐明, 本文就 MALAT1 与肿瘤血管生成关系进行综述, 以探讨 MALAT1 参与调节肿瘤血管生成的可能机制, 为临床抗肿瘤血管生成治疗提供新的靶点和预后生物标志物。

关键词: lncRNA; MALAT1; 血管生成

395. The peripheral blood CD4⁺ T cells/platelets can be used as indicator for prognosis of patients with metastatic/recurrent breast cancer

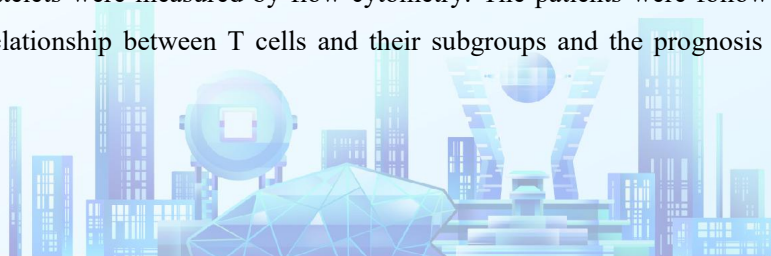
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Objective: To investigate the relationship between T cell subsets (CD4⁺T cells, CD8⁺T cells), platelet counts and the median progressive free survival (mPFS), median overall survival (mOS) in patients with metastatic/recurrent breast cancer.

Methods: The first-line chemotherapy of 312 patients with metastatic and recurrent breast cancer was registered in this study. The number of peripheral blood T cells, CD4⁺T cells, CD8⁺T cells, and the number of platelets were measured by flow cytometry. The patients were followed up for 5 years to explore the relationship between T cells and their subgroups and the prognosis of metastatic breast cancer.



Results: The mPFS and mOS in patients with metastatic and recurrent breast cancer were correlated with the number of CD4⁺ T cells/platelets, T cells and CD4⁺ T cells in the peripheral blood ($P<0.05$); the mPFS and mOS was not related to the changes in CD8⁺T ($P>0.05$).

Conclusion: The peripheral blood CD4⁺ T cells/platelets, the number of T cells and the number of CD4⁺ T in patients with metastatic and recurrent breast cancer can be used as indicators for judging the prognosis of patients.

Key words: Metastatic; CD4⁺ T cells; Breast cancer; prognosis

396. Nanoparticles targeting HER2 (TAA0287) are effective in overcoming drug resistance in HER2-positive breast cancer

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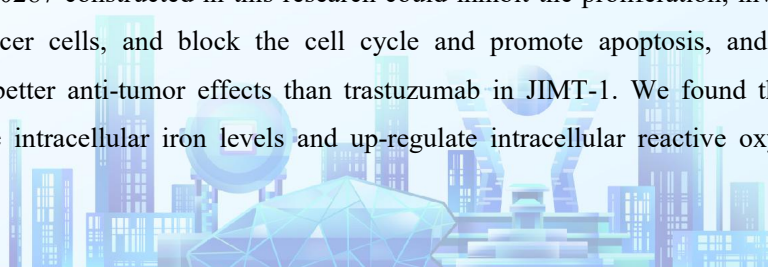
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Background: Trastuzumab has a very important position in the clinical treatment of patients with HER2-positive breast cancer. However, some patients still have primary or secondary resistance to trastuzumab during treatment. Trastuzumab resistance has become the focus and difficulty in the treatment of HER2-positive breast cancer. In recent years, Antibody Drug Conjugates (ADCs), as a new type of anti-cancer drug that conjugates monoclonal antibodies and cytotoxic agents, have received extensive attention, and its tumor specificity and targeting efficacy are both improved. Studies have shown that under the multivalent interaction between the targeted drug delivery nano-system and the cells, the targeted nano-drug delivery system can also produce a certain therapeutic effect on drug-resistant HER2-positive breast cancer. Therefore, we have developed drug-loaded nanoparticles (TAA0287) targeting HER2-positive breast cancer cells. Our research aims to evaluate the role and mechanism of TAA0287 in drug-resistant HER2-positive breast cancer cells.

Methods: The functional effects of TAA0287 in proliferation, invasion and migration of breast cancer cells (SK-BR-3 and JIMT-1) were examined by CCK8, cell cloning, transwell and scratch assay. The effects of TAA0287 on the cell cycle and apoptosis of breast cancer cells were detected by flow cytometry. Electron microscopy was applied to observe cell and mitochondrial morphology, and intracellular iron levels were detected by PGSK probe and reactive oxygen species levels by C11-BODIPY probe. The mRNA and protein expression levels of cellular functional pathways and ferroptosis-related indicators were detected by qPCR and western blotting techniques.

Results: The TAA0287 constructed in this research could inhibit the proliferation, invasion and migration of breast cancer cells, and block the cell cycle and promote apoptosis, and was able to show significantly better anti-tumor effects than trastuzumab in JIMT-1. We found that TAA0287 could down-regulate intracellular iron levels and up-regulate intracellular reactive oxygen species levels.



The mitochondria were smaller under electron microscopy, and COX-2, ACSL4 and other ferroptosis-related indicators were upregulated.

Conclusions: TAA0287 exerts anti-cancer effect through the cellular ferroptosis pathway induced by activation of ROS. TAA0287 is a valuable candidate for the treatment of trastuzumab-resistant HER2-positive breast cancer.

Key words: Target; Nanoparticles; Breast cancer; HER2; Drug resistance; Ferroptosis

397. The Oleanolic Acid Derivative ZQL-3d Exerts Anticancer Effects via miR-221-3p/ASPP2 and Modulates Trastuzumab Resistance in Breast Cancer

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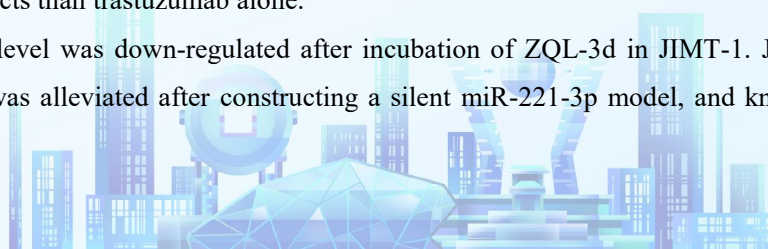
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Background: With the application of targeted drugs, survival and prognosis of HER2-positive breast cancer patients have improved significantly, but single-target small-molecule kinase inhibitors have developed resistance during clinical application due to mutations in residues at the target protein binding site. Therefore, the development of novel multi-target inhibitors that can overcome tumor resistance is an urgent problem in the current antitumor drug research. In recent years, oleanolic acid (OA) and its derivatives have attracted much attention because of their anti-tumor, anti-inflammatory, antiviral, anti-infective, immunomodulatory and other biological activities. In this study, we investigated the role of a novel OA derivative ZQL-3d in breast cancer and its relationship with trastuzumab resistance and its molecular mechanism.

Methods: The anticancer effect of ZQL-3d was detected by CCK8, cell cloning assay, flow cytometry, transwell, and scratch assay, and the expression levels of cell function-related pathway indicators were detected by qPCR and Western blotting and other molecular biology techniques. The micro RNA indicator miR-221-3p and downstream target ASPP2 related to drug resistance in HER2-positive breast cancer were predicted and screened by bioinformatics, and the correlation was verified by dual luciferase reporter gene assay. To investigate the overcoming effect of ZQL-3d on trastuzumab resistance in JIMT-1 and the changes of related pathway indicators when transfected with overexpression and silencing of miR-221-3p and ASPP2, respectively.

Results: ZQL-3d was able to exert anticancer effects in breast cancer cells of different molecular fractions, especially in JIMT-1, where ZQL-3d combined with trastuzumab showed significantly superior antitumor effects than trastuzumab alone.

The miR-221-3p level was down-regulated after incubation of ZQL-3d in JIMT-1. JIMT-1 resistance to trastuzumab was alleviated after constructing a silent miR-221-3p model, and knockdown of ASPP2



restored resistance. In the overexpression miR-221-3p model, SK-BR-3 appeared resistant to trastuzumab. Meanwhile, overexpression of ASPP2 could overcome the resistance.

Conclusions: The novel OA derivative (ZQL-3d) affects the apoptotic process through miR-221-3p regulation of ASPP2 to exert oncogenic effects and modulates the resistance to trastuzumab in HER2-positive breast cancer.

Key words: Oleanolic acid; HER2; Breast cancer; Micro RNA; Drug resistance

398. Distinct prognostic roles of S100 mRNA expression in hepatocellular carcinoma

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Objective: Hepatocellular carcinoma is still one of the malignant tumors with high mortality. Therefore, it's urgent to identify the potential prognostic markers to monitor and intervene in hepatocellular carcinoma.

Accumulating pieces of evidence have suggested that S100 proteins are closely associated with the progression of various cancers. However, the relationship between a lot of S100 families and hepatocellular carcinoma is still unknown. In this study, we further explore the prognosis value of each S100 member in hepatocellular carcinoma patients.

Methods: The relevance of individual S100 mRNA expression to OS was accessed on a database that was developed using gene-chip or RNA sequencing data with clinical information of space patients downloaded from Gene Expression Omnibus (GEO) and the Cancer Genome Atlas (TCGA). Briefly, 21 individual members of the S100 family were entered into the Kaplan Meier platter database to obtain the survival plots. HR (hazard ratio), 95%CI (confidence intervals), and log-rank P value were provided. P-value of <0.05 was considered to be statistically significant.

Results: It was discovered that S100A2, S100A6, S100A8, S100A9, S100A10, S100A11, S100A13, S100A14, and S100P mRNA high expression were significantly correlated with worse OS in all hepatocellular carcinoma patients. We also observed that the high expression of S100A5, S100A7, S100Z, and S100G were associated with better OS. Meanwhile, we assessed a link between the relapse-free survival and the S100 family. For S100A1, S100A10 and S100A13, high mRNA expression of those S100 members were correlated to lower relapse-free survival. For S100A4, S100A5, S100A11, S100B, S100Z, and S100G, their mRNA expression levels were associated with longer relapse-free survival. Then, we evaluated the prognosis roles of S100 members in different hepatocellular carcinoma patients, including the hepatocellular carcinoma patients, Asian hepatocellular carcinoma patients and patients with sorafenib treatment. In the hepatocellular carcinoma patients, higher S100A10 mRNA expression was found to be associated with a significantly worse prognosis. While, the S100A3, S100A5, S100A6, S100A8, S100A12, and S100P expression predicted

favorable prognosis. The mRNA expression levels of S100A2, S100A6, S100A9, S100A10, S100A11, S100A13 and S100P predicate worse prognosis in Asian patients; however, S100A5, S100A7, S100A12, S100Z and S100G were associated with better prognosis in Asian liver cancer patients. For patients with sorafenib treatment, high mRNA expression of S100A8, S100A16 and S100P were significantly associated with worse prognosis. Both S100A12 and S100B were modestly associated with better prognosis. Finally, we investigated the prognostic values of S100 expression in different pathological grades and the main risk factors of hepatocellular carcinoma patients. Higher S100A1, S100A2, S100A8, S100A9, S100A11, S100A13, S100A14, S100A16, and S100P mRNA expression were found to be associated with significantly worse OS in grade II liver cancer patients respectively. While, the S100A3, S100A5, S100A7 and S100G expression predicted better prognosis in grade II liver cancer patients. For grade III patients, the S100A2, S100A6, S100A9, S100A10, S100A11 and S100P expression were found to be correlated with shorter OS. While, the S100A1, S100A5, S100A7 and S100Z expression were related to longer OS. For patients with alcohol intake, The S100A1, S100A2, S100A7, S100A9, S100A11, S100A13, S100A14, S100A16, and S100P high expressions predicate the worse prognosis. While, the expression of S100A5, S100B, S100Z and S100G, suggest the better prognosis. For liver patients with hepatitis virus, the expression of S100A2, S100A6, S100A7, S100A9, S100A10, S100A11 and S100P were related with worse survival; while, for S100A5, S100A14 and S100G, the mRNA expression levels of them predicted favorable OS.

Conclusion: This study comprehensively and systematically investigated the diagnosis and prognosis of S100 family members for HCC. Interestingly, for patients with different populations, pathological grades and main risk factors, the S100A2, S100A6, S100A9, S100A10, S100A11, S100A13 and S100P were bad prognostic factors. While, the S100A5, S100Z, S100G and S100A12 were favorable factors. The study provides new insights into the effect of S100 proteins on the progression of hepatocellular carcinoma, which laid the foundation for the discovery of new molecular markers of liver cancer.

Key words: prognosis; hepatocellular carcinoma; S100 family

399. Research on the effect of Oleanolic Acid Derivatives and related mechanisms in breast cancer

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Background: In recent years, much attention has been paid to the application of oleanolic acid and its derivatives as anti-cancer drugs to limit the development of cancer. Studies have shown that oleanolic acid and synthetic derivatives have obvious anti-tumor effects. In this study, in order to solve the problems of poor bioavailability and severe adverse events of oleanolic acid and its derivatives, we developed a new compound (ZQL-3d) introducing chemical groups of Mannich base derivatives and Michael receptor derivatives, and evaluated the anti-tumor effect and related mechanism of ZQL-3d in breast cancer cells.

Methods: cck8, clone formation, scratch wound healing, and transwell assay were used to verify the biological function of ZQL-3d in breast cancer cells, and the cell cycle and apoptosis were analyzed by flow cytometry. The expression levels of cell cycle and apoptosis-related pathways were detected by molecular biotechnology including qPCR and Western Blot.

Results: We found that ZQL-3d had significant anti-cancer activity in three different molecular types of breast cancer cells (MCF-7, MDA-MB-231, SKBR3). In breast cancer cells incubated with ZQL-3d, the proportion of early apoptosis and the proportion of cells in G0/G1 phase increased in a dose-dependent manner, suggesting that ZQL-3d induced early apoptosis in breast cancer cells and blocked the cell cycle in G0/G1 phase. In the exploration of related pathway, we have proved that ZQL-3d promotes the expression of cell cycle-related protein (P21 , P27) in MDA-MB-231 cells, while inhibits the expression of STAT3.

Conclusion: ZQL-3d shows great anti-tumor activity in breast cancer cells, which may be related to apoptosis, cell cycle and JAK-STAT signal pathway. The novel oleanolic acid derivative (ZQL-3d) developed in this study may become an effective anti-cancer drug and provide a new idea for the clinical treatment of breast cancer.

Key words: Oleanolic acid derivatives; Apoptosis; Breast cancer cells; Anti-cancer drugs

400. Integrated NGS-panel analyse, a novel molecular classification strategy of endometrial carcinoma

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Background: The molecular classification of TCGA in endometrial carcinoma (EC) provides more accurate information for clinical treatment and prognosis determination, and has been recommended by NCCN guideline (2020 V2). However, due to the high complexity and cost of methods, its clinical application is restricted. Implementable strategy, instead of TCGA classification, is still being explored. This paper aims to classify endometrial cancer with the utilization of next generation sequencing (NGS) panel by overcoming the disadvantage of long detection period and limitation in detecting genetic variation information of multi-platform method.



Methods: NGS-Panel analyse was performed on FFPE samples from 86 patients pathologically assessed as endometrial cancer, followed by molecular classification according to the recommended criteria. Meanwhile, 45 matched samples were randomly selected for immunohistochemical staining of *p53*, *MLH1*, *MSH2*, *PMS2* and *MSH6*, and the ProMisE classification criteria were used for classification. The specificity and sensitivity of multi-platform method and the NGS-panel method were compared.

Results: The molecular classification of 86 cases of endometrial carcinoma was 12.79% for *POLE* type, 17.44% for MSI-H type, 48.84% for CN-L type and 20.93% for CN-H type. CN-L type is dominant in endometrioid carcinoma (54.41%), while CN-H type accounting for 8.82%. In contrast, serous endometrial carcinomas were all CN-H type. MSI-H type were significantly increased in clear cell carcinoma and mucinous endometrial carcinoma, while *POLE* type was absent. In the comparison of 45 cases based on ProMisE classification by IHC, three cases were determined to be dMMR by IHC and MSS by NGS analyse, of which two cases were only *MSH6* deletion and one case was *POLE* hypermutation. Two cases were wild-type of *p53* by IHC staining, but showed hot missense mutations in NGS analyse and thus determined to be CN-H type. Good consistency of the two determination methods was showed, with Kappa=0.902>0.75, $P<0.01$. ROC analysis showed that NGS-panel analyse had high specificity and sensitivity for four subtypes.

Conclusion: Integrated NGS-panel analysis provides equivalently important information for the molecular classification of endometrial carcinoma and can be used as an alternative to multi-platform detection. In consideration of the high requirements of specimen, long detection period and limited variation information of multi-platform method, NGS-pane has unique advantages in clinical practice from the perspective of health economics.

Key words: Endometrial carcinoma; molecular classification; NGS; TCGA

401. Exosomal circPACRGL promotes progression of colorectal cancer via the miR-142-3p/miR-506-3p-TGF- β 1 axis

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Background: Colorectal cancer (CRC) is the leading cause of cancer-related death worldwide. Exosome shave emerged as crucial regulators of intercellular communication and that abundant Circular RNAs (circRNAs) are enriched within exosomes. CircRNAs are novel members of noncoding RNAs regulating cancer proliferation and progression. However, the function and regulatory mechanism of cancer-derived exosomal circRNAs in CRC remains unclear.

Methods: CRC cells-derived exosomes were characterized using transmission electron microscopy, nanoparticle tracking analysis (NTA) and western blot. CCK-8, wound healing and transwell assays, and flow cytometry assays were conducted to assess whether exosomes would affect the proliferation, metastasis, and apoptosis of CRC cells, respectively. Moreover, we performed the RNA sequencing and RT-qPCR to identify circRNAs in exosome-stimulated CRC cells. Fluorescence in situ

hybridization (FISH) assay was used to detect the cellular distribution of circPACRGL. Bioinformatic analyses (StarBase 2.0) were used to pool the miRNA targets of circPACRGL. Luciferase assays were performed to verify the direct interaction. Finally, flow cytometry was used to detect the differentiation of N1-N2 neutrophils.

Results: Our study identified a novel CRC-derived exosomal circRNA, circPACRGL. We found circPACRGL was significantly upregulated in CRC cells after tumor-derived exosomes addition. Moreover, circPACRGL serves as a sponge for miR-142-3p/miR-506-3p to facilitate the transforming growth factor- β 1 (TGF- β 1) expression. As a result, circPACRGL promoted CRC cell proliferation, migration and invasion, as well as differentiation of N1 to N2 neutrophils via miR-142-3p/miR-506-3p-TGF- β 1 axis.

Conclusion: Our study, the first to reveal that cancer-derived exosomal circPACRGL plays an oncogenic role in CRC proliferation and metastasis, providing mechanistic insights into the roles of circRNAs in CRC progression and a valuable marker for CRC treatment.

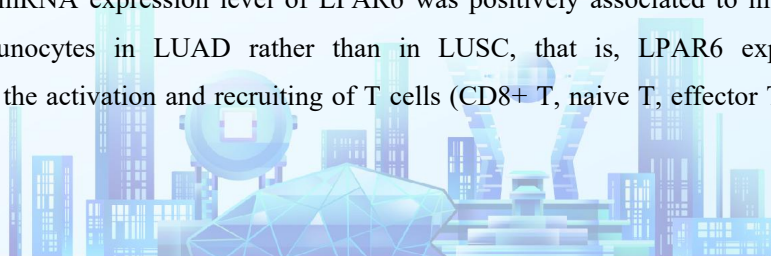
Key words: Colorectal cancer; Exosome; Invasion; Migration; TGF- β 1; circPACRGL; miR-142-3p; miR-506-3p

402. Lysophosphatidic acid receptor 6 is a potential biomarker associated with lung adenocarcinoma

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LPAR6 is the most recently determined G-protein-coupled receptor of lysophosphatidic acid receptor, and very few of study have demonstrated the performance of LPAR6 in cancers. Moreover, the relationship of LPAR6 to the potential of prognosis and tumor infiltration immune cells in different types of cancer is still unclarified. The mRNA expression of LPAR6 and its clinical characteristics were evaluated on various databases. The association between LPAR6 and immune infiltrates of various types of cancer were investigated via TIMER. IHC for LPAR6 in lung adenocarcinoma (LUAD) and lung squamous cell carcinoma (LUSC) tissue microarray with patients' information was detected. We constructed a systematic prognostic landscape in a variety types of cancer base on the expression level of mRNA. We enclosed that higher LPAR6 mRNA expression level was associated with better overall survival in some types of malignancy. Moreover, LPAR6 significantly affects the prognostic potential of various cancers in TCGA, especially in lung cancer. Tissue microarray's results demonstrated that a higher protein level of LPAR6 was correlated to better overall survival of LUAD rather than LUSC cohorts. Further research found that the underlying mechanism of this phenome might be the mRNA expression level of LPAR6 was positively associated to infiltrating statuses of devious immunocytes in LUAD rather than in LUSC, that is, LPAR6 expression potentially contributes to the activation and recruiting of T cells (CD8⁺ T, naive T, effector T cell) and NK cells



and inactivates Tregs, decrease T cell exhaustion and regulate T-helper cells in LUAD. Our discovery implies that LPAR6 is associated with prognostic potential and immune-infiltrating levels in LUAD. These discoveries imply that LPAR6 could be a novel promising biomarker for indicating the prognosis potential of LUAD patients.

Key words: LPAR6; tumor infiltration lymphocytes; prognosis; lung adenocarcinoma; biomarker

403. E- 钙黏蛋白表达与乳腺癌预后关系的系统评价和 Meta 分析

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目的: 应用系统评价和 Meta 分析的方法研究 E-钙黏蛋白表达与患者预后之间的关系,探讨 E-钙黏蛋白表达在乳腺癌预后中的角色。在本研究中,我们运用系统评价和 Meta 分析的方法,通过对已发表的原始研究进行统计分析,研究 E-钙黏蛋白的表达与乳腺癌预后的关系。为了解决 E-钙黏蛋白在乳腺癌中表达与预后作用中的争议,对 E-钙黏蛋白在乳腺癌中表达与预后的相关性进行系统评价,以探讨分析 E-钙黏蛋白表达水平如何影响乳腺癌预后

方法: 对 PubMed,Embase,Web of Science 等多个数据库进行系统的文献检索,检索时间截至 2020 年 12 月 1 日。筛选检索 E-钙黏蛋白表达与浸润性乳腺癌预后关系的文献,收集数据并统计分析。对文献进行系统评价,应用 meta 分析的方法,分析 E-钙黏蛋白表达与患者预后间的关系。应用计算机检索 PubMed,Embase,Web of Science,The Cochrane Library 以及中国生物医学文献数据库,万方数据库,中国学术期刊数据库。手工检索近 5 年重要国际肿瘤学会议记录,如美国临床肿瘤学会,圣安东尼奥乳腺癌会议。包括主题词,标题,摘要,关键词,及内容的检索。当有多个文献报道针对同一项研究数据时,只采用最近期,最全面的研究数据进行评估与分析。

结果: 按照纳入及排除标准,纳入 22 项关于 E-钙黏蛋白与乳腺癌预后关系的观察性研究进行 meta 分析。包括患者总数达 5971 人(表 1)。纳入的研究中共有来自 19 个研究中心的 20 项包含总生存(Overall survival, OS)的研究,包括了共 5571 名乳腺癌患者。首先对这 20 项 OS 研究进行合并分析,异质性检验提示研究间存在显著异质性($I^2 = 70.8\%$, $P < 0.001$),遂选用随机效应模型进行 meta 分析,结果显示:E-钙黏蛋白高表达是乳腺癌患者总生存(OS)的有利预后因素,合并效应量: $HR = 0.65$, $95\% CI = [0.50-0.87]$, $P = 0.003$,具有统计学意义(图 1)。纳入的研究中共有来自 13 个研究中心的 13 项研究包含乳腺癌无病生存率(Disease-free survival, DFS)的预后分析数据,对 13 项研究的预后数据进行 meta 分析,异质性检验提示研究间存在显著异质性($I^2 = 60.3\%$, $P < 0.001$),遂选用随机效应模型,结果显示:E-钙黏蛋白高表达是乳腺癌患者 DFS 的有利预后因素,合并的效应量: $HR = 0.57$; $95\% CI = [0.44-0.74]$, $P < 0.001$,具有统计学意义(图 2)。敏感性分析结果显示 Meta 分析结果不受单个研究影响。应用漏斗图分析结果提示本 Meta 分析发表偏倚不显著(图 3)。



结论： E-钙黏蛋白高表达是乳腺癌 OS 和 DFS 的有利预后因素，准确评估乳腺癌 E-钙黏蛋白可预测患者预后。

关键词： 乳腺癌；E-钙黏蛋白；预后；系统评价和 Meta 分析

404. Single-cell RNA-Seq reveals naïve B cells associated with better prognosis of hepatocellular carcinoma

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The immune cell types as well as their numbers and activities in the tumor microenvironment (TME) may contribute to tumor progression, metastasis, prognosis and clinical response to cancer immunotherapies. Hepatocellular carcinoma (HCC) is a typical type of highly heterogeneous solid tumor, causing high morbidity and mortality in the world, especially in China, however, the immune microenvironment of HCC has not been well-defined so far. In the present work, we first employed single-cell RNA sequencing on diethylnitrosamine (DEN)-induced mouse HCC model to depict the changing landscape of the immune cell composition, lineages and functional activities in TME during tumorigenesis, showing the distinct immune features in precancerous and cancerous lesions. The data indicated that the tumor-associated immune changes appeared early in pathological progression, since the specific subsets of T and B cells were preferentially enriched in TME of HCC. We identified the signature genes for these specific cell subsets, and then mapped them onto the HCC RNA-seq dataset from human The Cancer Genome Atlas (TCGA) database. We found a cluster of naïve B cells characterized by high expression of CD38 was associated with better prognosis of human HCC. In addition, the inter-cellular interaction map was established based on the receptor-ligand bonding at single cell resolution. Taken together, this study will be helpful to the comprehensive understanding of dynamic immune microenvironment and cellular networks, especial naïve B cells, during HCC pathogenesis, which could provide a novel insight into the therapeutics for the HCC.

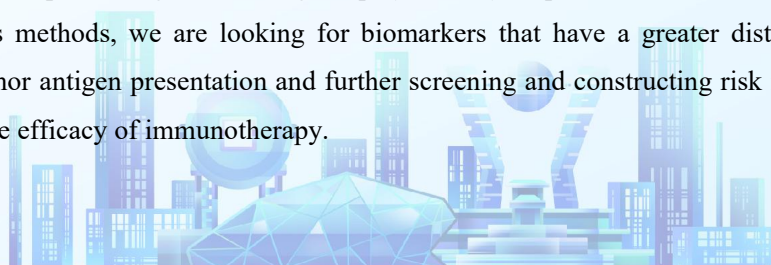
Key words: HCC; RNA-Seq; B cell; single-cell analysis; tumor microenvironment

405. Disturbance in tumour antigen presentation processing

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Purpose: Antigen presentation process is critical for T cell recognition of malignant cells. Current opinions believed that the processing of neoantigens plays a very important role in tumor immunity. Using bioinformatics methods, we are looking for biomarkers that have a greater disturbing effect in the process of tumor antigen presentation and further screening and constructing risk models, so as to use it to predict the efficacy of immunotherapy.



Method: We first classify patients according to the effectiveness of immunotherapy and the level of immune cell infiltration of the public data set. DEG analysis based on the level of immune infiltration and immunotherapy response is used to intersect with the genes we have sought that may change MHC-peptide dramatically. Gene enrichment analysis was conducted to show pathways and mainly biological process of candidate genes. Univariate COX analysis were used to screen risk genes and Lasso regression is used to construct a prognostic model to evaluate the efficacy of immunotherapy. We then classify the patients in validation cohort using the risk score and evaluate the overall survival of patients, immune checkpoint therapy response and immune cell infiltration within two groups.

Conclusion: We have established a prognostic model related to tumor antigen presentation, which can well reflect the neoantigen status of the tumor, so as to make a good assessment of the responsiveness of the patient clinical immune checkpoint treatment.

Key words: antigen presentation process; PD-1; cancer immune therapy

406. 血浆游离 DNA 甲基化组学用于早期卵巢癌鉴别诊断

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研究目的: 卵巢癌是妇科生殖系统恶性肿瘤中病死率第一的肿瘤, 严重威胁女性生命。卵巢癌发病隐匿, 约 70% 患者发病时已为晚期, 难以早期诊断。目前临床上尚缺乏较为有效的早筛手段, 本研究拟通过循环游离 DNA (cfDNA) 甲基化组检测寻找能够早期发现卵巢癌的分子靶标。

研究方法: 我们收集了 74 例上皮性卵巢癌患者, 86 例健康女性及 20 例卵巢良性肿瘤患者的血浆。使用游离 DNA 甲基化免疫共沉淀测序 (cfMeDIP-seq) 技术进行甲基化检测。在肿瘤组与非肿瘤组患者中, 我们找到了差异甲基化区域 (DMRs), 并用迭代训练和测试法评估这些 DMRs 对早期卵巢癌的诊断能力。

结果: 差异甲基化区域能够很好地区分肿瘤患者及健康人群 (ROC 为 0.86-0.98)。晚期上皮性卵巢癌中差异最大的 300 个 DMRs 不能有效鉴别早期卵巢癌或卵巢良性肿瘤。然而, 早期卵巢癌相关的甲基化标记在鉴别良恶性方面具有潜在价值。

结论: 本研究提示, 游离 DNA 甲基化组学可用于卵巢癌特异性生物标记物的鉴定, 尤其是针对早期卵巢癌。

关键词: 游离 DNA 甲基化组学; 上皮性卵巢癌; 早期; 分子标记物

407. 局部晚期鼻咽癌肿瘤体积及放疗中期肿瘤体积退缩率作为预后标志物的研究

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目的：评价鼻咽癌治疗前肿瘤体积、放疗中期肿瘤体积及肿瘤体积退缩率的预后意义。

材料与方法：我们回顾 2010 年 1 月至 2016 年 12 月期间在四川省肿瘤医院接受根治性放疗的 491 例鼻咽癌患者的诊疗记录及影像资料。所有患者在放疗第四周（20 次放疗）进行复查头颈部 MRI 及 CT。测量治疗前和放疗中期原发灶和转移淋巴结的大体肿瘤体积（GTV），并分析其预后意义。

结果：生存者平均随访 62.8 个月（4.83~131.1 个月）。5 年总生存率（OS）为 81.5%，无进展生存率（PFS）为 71.8%，无远处转移生存率（DMFS）82.7%，无局部复发生存率（LRFS）87.8%。治疗前肿瘤体积（PGTV）平均 53.3cm^3 （8.9~231.5 cm^3 ），放疗中期肿瘤体积（MGTV）平均 21.3cm^3 （1.8~189.4 cm^3 ），放疗中期肿瘤退缩率（TVRR）平均 21.3%（-49.6%~95.4%）。在多因素分析中，年龄（HR: 0.318, 95%CI: 0.214-0.473; $P<0.001$ ）,PGTV（HR: 0.448, 95%CI: 0.291-0.689; $P<0.001$ ）,MGTV（HR: 0.206, 95%CI: 0.108-0.393; $P<0.001$ ）,TVRR（HR: 2.545, 95%CI: 1.604-4.039; $P<0.001$ ）是 OS 的独立预后因素。PGTV,MGTV,TVRR 也是 PFS,DMFS,LRFS 的独立预后因素。

结论：PGTV,MGTV,TVRR 是局部晚期鼻咽癌患者根治性放射治疗的独立预后因素，可作为放疗过程中早期调整治疗方案的潜在标志物。

关键词：鼻咽癌; 肿瘤体积; 肿瘤退缩率; 预后

408. T 淋巴细胞定量检测在套细胞淋巴瘤预后评估中的作用

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目的：探讨套细胞淋巴瘤微环境中 T 淋巴细胞与患者预后的关系。

方法：1.2008 年 1 月 1 日—2020 年 9 月 8 日期间烟台毓璜顶医院，齐鲁医院，山东省立医院,西南医科大学附属医院，套细胞淋巴瘤患者病例共 120 例患者临床信息，并对患者进行预后随访。2. 对病理标本的 CD3 含量进行量化斑点免疫印迹（Quantitative Dot Blot, QDB）完全定量技术检测。3.应用 SPSS 19.0 分析软件进行统计学处理。Kaplan-Meier 对患者的生存预后参数及 CD3 的表达与预后行单因素生存分析，以 $P<0.05$ 为差异具有统计学意义。

结果：1.通过 ROC 曲线分析，以 0.044579701690702(nmol/g)作为分界值将患者分为 CD3-High 组和 CD3-Low 组，将生存时间以月为单位对两组患者的生存预后参数及 CD3 的完全定量结果进行单因素生存分析，结果表明两组的预后存在差异（ $P=0.005$ ）。



结论: T 淋巴细胞的数量对套细胞淋巴瘤患者的预后具有积极意义, T 淋巴细胞越多, 患者预后越好。

关键词: 套细胞淋巴瘤; 肿瘤微环境; QDB; CD3

409. A genetic variant in Long Non-Coding RNA HULC is associated with poor prognosis following the curative resection of hepatocellular carcinoma

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Background: Hepatocellular carcinoma up-regulated long non-coding RNA (HULC) is the first discovered lncRNA with aberrantly up-regulation in HCC, promoting HCC cell proliferation, autophagy and chemoresistance of HCC. We hypothesize that genetic variant in HULC gene is associated with survival of patients with hepatocellular carcinoma (HCC) following the curative resection.

Methods: In this study, we performed genotyping assays for HULC polymorphisms (rs1328866 T > A, rs1328868 C > T, rs7763881 A > C, rs2038540 C > G) in a cohort of 386 HCC patients who received curative resection. Multivariate Cox proportional hazards model and the Kaplan-Meier methods with log-rank test were used to evaluate the association between HULC SNPs and overall survival of HCC patients.

Results: Results found that HULC rs7763881 was significantly associated with overall survival of HCC patients after curative resection. HCC patients carrying AC/CC genotype had a significantly increased risk of death when compared with AA genotype carrier (adjusted hazard ratio (HR) = 1.29, 95% confidence interval (CI) = 1.01-1.66, $P = 0.044$). Kaplan-Meier analyses showed a significantly shorter survival time in HCC patients with AC/CC genotypes of SNP rs7763881 than AA genotype carrier (30.1 months vs. 41.1 months, P log-rank = 0.033). In addition, the stratification analysis showed that compared with SNP rs7763881 AA genotype carrier, patients with CA/CC genotypes had a significantly worse overall survival particularly evident in older subjects (age ≥ 50 years), patients with BCLC stage B/C, patients with AFP level ≥ 400 ng/mL ($P < 0.05$) and an interaction effect on overall survival of HCC between the SNP rs7763881 and age was found ($P = 0.023$).

Conclusions: This study suggests that HULC rs7763881 might contribute to overall survival in HCC patients received curative resection, which may serve as an independent prognostic marker for HCC patients.

Key words: Long Non-Coding RNA HULC; polymorphisms; prognosis; hepatocellular carcinoma



410. Functional characterization of PCCA in the proliferation and metastasis of clear cell renal carcinoma

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Objective: Abnormal lipid metabolism is one of the most important characteristics of ccRCC. Deregulated lipid metabolism is associated with enhanced RCC recurrence and metastasis. PCCA (Propionyl-CoA carboxylase α subunit) is the rate-limiting enzyme involved in the odd-chain fatty acid oxidation process. The role of PCCA in ccRCC recurrence and metastasis is unclear. In this study, we aim to explore the function and mechanism of PCCA in RCC progress.

Methods: Lipidomic analysis was used to evaluate the content of propionyl-CoA in clinical RCC and pan-RCC samples. TCGA database analysis was used to detect PCCA expression in RCC tumor tissue and cell lines, which was then validated by Western blot. Moreover, cell CCK-8 assay, cell migration and invasion assay, xenograft model can be used for studying the function and mechanism of PCCA in RCC progress.

Results: Our preliminary data showed that the Propionyl-CoA level was decreased in RCC samples. Moreover, overexpression of PCCA prevented 786-O proliferation and migration in vitro, and delayed RCC development in xenograft model. Further analysis revealed that the expression of PCCA was negatively correlated with the level of AKT phosphorylation, which has been reported as a causative reason for tumor recurrence and metastasis. Therefore, we proposed our hypothesis as follows: PCCA is a tumor suppressor at least in terms of ccRCC development. PCCA potentially inhibits tumorigenesis and metastasis via the inhibition of AKT phosphorylation. As a result, PCCA is down-regulated in ccRCC to overcome the tumor inhibitory effect.

Conclusions: Our data revealed that PCCA can act as a tumor suppressor gene that inhibits ccRCC proliferation and metastasis. Moreover, PCCA can inhibit the P-AKT in 786-O cell line. By working on this project, we will explore the mechanism of PCCA regulates ccRCC proliferation and metastasis and provide a piece of new regulatory machinery that lipid metabolic networks cross-talk with ccRCC development signaling, which shed light on the development of anti-cancer therapeutic approaches.

Key words: PCCA; Proliferation and metastasis; P-AKT; Renal cell carcinoma

411. Immunosequencing unmasks T cell repertoire signatures associated with NPC

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Nasopharyngeal carcinoma (NPC) is an endemic in Southeast Asia, especially in South China. Epstein-Barr virus (EBV) plays an important role in NPC development, besides, the strong association between NPC risk and human leukocyte antigen (HLA) locus confirmed by many gene-related research come into the spotlight, which serve as the key components required by T cell immunity. T cell response, involved in NPC development, witnessing the whole process from EBV infection to tumor formation, undergoes virus- and cancer-specific changes which have been imprinted in the TCR repertoires of each patients. Therefore, we expected to develop a TCR-based biomarker for early detection by investigating the landscape of the TCR repertoires in NPC patients. For this purpose, we delineate TCR repertoires through large-scale TCR β sequencing analysis of patients with NPC in contrast with healthy individuals in a large cohort of 169 cases and 499 controls recruited from southern China. We identified a set of NPC-associated TCRs in the peripheral blood, and developed a TCR-based score that was powerful to predict NPC from EBV VCA-IgA positive or negative population and validated in an independent cohort. The NPC-associated TCRs, which are specifically enriched and expanded in NPC patients, have the potential to be used in clinical diagnosis of NPC. Besides, T cell repertoire signatures associated with NPC provides an unbiased and comprehensive insight into the public T cell response in NPC, and lays the groundwork for the development of T cell immunotherapy for NPC in southern China.

Key words: Nasopharyngeal carcinoma (NPC); T cell receptor (TCR); TCR β sequencing; clinical diagnosis

412. 结直肠癌中 miR-92a 的表达及相关性研究

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目的: 通过检测 miRNA-92a 在粪便中的表达水平研究其对结直肠癌和结直肠息肉临床应用中的价值。

方法: 收集佳木斯大学附属第一医院 2019-2020 年结直肠癌患者, 结直肠息肉患者粪便标本 47 例, 同时采集健康人群粪便标本 15 例, 采用 RT-PCR 法检测 26 例结直肠癌及 21 例息肉患者中 miRNA-92a 的表达情况与 15 例正常人进行对比, 同时绘制 ROC 曲线判断其诊断价值。结果与健康人群相比较, 结直肠癌患者和息肉患者粪便当中 miR-92a 的表达水平显著高于健康人群对照组 ($P<0.05$)。

结论: miR-92a 在结直肠癌及结直肠息肉中表达增高, 有望作为辅助诊断结直肠癌及结直肠息肉的肿瘤标志物。

关键词: 结直肠癌; miR-92a; 筛查; 诊断

413. 自噬与凋亡在乳腺癌中的作用



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乳腺癌（Breast Cancer, BC）是起源于乳房组织乳腺导管上皮细胞或者乳腺小叶的恶性细胞进展而引起的女性生殖系统恶性肿瘤。中国乳腺癌发病率全球第一，占全球发病率 12.2%[1]，约 3%~10% 的新发乳腺癌病例在确诊时即有远处转移，30%~40% 的早期患者可发展为晚期乳腺癌，5 年生存率仅 20%，中位总生存时间为 2~3 年[2]。由于乳腺癌存在病因尚不明确，在分子水平上是一组高度异质性疾病，临床上出现对药物治疗无反应或耐药等难治性乳腺癌病例，故进一步研究乳腺癌发病机制及复发转移分子机制是亟需解决的科学问题。细胞凋亡（Apoptosis）是一种高度调节的细胞死亡方式，对所有高级生物平衡组织内环境稳定，控制细胞增殖以及清除受损或不必要的细胞至关重要。细胞自噬（Autophagy）自噬是细胞中高度保守的生理过程，依赖于溶酶体系统降解过量或者受损的细胞器，借此实现细胞本身的代谢需要和某些细胞器的更新。自噬有利于维持细胞内环境稳态及维持细胞存活，是一种细胞面临营养缺乏或氧化应激状态时的保护机制。自噬与凋亡之间存在着复杂的交互调控——二者能被多种应激因子共同激活，共享多个调节分子，甚至互相协调转化使我们对于乳腺癌病理生理学的理解变得复杂。最近的研究证实，自噬和凋亡在乳腺癌的发生发展过程中起着至关重要的作用，它们在细胞应激状态下通过调节信号分子，诱导蛋白质和（或）细胞器降解从而导致细胞程序性死亡，维持乳腺癌细胞内环境稳态。现就自噬与凋亡在乳腺癌发生发展中的相互作用关系做一篇综述，以其加深对乳腺癌疾病的认识，思考乳腺癌治疗干预的潜在靶点。

关键词：乳腺癌；自噬；凋亡；相互调节

414. The dynamic changes of AFP from baseline to recurrence as a excellent prognostic factor of hepatocellular carcinoma after locoregional therapy: a 5-year prospective cohort study

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Background: Although many studies have confirmed the prognostic value of preoperative alpha-fetoprotein (AFP) in patients with hepatocellular carcinoma (HCC), no one study has systematically elucidated the association of AFP at baseline (b-AFP), subsequent AFP at relapse (r-AFP), and AFP alteration with overall survival in HCC patients receiving locoregional therapy.

Patients and Methods: A total of 583 subjects with newly diagnosis of virus-related HCC who were admitted to Beijing You an Hospital, Capital Medical University from January 1, 2012 to December 31, 2016 were prospectively enrolled. The influence of b-AFP, subsequent r-AFP, and AFP alteration on relapse and post-recurrence survival were analyzed.



Results: By the end of follow-up, a total of 431 (73.9%) patients relapsed and 200 (34.3%) died. Patients with positive b-AFP had a 24% increased risk of recurrence compared with those who were negative. Patients with positive r-AFP had a 68% increased risk of death after relapse compared with those who were negative. The cumulative recurrence-death survival (RDS) rates for 1, 3, 5 years in patients with negative r-AFP were 85.6% (184/215), 70.2% (151/215), and 67.4% (145/215), while the corresponding rates were 75.1% (154/205), 51.2% (105/205), and 48.8% (100/205) in those with positive AFP ($P<0.001$). 35 (21.6%) of the 162 patients with negative b-AFP turned positive at the time of recurrence, and of this subset, only 12 (34.3%) survived. Of the 255 patients with positive b-AFP, 86 (33.7%) turned negative at the time of relapse, and of this subset, only 30 (34.9%) died. The 1-, 3-, and 5-year cumulative RDS rates were also compared among groups stratified by AFP at baseline and relapse. The present study found that patients with positive AFP at baseline and relapse, as well as those who were negative turned positive, had the shortest RDS and OS.

Conclusions: Not only AFP at baseline but also subsequent AFP at relapse can be used to predict a post-recurrence survival, which can help evaluate mortality risk stratification of patients after relapse.

Key words: Hepatocellular carcinoma; AFP; locoregional therapy; prognosis; prospective

415. 结直肠癌肝转移相关乙酰化修饰蛋白的筛选与验证

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目的: 远处转移是影响结直肠癌患者预后的重要因素,肝脏是结直肠癌远处转移的重要靶器官。目前对于结直肠癌肝脏转移的机制尚未完全探究清楚。赖氨酸乙酰化修饰是一种与细胞内的多种生物学过程密切相关的重要蛋白质翻译后修饰。本研究旨在深入探讨结直肠癌远处转移过程中蛋白质乙酰化修饰的改变,为进一步了解蛋白质乙酰化修饰在结直肠癌中的作用奠定基础。

材料与方法: 收集北京大学人民医院手术切除的新鲜结直肠癌及配对肝转移组织样本,通过 TMT (Tandem Mass Tag)标记,乙酰化修饰肽段富集技术以及基于质谱的定量蛋白质组学技术等对样本中的乙酰化修饰蛋白进行鉴定。以 1.2 倍为变化阈值筛选结直肠癌肝转移相关差异乙酰化蛋白及位点。对筛选得到的蛋白质进行系统的生物信息学分析以透彻这些蛋白的功能及特征。通过 STRING 蛋白网络互作数据库挖掘差异乙酰化蛋白的相互作用关系,通过 Cytoscape 软件中的 cytoHubba 插件分析蛋白互作网络中的关键蛋白。构建上述蛋白质粒,通过免疫沉淀实验,用赖氨酸乙酰化抗体检测其乙酰化水平。随后依据质谱获得的差异乙酰化位点,构建上述蛋白的乙酰化位点突变质粒,行免疫沉淀后检测个蛋白乙酰化水平改变以验证相应位点的乙酰化修饰。

结果: 本研究共收集结直肠癌肿瘤组织及配对肝转移组织的新鲜标本共 3 对。通过乙酰化蛋白质组定量研究,相较于肿瘤组织,配对肝转移组织中 47 个蛋白的 287 个乙酰化位点上调,59 个蛋白的 198 个乙酰化位点下调。蛋白修饰的基序分析显示,xxxK_K_Sxxx, xxxY_K_Nxxx,

xxxF_K_Nxxx 是乙酰化修饰最丰富的基序。对差异修饰蛋白进行亚细胞结构预测和分类统计表明, 差异乙酰化蛋白主要分布于细胞浆 (32.69%) 以及细胞核 (21.15%)。基因本体论 (Gene Ontology, GO) 以及京都基因与基因组百科全书 (Kyoto Encyclopedia of Genes and Genomes, KEGG) 富集分析表明, 差异乙酰化蛋白则主要参与补体活化及凝血, 糖代谢等过程。通过 cytoHubba 插件中的 MCC, DMNC, MNC, Degree, EPC 共 5 种方法分别计算前 20 位蛋白并取交集, 结果显示纤维蛋白原 α 链 (Fibrinogen alpha chain, FGA), 玻连蛋白 (Vitronectin, VTN) 以及纤溶酶原 (Plasminogen, PLG) 等则是参与结直肠癌肝转移的重要乙酰化蛋白。通过免疫沉淀实验验证了上述蛋白及对应位点的乙酰化修饰。

结论: 本研究鉴定了结直肠癌肝转移过程中的差异乙酰化蛋白及位点, 为进一步了解乙酰化修饰在结直肠癌远处转移中的作用提供了理论基础, 并为结直肠癌肝转移的诊断和治疗提供了潜在的分子标志物及治疗靶点。

关键词: 结直肠癌肝转移; 乙酰化修饰

416. MSI2 promotes the proliferation of hepatocellular carcinoma through the WNT signaling pathway

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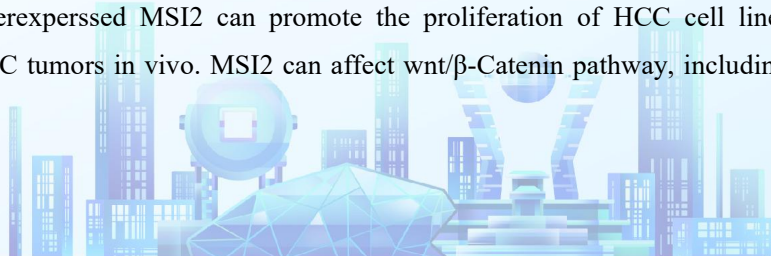
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Background: Hepatocellular carcinoma (HCC) is a tumor with strong proliferation. The role of Musashi RNA Binding Protein 2 (MSI2) in HCC through the Wnt signaling pathway requires further investigation.

Materials and methods: The MSI2 expression of the HCC and normal liver in TCGA and GTEx were analyzed. MSI2 mRNA and protein expression were detected by PCR and Western blot. The proliferation effect of MSI2 in HCC cell lines was tested by CCK-8 and plate clones. Subcutaneous xenografted nude mice models of HCC were established to test MSI2 promotes tumorigenicity ability. In addition, whether the MSI2 can affect the Wnt/ β -catenin signal pathway was detected by PCR and Western blot. In rescue experiment, it is detected whether the MSI2 is used to play a biological effect by β -catenin in the HCC.

Results: Data in TCGA and GTEx demonstrated that MSI2 was high expression in HCC compared with normal liver tissue, and MSI2 expression had clinical significance. After the MSI2 knocking, the HCC cell line proliferation was suppressed and the growth of subcutaneous tumors in nude mice was inhibited. Overexpressed MSI2 can promote the proliferation of HCC cell line and promotes the growth of HCC tumors in vivo. MSI2 can affect wnt/ β -Catenin pathway, including β -Catenin, TCF-4



and TEF-1. In vitro and in vivo experiments confirmed that β -catenin knockdown can reverse the proliferation effect caused by MSI2 overexpression.

Conclusion: MSI2 can promote HCC cell line proliferation and increase tumor formation capacity, and promote value-added biological effects by β -catenin.

Key words: MSI2; Proliferation; WNT signaling pathway; Hepatocellular Carcinoma

417. A Comprehensive Risk Score for Effective Risk Stratification and Screening of Nasopharyngeal Carcinoma

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Purpose: Nasopharyngeal carcinoma (NPC) is endemic in certain regions of East Asia, North Africa and the Arctic, with Epstein-Barr virus (EBV) and genetic factors implicated in its causation. Screening for the high-risk individuals becomes extremely important for the early detection and prevention of NPC in endemic populations.

Experimental Design: We develop a comprehensive risk score (CRS) that combines risk effects of EBV and human genetics for NPC risk stratification and validate this CRS within an independent, population-based dataset.

Results: Comparing the top decile with the bottom quintile of CRSs, the odds ratio of developing NPC is 21 (95% confidence interval: 12 - 37) in the validation dataset. When combining the top quintile of CRS with EBV serology tests currently used for NPC screening in southern China, the positive prediction value of screening increases from 4.70% (serology test alone) to 43.24% (CRS plus serology test).

Conclusions: This CRS approach affords new opportunity for predicting personalized risk and screening high-risk individuals in endemic areas to promote the early detection and prevention of NPC.

Key words: Epstein-Barr virus; Nasopharyngeal carcinoma; Risk stratification; Population screening; Personalized risk prediction

418. 髓性热带病毒整合位点 2 蛋白表达在胃癌预后评估中的作用

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目的: 胃癌是我国第三高发恶性肿瘤, 虽然治疗手段不断发展, 但我国胃癌患者的预后仍较差, 5 年生存率仅为 35.9%。髓性热带病毒整合位点 2 (MEIS2) 是一种同源盒基因 (homeobox

genes), 属于 TALE (three amino acid loop extension) 基因家族, 在神经系统的正常发育中起作用, 也与肿瘤发生有关。不同肿瘤中, MEIS2 表达与患者生存的关系不同。MEIS2 低表达与前列腺癌和子宫内膜癌的进展和不良预后相关, 但可以预测非小细胞肺癌患者化疗后的良好生存。MEIS2 蛋白表达水平与胃癌患者预后的关系尚不明确。本研究旨在评估 MEIS2 在胃癌组织中的表达水平, 探讨 MEIS2 对胃癌预后评估的预测价值。

方法: 本研究纳入了 2011 年至 2016 年间, 在吉林大学第一医院胃结直肠外科接受胃癌根治术, 手术切缘为阴性且无远处转移的 263 例胃癌患者为研究对象。使用患者术后经石蜡包埋的胃癌病理组织切片进行免疫组织化学法染色, 评估胃癌组织中 MEIS2 的表达水平; 以细胞核内棕黄或棕褐色颗粒为着色, 采用染色强度 (几分到几分) $\times$ 着色细胞百分比进行 H-score 评分, 以总分高于 50 定义为 MEIS2 高表达。于患者术后第 3 个月, 6 个月, 1 年及之后每年随访收集患者的临床和生存信息。采用 X² 检验分析 MEIS2 表达与临床病理特征的关系; Kaplan-Meier 方法绘制生存曲线, log-rank 检验比较生存曲线的差异; 采用单因素和多因素 Cox 风险回归模型计算风险比 (HR) 值及其 95% 置信区间 (CI), 评价 MEIS2 在肿瘤组织的表达水平与胃癌患者长期生存的关系。

结果: 在 263 例患者的胃癌组织中, MEIS2 高表达率为 82.5%, 其表达水平在不同年龄, 性别, 肿瘤大小, 肿瘤浸润深度, 肿瘤类型以及是否发生淋巴结转移, 脉管浸润, 神经束膜浸润等临床病理特征间均无统计学差异 (均 $P > 0.05$)。研究对象中位生存期 36.2 个月, 多因素分析结果显示 MEIS2 阳性表达的患者比阴性表达的患者生存期长 (中位生存期 39.2 个月 vs 26.5 个月), 预后好 (HR=1.50, 95%CI: 1.01-2.21); 分层分析的结果显示, 在存在淋巴结转移, 组织学分级为高级别, 有脉管浸润和有神经束膜浸润的患者中, MEIS2 阳性表达是患者良好预后的独立影响因素 (HR= 1.57, 95%CI: 1.04-2.35; HR= 1.56, 95%CI: 1.03-2.01; HR= 1.57, 95%CI: 1.02-2.43; HR=1.568, 95%CI: 1.02-2.42)。

结论: MEIS2 在胃癌组织中的高表达与患者良好预后相关, 有望作为评估胃癌患者预后的生物标志物。研究对象的中位随访时间未达到 5 年, 仍需更长时间的随访, 以便进一步探讨 MEIS2 对胃癌长期生存的影响。

关键词: 胃肿瘤; 预后; 免疫组织化学; 基因; 同源盒

419. 基于 GEO 和 TCGA 生物信息学分析环状 RNA 作为非小细胞肺癌的潜在生物标志物

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非小细胞肺癌是一种常见的肺癌类型（约占 85%），大多非小肺癌患者临床症状不明显，确诊多为晚期，预后不良。越来越多证据表明环状 RNA（circRNA）参与到各种癌症的发生发展的调节中，本研究旨在通过生物信息学分析非小细胞癌差异表达的 circRNA，寻找非小细胞肺癌新的 circRNA 生物标志物。通过利用高通量基因表达数据库（Gene Expression Omnibus（GEO））联合分析 GSE158695,GSE112214,GSE101684,GSE101586 四个非小细胞肺癌芯片表达数据，合计 17 对样本。通过 R 包 RobustRankAggreg 最终实现四个不同芯片表达分析，得到 80 个差异表达 circRNA，其中 8 个 circRNA 上调，72 个 circRNA 下调。生物信息学分析发现 hsa_circ_0061817 在非小细胞肺癌中表达下调，进一步通过 starbase 预测 hsa_circ_0061817 结合的 miRNA，得到 45 个潜在结合的 miRNA。随后通过对 TCGA 数据库中肺癌 miRNA 基因表达数据进行分析，分析得到 132 个 miRNA 表达下调，603 个 miRNA 表达上调。联合 starbase 预测与 TCGA 数据库中肺癌 miRNA 基因表达数据，最终得到可能与 hsa_circ_0061817 结合且与肺癌进展相关的 miRNA 共 6 个（包括：hsa-miR-148a-5p,hsa-miR-1910-3p,hsa-miR-3677-3p,hsa-miR-424-5p,hsa-miR-15b-5p,hsa-miR-145-3p），随后通过 mirPath 的 KEGG 和 GO 分析发现 hsa_circ_0061817 可能通过与 hsa-miR-148a-5p 结合参与半乳糖代谢,细胞间隙连接,N-糖苷合成,干细胞多能性及 TGF- β 信号等相关信号通路来调控 NSCLC 发展的进程。

关键词: 非小细胞肺癌；生物信息学分析；hsa_circ_0061817；生物标志物

420. 18 个代谢相关基因的肺腺癌预后模型的建立及验证

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目的: 基于代谢基因的生物信息学构建肺腺癌预后模型及验证。

方法: 获取 TCGA 和 GEO 数据库肺腺癌相关数据，LASSO 回归构建多基因预后模型并计算风险值 (riskscore,RS)。单,多因素 Cox 独立预后分析，通过 ROC 曲线评价模型的 AUC 面积并进行 K-M 生存分析。构建列线图评价模型的可行性，通过 GSEA 进行代谢基因功能富集分析。TIMER 数据库分析患者 RS 与免疫细胞浸润以及与免疫检查点分子表达的相关性。

结果: 运用 TCGA 数据库基于 18 个代谢相关基因构建肺腺癌预后模型，RS 可以作为独立的预后因子(HR=4.242,95%CI=3.040-5.919, $P<0.001$)。ROC 曲线下面积为 0.713。生存分析显示，与高风险组相比，低风险组总体生存率更高($P<0.001$),预后模型与免疫细胞的浸润以及与免疫检查点分子的表达有关。

结论: 代谢相关基因构建的肺腺癌预后模型的 RS 是独立预后因子，模型具有较高的预后判断价值，对指导个体化治疗方面具有一定的临床应用前景。

关键词: 肺腺癌；代谢基因；预后模型；生物信息学



421. Identification of chromatin organization-related genes associated with clinical and prognostic features of hepatocellular carcinoma

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Background: Chromatin organization is a well-studied concept, but no studies have comprehensively analyzed the association between chromatin organization-related genes (CORGs) and hepatocellular carcinoma (HCC) prognosis.

Methods: Gene candidates were selected from differentially expressed genes and prognostic genes in The Cancer Genome Atlas (TCGA) database. A gene risk score for overall survival prediction was established using the least absolute shrinkage and selection operator (LASSO) regression, Learning Vector Quantization (LVQ) and random forest (RF) analysis, and this was validated using data from the International Cancer Genome Consortium (ICGC) database. Functional analysis was conducted using gene ontology enrichment, Kyoto Encyclopedia of Genes and Genomes analysis, gene set enrichment analysis, and immune microenvironment and copy number variations (CNV) analyses.

Result: Initially, 121 CORGs from the TCGA database were screened as differentially expressed between normal and tumor tissues and as genes associated with HCC prognosis. Then, four CORGs (BEND3, CENPA, HDAC1, KDM1A) were identified using the LASSO regression, LVQ and RF analysis. The four CORGs were used to develop a risk score in the training set, and the risk was validated to have a significant prognostic value in the ICGC set ($P < 0.05$). Patients with high risk scores had lower tumor differentiation, higher stage, and worse prognosis (all $P < 0.05$). Multivariate Cox regression analyses also confirmed that the risk score was an independent prognostic factor for HCC in both the TCGA and ICGC sets (all $P < 0.05$). Further analysis showed that a high risk score was correlated with the tumor immunity and mutation.

Conclusion: The risk score predicts HCC prognosis and could thus be used as a biomarker not only for predicting HCC prognosis but also for deciding on treatment.

Key words: chromatin organization; gene; hepatocellular carcinoma; tumor immunity; copy number variations; risk score

422. Impact of hepatocellular carcinoma-related genes on TACE

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Abstract



Background: Transcatheter arterial chemoembolization (TACE) is an effective treatment for hepatocellular carcinoma (HC). However, this treatment has different therapeutic effect on different stages of hepatocellular carcinoma, and identifying the role of HC-related genes can help to improve the effectiveness of TACE.

Method: To investigate the role of HC-related genes in TACE and to provide valid data for TACE treatment, we conducted a comprehensive bioinformatics analysis. By text mining (“hepatocellular carcinoma”) and microarray data analysis (GSE104580), we obtain a common set of genes. Gene Ontology and Kyoto Encyclopedia of Genes and Genomes analysis performed to clarify the function of genes. Functional enrichment analysis was used to reveal the pathway that key genes involved in. The significant genes clustered in the PPI network were chose to execute gene-drug interaction analysis for potential drug discovery. Prognosis analysis indicated the relationship between HC-associated genes and TACE. The correlations between HC-related genes and tumour-immune infiltration was evaluated using Pearson’s correlation analysis. Platelet aggregation using optical turbidimetry and thromboelastography.

Results: Screening for HC-related genes associated with TACE. Functional enrichment analysis revealed these genes mainly involved in the coagulation cascade, proximal tubule bicarbonate recovery and bile secretion. Prognosis analysis indicated a poor survival rate in HC patients with high expression of SERPINE1, SPP1, MMP12 and low AQP1 expression. A prognostic model constructed using the five prognostic genes mentioned above can predict overall survival of HC patients with moderate to high accuracy. Significant correlation was observed between target genes and immune-cell infiltration. Platelet aggregation function is reduced in patients with HC.

Conclusions: In conclusion, we screened for key genes affecting TACE treatment and identified a prognostic signature for HC patients containing four genes (SERPINE1, SPP1, MMP12 and AQP1). HC-related genes may be strongly associated with prognosis in TACE.

Key words: hepatocellular carcinoma; TACE; bioinformatics analysis; thrombosis

423. 66 例乳腺癌 BRCA1/2 胚系基因突变研究

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目的: 经过对 66 例乳腺癌患者 BRCA1/2 基因外显子区域进行剖析, 分析乳腺癌患者 BRCA1/2 基因突变状态及其在临床特征方面的差异。

方法: 选取 2017 年月至 2021 年 6 月期间我院收治的 66 例乳腺癌患者作为研究对象, 用 NGS 技术对患者外周血样本中的 BRCA1/2 基因的全外显子及其邻近 20bp 内含子区域进行测序, 对其 BRCA1/2 的点突变及小片段插入缺失变异进行分析, 同时对其临床特征进行比较。

结果: 1, 在 66 名乳腺癌患者中, 有 6 名患者携带 BRCA1/2 基因的致病性胚系变异, 总突变率为 9.09% (6/66), 在这 6 例患者当中, 有 4 例携带 BRCA1 基因变异, 突变率为 6.06%, 2 例携

带 BRCA2 基因突变, 突变率为 3.03 %。2,同时, 在 66 例样本中检测到了 4 例意义未明突变位点, 均为 BRCA2 基因变异, 分别是 c.4376A>G, c.-41_-40+5delGGGTTAG, c.572A>T 和 c.6334A>G, 这可能是由于目前研究发现的乳腺癌中 BRCA2 基因变异频率低于 BRCA1 基因, 所以对 BRCA1 基因变异的发现和解读的相关研究更多, 因此对于这些 BRCA2 基因意义未明变异的研究还需要更多的队列及更长的随访以明确它们是否具有致病性。3,BRCA1/2 基因致病性突变组与未突变组在年龄上的比较, 突变阴性个体的诊断年龄与突变阳性个体没有显著差异。4,将三阴性乳腺癌和非三阴性乳腺癌的 BRCA1/2 基因致病性突变情况做对比, 发现 17.86% (5/28) 的 BRCA1/2 基因致病性个体均为三阴性乳腺癌, 明显高与在非三阴性乳腺癌中的比例 2.63% (1/38), 这与目前的报道中的三阴性乳腺癌中 BRCA1/2 基因致病性变异发生率显著高与非三阴性乳腺癌的结果一致。

结论: 1,本研究通过分析家族性和散发性乳腺癌患者的临床特征, 发现 BRCA1/2 基因突变者与未突变者在年龄方面没有统计学差异, 不排除由于样本数量不足, 导致无法区分两组间的年龄差异的可能性。2,BRCA1/2 基因在三阴性乳腺癌人群中的突变频率高与非三阴性乳腺癌人群, 推荐三阴性乳腺癌患者进行 BRCA1/2 基因的筛查。

关键词: 乳腺癌; 易感基因; BRCA1/2; 胚系变异; NGS

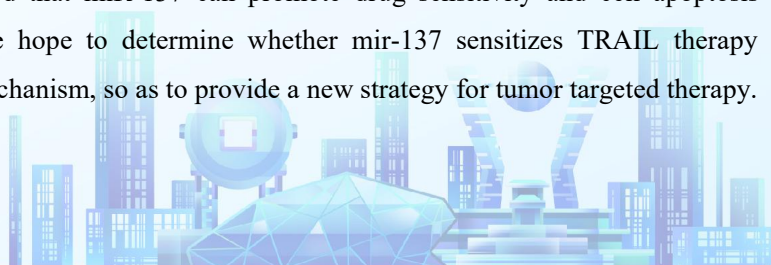
424. A miR-137-XIAP Axis Contributes to the Sensitivity of TRAIL-induced Cell Death in Glioblastoma

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Aims: Glioblastoma (GBM) is the most aggressive form of brain tumors, with a median survival time no more than 16 months. Despite considerable advances in GBM therapy, it remains one of the most challenging diseases. TRAIL (TNF-related apoptosis-inducing ligand) is a promising anticancer agent that can be potentially used as an alternative or complementary therapy because of its therapeutic potential as a tumor-specific apoptosis inducer without affecting normal cells. However, the subsequent studies showed that many tumors were resistant to TRAIL. MicroRNAs (miRNAs), evolutionarily well-conserved, small non-coding RNA, play an important role in the post-transcriptional regulation of target mRNA via mRNA degradation or translational repression through binding with 3'-untranslated regions (UTRs) of target genes. Accumulating evidences demonstrated that miRNAs play a critical role in the regulation of malignant behaviors of cancer cells. And some studies showed that miR-137 can promote drug sensitivity and cell apoptosis in tumor treatment. Therefore, we hope to determine whether mir-137 sensitizes TRAIL therapy and clarify its new regulatory mechanism, so as to provide a new strategy for tumor targeted therapy.



Methods: Firstly, GBM cells were transiently transfected with miR-137 mimics, and treated with TRAIL 24 hours later, then analyzed cell apoptosis rate using FACS 48 hours after the treatment. Then we predicted the potential target genes of miR-137 by bioinformatics prediction tool. Subsequently, double luciferase reporter assay was used to test the relationship between miR-137 and target gene. Then mRNA and protein expression level were tested by qRT-PCR and western blot assays 48h after miR-137 transfection. Also, gain and loss of functional experiments were employed to further confirm the important roles of target gene in TRAIL-induced cell apoptosis. Finally, the correlation between miR-137 and target gene expression was analyzed in cancer cell lines and clinical samples using qRT-PCR. Finally, we established the subcutaneous tumor model in nude mice, TRAIL and miR-137 were used to treat tumor in order to confirm the therapeutic effect.

Results: We found that exogenous expression of miR-137 can significantly sensitize TRAIL-induced apoptosis in GBM cells. By combinational use of bioinformatic prediction, reporter assay, qRT-PCR and western blot, we confirmed that XIAP, X-linked inhibitor of apoptosis protein, is one of new direct target genes of miR-137. Further studies revealed that enforced expression of XIAP reversed the effect of miR-137 in sensitizing TRAIL-induced apoptosis. Finally, analysis of qRT-PCR showed a reciprocal relationship between miR-137 and XIAP in clinical cancer tissues and multiple types of tumor cell lines. More importantly, in the xenograft model, enforced expression of miR-137 and TRAIL increased tumor cell apoptosis and suppressed tumor growth.

Conclusions: MiR-137 can significantly sensitize TRAIL-induced apoptosis through down-regulating XIAP in GBM cells, and suppress tumor growth.

Key words: miR-137; XIAP; TRAIL; cell apoptosis; glioblastoma

425. 基于转录组数据识别胰腺癌同源重组缺陷的定性标志

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研究目的: 胰腺癌是一种预后不良的恶性肿瘤。仅有 20% 的胰腺癌患者适合手术，而大多数患者在手术切除后复发，且其他患者从化疗和放疗中获益有限。近来，胰腺癌的靶向治疗取得了突破性进展。据报道，具有同源重组缺陷（homologous recombination deficiency, HRD）的胰腺癌患者受益于聚 ADP 核糖聚合酶（Poly ADP-ribose polymerase, PARP）抑制剂的维持治疗。然而，从转录组水平准确鉴定胰腺癌患者 HRD 状态仍面临挑战，基于群体水平的传统定量方法受实验批次效应等因素影响，在临床中的应用受限。因此，本研究基于样本内基因相对表达大小秩序（relative expression ordering, REO），识别 HRD 标志用于判别胰腺癌患者的 HRD 状态。

材料方法: 基于 The Cancer Genome Atlas (TCGA) 胰腺癌 RNA-seq 数据，本研究采用 REO 算法，构建了由 24 个基因对组成的 HRD 标志（24-GPS）。并且，24-GPS 的效能在多套胰腺癌组织



数据（GSE17891, GSE57495, ICGC-AU）和细胞系药效数据（GDSC, CTRP）以及基因敲除细胞系的表达数据中得以验证。此外，本研究采用 ESTIMATE 和 ImmuneCellAI 免疫评分工具分析 HRD 胰腺癌患者的免疫微环境。

结果：相比于非 HRD 样本，24-GPS 分类的 HRD 样本显示出较差的总体生存率以及较高的 HRDscore/HRDetect score 特征。TCGA 多维组学数据分析揭示 HRD 样本具有高度不稳定的基因组特征(包括 HRD 相关基因的突变以及频繁的拷贝数变异等)，并且在表观基因组学和蛋白质组学水平上也显示出 HRD 相关的生物学扰动。此外，PARP 药物敏感性分析结果显示 24-GPS 鉴定的 HRD 细胞系倾向于对 PARP 抑制剂（奥拉帕尼和尼拉帕尼）敏感，说明由 24-GPS 判别的 HRD 样本确实具有 PARP 抑制剂获益这一重要特征。另外，HRD 免疫微环境分析结果显示 HRD 样本具有免疫评分较低,CD4,CD8 T 细胞浸润比例均较低以及免疫检查点基因低表达的特点，说明 HRD 样本处于一个免疫抑制的微环境中，可能不适用免疫抑制剂的治疗。在转录组以及蛋白质组水平中，均发现了 HRD 伴随有细胞周期功能失调。并且，本研究发现同时抑制 PARP 相关基因和 ATR 基因表达的胰腺癌细胞的存活能力降低，说明 PARP 抑制剂与 ATR 基因抑制剂联合用药是一个潜在的组合用药方案。

结论：24-GPS 可在个体化水平上识别具有 HRD 状态的胰腺癌患者，扩大 PARP 抑制剂的受益群体，并对临床上选择可能受益于 PARP 抑制剂的胰腺癌患者具有潜在意义。

关键词：胰腺癌；同源重组缺陷；PARP 抑制剂；多维组学

426. 基于染色质调控因子遗传互作识别癌细胞药效标志

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研究目的：染色质调控因子是肿瘤发展过程中必不可少的上游调控因子之一。在癌症基因组中，染色质调控因子与其他基因同时失调，导致癌细胞生存能力增强或者减弱，从而形成染色质调控因子的合成致活遗传互作和合成致死遗传互作，并最终影响患者的药物响应以及预后生存。然而，现阶段我们对染色质调控因子相关的遗传互作及其与药物响应的关系仍然知之甚少。因此，本工作主要识别癌症中染色质调控因子的遗传互作，并对遗传互作与药物响应之间的相关性进行探究。

材料方法：本工作通过整合大规模 CRISPR-Cas9 筛选和药物基因组响应数据集，基于单侧秩和检验识别特定癌症类型中潜在的与药物响应相关的染色质调控因子遗传互作。并进一步基于系统的网络分析和共表达分析对染色质调控因子遗传互作之间的关系进行探究。此外，本工作还基于癌症基因组图谱中的基因表达,DNA 甲基化,同源重组缺陷,肿瘤微环境 and 治疗结果等数据对染色质调控因子的遗传相互作用进行分析，识别染色质调控因子对患者多维组学的扰动。



结果：本工作共识别到 625 个潜在的与药物响应相关的染色质调控因子合成致死关系以及 288 个潜在的染色质调控因子合成致活关系。其中，83%的染色质调控因子合成致死相互作用以及 75%的染色质调控因子合成致活相互作用存在直接或间接的蛋白质相互作用；另外，超过 75%的染色质调控因子遗传相互作用存在共表达或者共甲基化关系。以上结果表明染色质调控因子与其形成合成致死或者合成致活互作关系的基因之间存在生物学功能联系。此外，本工作发现染色质调控因子遗传互作会导致基因差异表达，DNA 甲基化，同源重组缺陷等多维组学以及免疫微环境发生异常改变，影响患者对不同药物的响应以及预后生存。其中，染色质调控因子集合 (EP300, MSH6, NSD2 和 TRRAP) 突变介导 MAP2 低表达的结肠癌患者患者预后更好，并有更大的可能受益于 taxanes 药物。而至少携带一个 Vorinostat (HDAC 抑制剂) 模块中染色质调控因子合成致活相互作用的结肠癌患者预后较差，可能对 Vorinostat 治疗产生耐药性。

结论：药物响应相关染色质调控因子遗传互作图谱为肿瘤相关染色质调控因子的相互作用研究提供丰富的资源，并可作为有效的生物标志物识别策略，为肿瘤药物，尤其是表观遗传学相关药物的合理使用提供指导和帮助。

关键词：染色质调控因子；合成致死 合；成致活 药物响应

427. NSCLC 骨转移风险预测模型的建立和验证

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目的：构建列线图来预测非小细胞肺癌 (NSCLC) 患者骨转移的发生风险。

方法：回顾性分析在医院确诊的 NSCLC 患者的临床资料，包括是否发生骨转移,年龄,性别,病理类型,吸烟状况,PS 评分,T,N 分期,骨转移前是否有其他部位的转移,癌胚抗原 (carcinoembryonic antigen,CEA) 水平,甲胎蛋白 (alpha fetoprotein,AFP) 水平,血清钙浓度 (Ca²⁺),血清磷浓度 (P),碱性磷酸酶 (alkaline phosphatase,ALP) 水平,利用单因素及多因素 Logistic 回归分析建立预测模型,使用受试者工作特征曲线 (receiver operating characteristic curve,ROC),决策曲线分析法 (decision curve analysis ,DCA) 验证模型的准确性及临床获益度,使用列线图进行模型可视化。

结果：ROC 曲线下面积 (AUC) 显示,在建模组 (n=138) 及验证组(n=92)中,联合指标 (年龄,性别,病理类型,CEA,ALP) 预测的 AUC 值(建模组=0.792, 验证组=0.629)均高于单一指标预测值。

结论：本研究构建的预测模型效果良好,可为临床筛选 NSCLC 骨转移的高危患者提供参考。

关键词：非小细胞肺癌；骨转移；危险因素；列线图



428. 血浆游离热休克蛋白 90 α 在 EGFR 突变非小细胞肺癌患者中的预后价值

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目的: 探究不同 EGFR 突变非小细胞肺癌患者的血浆热休克蛋白 90 α (HSP90 α)表达水平, 以及与临床特征和表皮生长因子受体(EGFR)基因突变的相关性。

方法: 收集分析 1347 例病理诊断明确为肺癌的患者的血浆 HSP90 α 及性别,临床分期及预后状态和时间,探究其与 EGFR 基因突变间的关系。

结果: 高血浆 HSP90 α 表达与小细胞肺癌,高肿瘤分析,高 TNM 分期,和较差预后结局均相关,差异有统计学意义($P<0.05$);EGFR 基因突变组非小细胞肺癌患者血浆 HSP90 α 水平升高与 L858R 野生型,20 外显子突变型相关($P<0.05$); 利用最佳 Cutoff 值筛选, HSP90 α 小于 62.1 ng/ml 的低风险组患者拥有更佳的预后($P<0.001$),且并不取决于 EGFR 突变类型。

结论: 血浆 HSP90 α 的表达升高与 NSCLC 患者较差的 OS 结果相关, 且血浆 HSP90 α 是独立于不同 EGFR 突变类型的预后指标。

关键词: 非小细胞肺癌; 基因突变; 热休克蛋白 90 α 预后

429. 循环肿瘤细胞在肿瘤高风险人群及癌症患者血液中的分布及其临床意义分析

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循环肿瘤细胞(CTCs)已经存在于早期肿瘤甚至癌前病变患者的外周血中。本研究旨在确定肿瘤高风险人群和泛癌种患者外周血中 CTCs 的水平情况。我们通过制备高表达上皮型肿瘤细胞的上皮细胞粘附分子(EpCAM)免疫脂质体磁珠(Ep-LMB),高表达间质型肿瘤细胞的波形蛋白(Vimentin)免疫脂质体磁珠(Vi-LMB), 分别对 136 例肿瘤高风险人群(包括:腰椎间盘突出症,冠心病,糖尿病,慢性胃炎,阑尾炎,急性支气管炎,类风湿性关节炎等。), 1521 例不同肿瘤患者(肺癌 167 例,胃癌 152 例,结直肠癌 184 例,肝癌 249 例,食管癌 148 例,胰腺癌 164 例,乳腺癌 283 例,卵巢癌 174 例)的 7.5mL 外周血中 CTCs 进行富集鉴定,同时入组 62 例健康人群外周血样本作为对照研究,并结合患者临床特征进行分析。结果显示,制备的免疫脂质体磁珠具有高特异性(92.1%)和高灵敏度(94.6%),对不同肿瘤细胞系的增殖率均大于 90%,捕获率在 90%以上;血液样本 CTCs 计数结果显示,健康人群 CTCs 平均数量(Aq)为 0.6(Ep-LMB: Aq=0.5,Vi-LMB: Aq=0.1),高风险人群 CTCs 平均数量为 2.5(Ep-LMB: Aq=2.2,Vi-LMB:

Aq=0.3), 肿瘤患者 CTCs 平均数量为 7.4 (Ep-LMB: Aq=3.9, Vi-LMB: Aq=3.5)。不同肿瘤患者之间的 CTCs 平均数量无明显差异 ($P>0.05$), 不同肿瘤患者的 CTCs 平均数量明显高于肿瘤高风险人群 ($P<0.05$), 肿瘤高风险人群的 CTCs 平均数量明显高于健康人群 ($P<0.05$), 健康人群和肿瘤高风险人群的上皮型 CTCs 平均数量明显高于间质型 ($P<0.05$), 不同肿瘤患者的上皮型与间质型 CTCs 平均数量无显著差异 ($P>0.05$), CTCs 数量大于平均数量的癌症患者生存期明显缩短 ($P<0.05$)。综上所述, 研究证实 CTCs 数量与肿瘤的发生发展有关, 且在肿瘤高风险人群和亚健康人群中均可以检测到 CTCs。通过 CTCs 检测可以实现肿瘤的风险评估, 早期筛查, 预后评估及监控肿瘤复发转移。

关键词: 循环肿瘤细胞; 高风险; 亚健康; 风险评估; 预后评估

430. 基于 NGS 的液体活检技术在肺癌早期诊断中的应用

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从全球范围内看, 肺癌在全世界普遍流行, 其发病率和死亡率均处于癌症谱前列。肺癌如能在早期发现并进行手术治疗, 生存率是值得肯定的。而晚期肺癌患者生存率较低, 因此, 及早识别出肺癌患者, 可显著改善患者预后。探索和寻找肺癌早期诊断特异性生物标志物和方法, 一直是肺癌相关研究领域的热点。本文主要简述基于 NGS 的液体活检技术在肺癌早期诊断中的一些研究进展。

关键词: 肺癌早期诊断; NGS; 液体活检

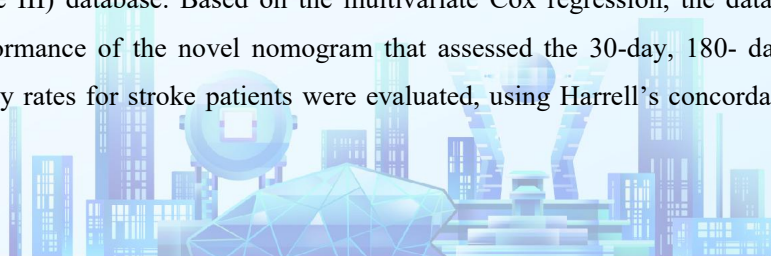
431. A novel nomogram for predicting mortality in patients with stroke: a survival analysis based on the MIMIC-III clinical database

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Background: Stroke is a procedure of sudden cerebral ischemia, which is the second largest cause of death around the world. We aim to develop and validate a nomogram for predicting the overall survival of patients, suffering from stroke, during the initial 24 hours following admission.

Methods: All data utilized in this study were obtained from the MIMIC-III (Medical Information Mart for Intensive Care III) database. Based on the multivariate Cox regression, the data were analyzed and then the performance of the novel nomogram that assessed the 30-day, 180-day, and 360-day all-cause mortality rates for stroke patients were evaluated, using Harrell's concordance index (C-index)



and the area under the receiver operating characteristic curve (AUC). Calibration curve and decision curve (DCA), meanwhile, were introduced to test the clinical value and effectiveness of our prediction model.

Results: A total of 767 patients with stroke were randomly split into a derivation (n=536) and validation (n=231) cohort at a ratio of 7:3. Multivariate Cox regression showed that eleven independent predictors including age, weight, ventilation, cardiac arrhythmia, cancer, OASIS score, DiasBP, bicarbonate, chloride, red blood cells and white blood cells played an important role in the survival of stroke patients. The predicted values were compared using C-indexes, calibration plots and DCA.

Conclusions: The proposed nomogram performed favourable predictive accuracy for stroke, which were provided with the potential to contribute to clinical decision-making and treatment, as well as providing consultation services for patients.

Key words: stroke, nomogram; MIMIC-III database; Mortality rate

432. ADP 核糖基化因子样蛋白 8A：结直肠癌肝转移的潜在标志物

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目的: 远处转移是影响结直肠癌患者预后的重要因素, 肝脏是结直肠癌远处转移的重要靶器官。本研究旨在深入探讨结直肠癌肝转移的关键分子, 为进一步了解结直肠癌肝转移的机制, 发现潜在的分子标志物及治疗靶点奠定基础。

方法: 收集北京大学人民医院手术切除的新鲜结直肠癌肿瘤组织及肝转移组织, 利用定量蛋白质组学技术筛选差异表达的蛋白。从癌症基因组图谱数据库下载结直肠癌基因表达数据及对应临床信息, 分析差异表达的蛋白在结直肠癌样本中的表达及与远处转移和预后的关系, 筛选转移相关的关键分子。通过基因集富集分析和基因共表达分析探讨关键分子参与结直肠癌发生发展的可能机制。通过 CIBERSORT 计算不同免疫细胞在结直肠癌中的浸润水平, 分析关键分子表达与不同免疫细胞浸润的关系。收集随访信息完整的结直肠癌患者肿瘤组织及其癌旁正常组织, 应用免疫组织化学方法检测上述关键分子表达, 分析其与结直肠癌患者预后及远处转移的关系。最后通过 CCK8, 克隆形成以及细胞侵袭迁移实验验证上述关键分子对于结直肠癌生物学行为的影响。

结果: 本研究筛选出结直肠癌肝转移相关蛋白共 102 个。基于癌症基因组图谱数据库中结直肠癌样本的表达谱数据分析表明, ADP 核糖基化因子样蛋白 8A (ADP-ribosylation factor-like 8A, ARL8A) 对结直肠癌远处转移具有较好的预测价值。与正常组织相比, 结直肠癌患者肿瘤组织中 ARL8A 高表达 (5.482 ± 0.286 vs. 6.133 ± 0.383 , $P < 0.001$)。ARL8A 的表达水平与肿瘤浸润深度, 淋巴结转移, 远处转移以及肿瘤分期具有明显相关性 ($P < 0.05$)。ARL8A 高表达与患者不

良预后有关,多因素分析表明年龄,远处转移,肿瘤分期以及 ARL8A 表达为影响结直肠癌预后的独立因素 ($P<0.05$)。ARL8A 可能通过调节上皮间质转化,Wnt 信号通路以及血管形成等参与结直肠癌发生发展。ARL8A 与结直肠癌肿瘤微环境中巨噬细胞极化具有显著相关性。免疫组化检测 ARL8A 高表达结直肠癌患者的平均生存时间短于低表达患者 (41.6 ± 5.3) 个月 vs. (59.5 ± 6.0) 个月, $P<0.05$ 。CCK8,克隆形成以及细胞侵袭迁移实验表明 ARL8A 可以促进结直肠癌细胞的恶性生物学行为。

结论: 本研究鉴定了影响结直肠癌肝转移相关关键分子 ARL8A,可能作为结直肠癌的潜在预后标志物及治疗靶点。

关键词: 结直肠癌;肝转移;ADP 核糖基化因子样蛋白 8A

433. 肺腺癌预后生物标志物和治疗靶点的筛选与研究

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目的: 通过生物信息学分析方法,挖掘并筛选出有前景的生物标志物能够高灵敏度和高特异度预测肺腺癌患者总生存期,寻找肺腺癌新的治疗靶点改善患者预后。

方法: 通过 NCBI-GEO 数据库中包含肺腺癌组织和癌旁正常组织基因表达谱的芯片 GSE32863,基因芯片包括 58 例正常肺组织和 58 例肺腺癌患者癌组织样本,然后筛选标准且 $P<0.05$ 筛选出肺腺癌组织与正常组织之间的差异表达基因。随后将基因芯片的差异表达基因进行基因本体论(Gene Ontology, GO)分析和 KEGG (Kyoto Encyclopedia of Genes and Genomes) 通路富集分析,以确定这些差异表达基因的生物学功能。此外,还构建了蛋白质-蛋白质相互作用(PPI)网络,以找出这些基因之间的相互作用。在 Cytoscape 软件中筛选出核心基因,并在 GEPIA, Kaplan-Meier plotter 数据库进一步验证核心基因的表达水平以及不同表达水平对肺腺癌患者预后的影响。最后借助 HCMBD 数据库分析基因的功能。

结果: 从 GSE32863 中获得了 1268 个差异表达基因,其中 755 个基因显著上调,513 个基因显著下调。根据 GO 功能分析差异基因主要参与细胞粘附,药物反应以及细胞外基质的组成等。KEGG 通路分析主要通过参与细胞外基质的受体作用以及凝血级联反应等信号通路。本研究筛选出 4 个核心基因,进一步通过 GEPIA 数据库,Kaplan-Meier plotter 数据库分析验证发现,其中 KIAA0101, TOP2A, MCM4, CDC20 四个基因在肺腺癌中表达水平平均高于正常组织且均与肺腺癌的预后密切相关,即核心基因表达水平较高的患者总体生存时间较短。结合这些基因的具体功能,最终选出 4 个基因有望成为肺腺癌预后预测生物标志物和潜在的治疗靶点。

结论: 我们筛选出了与肺腺癌发展及预后高度相关的核心基因,有助于进一步了解肺腺癌的分子基础,并有可能成为指导临床肺腺癌患者的治疗靶点和诊断靶点。



关键词：肺腺癌；生物信息学；预后；治疗靶点；生物标志物；差异表达基因

434. 镉对 NCL-H292 细胞生长的影响与 miR-216a-5p 关系

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目的：镉(Cd)在自然界中大多以化合态存在，不仅在环境中蓄积，而且可在生物体内及农作物中富集，能对人体产生很强的致癌性，可危害人体呼吸系统、神经系统、骨骼组织等。人体镉中毒最重要的途径之一就是吸烟经由肺部吸入人体，和肺癌的发生及演进关系密切。本研究旨在探索 miR-216a-5p 在镉中毒所致肺癌中能否作为诊断和预后的潜在癌症生物标志物和治疗靶点。

方法：利用阳离子转染试剂将外源性 miR-216a-5p 模拟物及 FAM 标记的阴性对照转染人肺癌细胞 NCL-H292，氯化镉 (CdCl₂) 处理构建镉致毒模型，cck-8 法测量细胞活力，线粒体膜电位 JC-10 染色法，Annexin-V PE / 7-AAD 染色法测细胞凋亡。通过 miRwalk，RNAinter 数据库进行 miR-216a-5p 靶基因预测，并结合 TCGA，CCLE，Chilibot 中筛选出与肺癌发生相关的靶基因，构建调控网络。

结果：经荧光显微镜观察和茎环 PCR 检测表明 miR-216a-5p 模拟物转染效率达到 83.45±2.71%，miR-216a-5p 表达水平明显上调；20μmol/LCdCl₂ 处理细胞 24h 时癌细胞活力最高 ($P<0.05$)，对照组 OD 值为 1.61±0.12，转染组细胞活力显著下降 ($P<0.05$)。与对照组相比，转染组线粒体膜电位细胞显著上升 ($P<0.05$)，细胞凋亡率为 16.35±1.44%，对照组细胞凋亡 7.58±0.21% ($P<0.05$)。生物信息学分析结果表明 miR-216a-5p 候选靶基因中有多个肺癌发生相关癌基因。

结论：在 96h 内 20μmol/LCdCl₂ 可促进体外培养 NCL-H292 细胞增殖，处理 24h 的促增殖作用最大；miR-216a-5p 转染后细胞增殖减少，凋亡增加，提示 miR-216a-5p 可抑制 CdCl₂ 对 NCL-H292 细胞的促增殖作用，可能和其负向调控肺癌发生癌基因有关。

关键词：氯化镉；肺癌；miRNA；增殖；凋亡

435. 乏氧微环境活化 MXRA5 调控三阴乳腺癌基质重塑介导其侵袭转移的机制研究

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2. 临床三系

3. 科学实验中心

4. 辽宁省肿瘤医院



目的: 三阴性乳腺癌 (triple negative breast cancer, TNBC) 是最具侵袭性的乳腺癌亚型, 因缺乏特异性治疗靶点, 且复发转移率高, 患者整体生存较差。细胞外基质成分 (Extracellular matrix, ECM) 重塑参与肿瘤形成、生存、迁移和侵袭, 乏氧微环境和其关系密切。基质重塑相关蛋白 5 (Matrix remodelling-associated protein 5, MXRA5) 在细胞粘附和基质重建中发挥作用, 但其在 TNBC 中的表达和意义研究尚不明确。

方法: 通过 GEO, TIMER2, GEPIA2, Ualcan, TCGA, GTEx 等数据库分析肿瘤乏氧信号通路, TNBC 侵袭转移相关基因与 MXRA5 关系; 利用阳离子转染试剂 lipofectamine 将 MXRA5 siRNA 及 FAM 标记阴性对照转染 TNBC 细胞系, 低氧处理后, 细胞划痕及 Transwell 小室观察细胞迁移和侵袭; 定量 PCR 和 western 检测乏氧诱导因子-1 α , MXRA5 和 ECM 相关基因分子水平改变。

结果: 生物信息学分析结果表明 MXRA5 作为关键基因 (hub gene) 在 TNBC 侵袭转移的网络调控中处于核心地位; 通过对其关联基因和通路的富集分析, 提示乏氧通路与 MXRA5 表达在 TNBC 中密切相关, 并与肿瘤侵袭转移高度相关; MXRA5 siRNA 转染能显著下调细胞内 MXRA5 mRNA 和蛋白表达水平; 乏氧处理 24h 组, MXRA5 siRNA 转染组细胞划痕愈合速度明显减慢, Transwell 实验可见进入下面小室内的细胞数量明显减少 ($P < 0.05$); MXRA5 和 ECM 相关基因分子水平表达相关。

结论: MXRA5 在 TNBC 发生发展中发挥核心调控作用, 在乏氧微环境中其表达水平与该肿瘤的侵袭转移有关。

关键词: 乏氧; 微环境; 三阴乳腺癌; 基质重塑; 侵袭转移

436. 恶性肿瘤患者外周血 T 淋巴细胞亚型功能评估及其临床意义

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目的: 探讨恶性肿瘤患者外周血 T 淋巴细胞亚型变化规律, 评估肺癌患者化疗及 TKI 治疗前后外周血 T 淋巴细胞亚型分布情况, 为肿瘤治疗预后判断及临床免疫治疗决策提供依据。

方法: 收集 181 例成人恶性肿瘤包括 43 例肺癌患者的临床资料, 选取同时期体检的健康人群作为对照组, 消除性别和年龄的偏倚。选取 127 例健康人群与 156 例恶性肿瘤症患者, 采用流式细胞术检测 CD3⁺T, CD4⁺T, CD8⁺T, NK 和 $\gamma\delta$ T 细胞亚型的分子标记。此外, 对 15 例化疗和 8 例 TKI 治疗肺癌患者, 分别比较其化疗和 TKI 治疗前后外周血淋巴细胞亚型的变化情况。

结果: 恶性肿瘤患者外周血中总 CD3⁺T 细胞, CD4⁺T 细胞的比例下降, CD8⁺T 细胞, NK 细胞的比率上升 ($P < 0.05$)。初始化 CD4⁺和 CD8⁺T 细胞, 中心记忆 CD4⁺和 CD8⁺T 细胞均下降, 同时 CD3⁺CD8⁺CCR7-CD45RA-CD127⁺表型和 CD3⁺CD8⁺CD28⁺表型细胞下降, 而 CD3⁺CD8⁺CD28⁻CD57⁺亚型细胞呈上升趋势 ($P < 0.05$)。此外, CD56⁺/CD56⁻比率倒置,



CD3⁺CD56⁺NKP30⁺,Vδ2⁺T 细胞,功能性 Vδ1⁺ T 细胞,CD3⁺γδTNKP30⁺Vδ1⁺ 和 CD3⁺γδTNKP30⁺Vδ2⁺均下降 ($P<0.05$)。经过化疗后的肺癌患者,功能性 Vδ1⁺γδT 细胞的比率上升,衰竭 CD8⁺T 细胞上升,效应性记忆 CD4⁺T 细胞,总记忆 CD8⁺T 细胞下降 ($P<0.05$)。肺癌患者经过靶向治疗后,初始化 CD4⁺和 CD8⁺T 细胞上升,终末分化 CD4⁺ (CD3⁺CD4⁺CD45RA⁺CCR7⁻) T 细胞下降,中心记忆 CD4⁺和 CD8⁺T 细胞上升,CD3⁺CD8⁺CD28⁺T 细胞上升,Vδ2⁺T 细胞减少 ($P<0.05$)。

结论: 本研究发现恶性肿瘤患者外周血 T 细胞大多处于功能衰竭或衰老状态。①T 细胞衰老和衰竭;②活化的 NK 细胞和功能性 γδT 细胞下调;③初始化 CD4⁺和 CD8⁺T 细胞下降。初始化 CD4⁺T 细胞和初始化 CD8⁺T 细胞对于未治疗的肿瘤患者具有潜在的预测价值。肺癌患者化疗后免疫功能短时间有所回升,但总的记忆 CD8⁺T 细胞的比率下降,提示具有抗肿瘤活性的 T 细胞明显处于功能抑制,化疗可能诱导与促进免疫抑制性的肿瘤微环境。肺癌患者经 TKI 靶向治疗后免疫功能有所提升,但具有抗肿瘤活性的 Vδ2⁺ γδT 亚型细胞经靶向治疗后仍下降,这一现象可能是 TKI 耐药肺癌患者抗肿瘤免疫功能障碍的基础。

关键词: 肺癌;外周血淋巴细胞亚型;T 细胞免疫功能;临床评估

437. 依菲维伦联合放线菌素 D 治疗黑色素瘤细胞作用机制的研究

常会波*

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黑色素瘤恶性程度高,现有的治疗方案对部分病例的治疗无法起到满意的疗效,治疗方案有待优化和提高。我们利用 MTT 实验发现依菲维伦和常见的化疗药物放线菌素 D 联合治疗效果优于单独治疗效果。我们利用 Western Blot 实验发现联合治疗导致 p53 及其通路蛋白的改变。本实验发现依菲维伦和放线菌素 D 联合治疗有效果,其作用可能通过 p53 通路的改变来实现

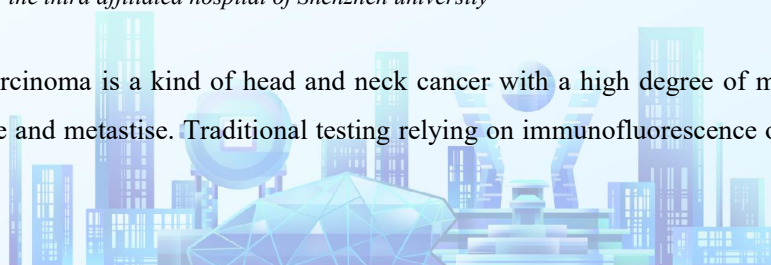
关键词: 黑色素瘤细胞;依菲维伦;放线菌素 D

438. A Single-cell Raman-based Platform for Nasopharyngeal Carcinoma Cell Line Identification and Cancer Discrimination

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Nasopharyngeal carcinoma is a kind of head and neck cancer with a high degree of malignancy, which is easy to relapse and metastasise. Traditional testing relying on immunofluorescence or fluorescent in situ



hybridization were proved to be tedious and expensive. Accurate, quick, and intact diagnosis is important for improving the survival rate of those patients with nasopharyngeal carcinoma. A Raman-based cell assay is a promising tool for evaluating cancer progress. because it can provide abundant varied compound fingerprints of cancer cells in comparison with normal cells, Herein, we developed an efficient and accurate method on a label-free and noninvasive single-cell Raman microspectroscopy (SCRM) platform, to distinguish NPC cell lines 5-8F,6-10B, SUNE1, CNE1, CNE2, C666-1, HK1 from nasopharyngeal normal cell line NPEC1-BMI1. NPC cancer cells and non-cancer cells can be differentiated by analyzing their intrinsic phenotypic Raman spectra at a large scale (5337cm⁻¹ Raman spectra in total). The Raman spectra of glycogen, nucleic acids, and tyrosine in NPC cancer cells were significantly higher than those in non-cancer cells. However, the Raman spectra of lipids in NPC cancer cells were significantly lower than those in non-cancer cells. Those results are consistent with the high expressions of glycogen, nucleic acids, and tyrosine and low expression of lipid in NPC cancer cells. Support Vector Machine (SVM) analysis distinctly differentiates NPC cancer cells from non-cancer cells with 97.85% accuracy. Nasopharyngeal tissues were also clearly distinguished from control tissues with 93.95% accuracy. Together, our study developed an efficient SCRM-based method to evaluate the cells canceration of nasal tissue in advance which shed light on established quick and accurate diagnose during surgery of Nasopharyngeal carcinoma. As a complementary tool, the platform was expected to view the real-time dynamic cancerization status and contributed to improving the diagnosis and operation effects.

Key words: Nasopharyngeal cancer; Raman spectroscopy; Machine learning; Biomarker

439. Research progress on the role and mechanism of ID1 in tumor immunity

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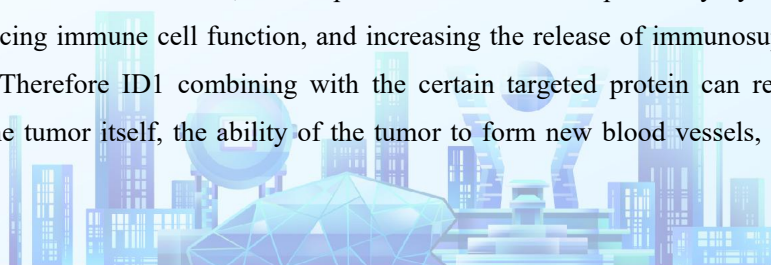
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Differentiation suppressor 1 (ID1) is usually present in the embryo, also in cancer patients and promotes tumor progression. Because the activation of the ID1 gene will inhibit the ability of the immune system to defend effectively, and increase the growth and proliferation of the tumor. ID1 is widely expressed in tumor tissues and closely related to tumor proliferation, migration, and angiogenesis. Recent studies have found ID1 also plays a huge role in tumor immunity. ID1 enables a tumor to escape from immune surveillance, which promotes tumor development by synergizing with tumor antigens, reducing immune cell function, and increasing the release of immunosuppressive factors, to name a few. Therefore ID1 combining with the certain targeted protein can reduce the metastatic potential of the tumor itself, the ability of the tumor to form new blood vessels, and restore the total



immune function of patients through the different methods of treatments. This paper will review the research status and applications of ID1 in tumors and tumor immunity.

Key words: Differentiation inhibitor 1 (ID1); Tumor immunity; Immune escape; Tumor immunotherapy; Targeted protein

440. N6-甲基腺苷 (m6A) 修饰介导结直肠癌免疫微环境特征

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目的: 结直肠癌是一种与肿瘤微环境细胞浸润密切相关的异质性恶性肿瘤。已有相关研究发现 mRNA 的 N6-甲基腺苷 (m6A) 修饰在调节结直肠癌的免疫微环境中起着至关重要的调节作用。然而,目前缺乏适当 m6A 修饰的评估方法是一个重大问题。在这项研究中,我们试图建立基于 m6A 相关免疫基因的肿瘤微环境特征,并研究 m6A 相关基因与肿瘤微环境细胞浸润之间的潜在关联。

方法: 我们综合评估了来自癌症基因组图谱 (TCGA) 的结直肠癌组织和正常结直肠组织的 m6A 修饰模式,并使用 CIBERSORT 算法评估微环境细胞浸润特征。通过已有的文献报道肿瘤微环境中细胞的标记基因,构建免疫相关基因集。相关分析用于鉴定与 m6A 调控因子相关的免疫基因。根据单因素 Cox 回归和 Lasso 回归分析,建立由 m6A 相关免疫基因和肿瘤微环境浸润特征组成的预后风险模型。

结果: 我们开发了一个新的评估系统,以有效预测结直肠癌患者的免疫浸润和预后情况。单因素和多因素 Cox 回归分析发现 m6A 相关免疫基因评分是结直肠癌独立的因素,高 m6A 相关免疫基因评分组患者有着不良的预后。对于肝癌的预后预测效能中,我们发现评分模型在训练队列 (AUC=0.914,3 年) 和验证队列 (AUC=0.890,3 年) 中均显示出良好的预测性能。低评分组的特点是抗原呈递和免疫检查点相关基因的 mRNA 表达水平显著增加,同时我们进一步发现高分组中调节性 T 细胞显著富集,存在免疫抑制状态。最后我们对 stage II-IV 期的结直肠癌患者进行化疗获益评估,我们发现对于 stage III-IV 期的肝癌患者,无论高低评分,术后辅助化疗都能使患者生存获益 ($P=0.001$)。然后对于高分的 stage II 期患者,化疗和无化疗患者在生存时间方面并无显著差异 ($P=0.230$); 对于低评分的 stage II 期患者,接受术后辅助化疗的患者比未接受化疗患者有着显著的生存获益 ($P=0.004$)。

结论: 本研究构建了一个 m6A 相关免疫基因评分系统来检查 m6A 修饰特征在预测结直肠癌免疫微环境浸润水平和预后的能力,此外, m6A 相关免疫基因评分系统有望作为一个独立的预后标志物来预测结直肠癌患者的预后以及为临床医生制定新的临床治疗策略。

关键词: 结直肠癌; N6-甲基腺苷修饰; 肿瘤微环境; 预后; 治疗



441. ITGB5 通过 Wnt/ β -catenin 信号通路促进结直肠癌细胞的转移

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目的: 研究表明, 在多种癌症中都发现了 ITGB5 表达水平的失调。然而, ITGB5 基因在结直肠癌中的作用机制和临床价值尚不清楚。

方法: 通过癌症基因组图谱 (TCGA) 数据库, 基因表达综合数据库 (GEO) 分析, 实时荧光定量 PCR, Western blot 和免疫组化等方法评估结直肠癌组织的 ITGB5 基因转录和转录后水平。通过 GEO 数据库中结直肠癌数据集的临床数据进一步探索 ITGB5 与临床特征和预后的关联。KEGG 通路富集分析探讨 ITGB5 参与的基因功能和信号通路。最后在结直肠癌细胞中敲低 ITGB5 的表达, 研究 ITGB5 对结直肠癌细胞生长、迁移和侵袭的影响以及下游信号通路的调控。

结果: TCGA 数据库发现 ITGB5 基因在多种癌症中均高表达, 实时荧光定量 PCR, Western blot 和免疫组化等方法证实 ITGB5 在结直肠癌组织中表达显著升高 ($P < 0.01$), 并与 TNM 分期、浸润深度、淋巴结转移和远处转移分期显著相关。GSE39582 和 GSE17538 数据集的生存分析表明, ITGB5 的高表达是患者生存预后的高危因素。单因素和多因素 Cox 分析进一步表明 ITGB5 是结直肠癌的独立预后因素。之后我们通过 KEGG 分析发现 ITGB5 高表达广泛富集于细胞外基质、细胞粘附和 ECM-受体相关信号通路。此外我们的研究发现 ITGB5 还参与结直肠癌肿瘤微环境的调控, ITGB5 的表达与 M2 型巨噬细胞显著正相关 ($R = 0.42, P < 0.001$)。最后我们通过结直肠癌细胞株 HCT116 中敲低 ITGB5 的表达, 发现下调 ITGB5 表达会阻断 Wnt/ β -catenin 信号通路从而抑制结直肠癌细胞的增殖和侵袭。

结论: 在本研究中, 我们深入探究了 ITGB5 在结直肠癌中的角色及调控结直肠癌进展的机制, ITGB5 可能是结直肠癌新的预后标志物 and 新的治疗靶点。

关键词: 结直肠癌; ITGB5; 预后; 肿瘤微环境; Wnt/ β -catenin

442. WTAP 通过 DNA 损伤修复在肝细胞癌中发挥功能

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肝细胞癌 (HCC) 是最常见的恶性肿瘤之一, 近年来肝细胞癌的死亡率呈上升趋势。目前肝细胞癌的发生发展机制尚不明确, 亟需对肝细胞癌的有关机制进行深入研究。WTAP 在正常生理过程和肿瘤发生发展中均起到重要调控作用, 而 WTAP 在肝细胞癌中的表达和作用尚无报



道。本课题旨在探究肝细胞癌中 WTAP 的表达和生物学功能,探索其与 DNA 损伤修复的关系,将 DNA 损伤修复过程与 RNA 甲基化相结合,探索 RNA 水平上的 m6A 修饰,从表观遗传学的角度解析发病机制,为开发以 m6A 调节蛋白为靶点的新药提供切入点,同时也为临床探索新的肝癌治疗方法和预后指标奠定基础。

首先,通过生物信息学分析发现,肝细胞癌中 WTAP 表达明显上调,且上调水平与预后密切相关,高表达 WTAP 往往提示预后不良。构建 WTAP 干扰及过表达稳定株后,在肝癌细胞系 7402 和 7721 中进行细胞功能实验。通过克隆形成,CCK8 实验发现干扰 WTAP 表达会抑制肝癌细胞增殖。相应地,流式凋亡检测显示下调 WTAP 表达会促进细胞凋亡。而裸鼠成瘤实验则提示敲低 WTAP 会抑制体内肿瘤形成。功能实验结果均符合 WTAP 在肝癌细胞中作为致癌基因来发挥作用,为进一步明确其作用机制,进行了 Western blot 实验,结果表明干扰 WTAP 会下调 DNA 损伤修复通路的相关蛋白。荧光报告实验则明确表示 WTAP 与 DNA 损伤修复通路中的同源重组修复(HR)相关。随后,通过免疫荧光和中性细胞凝胶电泳实验进一步证实了 WTAP 与 DNA 损伤修复之间存在联系。因此,可以得出结论:在肝细胞癌中 WTAP 通过抑制 DNA 损伤修复过程来发挥癌基因作用。

关键词: WTAP; 肝细胞癌; DNA 损伤修复; 预后; 增殖; 凋亡

443. microRNA 海绵沉默人肝癌和骨肉瘤细胞中 microRNA-122 肿瘤抑制功能的研究

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目的: microRNA-122 (miR-122) 是一种高度丰富的肝脏特异性 miRNA, 占总肝脏 miRNA 表达的 70%, 与丙型肝炎病毒感染和复制有关, 调节肝脏代谢和肝细胞癌发生。miR-122 的过表达通过抑制血管生成影响肝细胞癌肝内转移, 并通过靶向调节参与转移的去整合素, 金属蛋白酶 10 (ADAM10) 和 ADAM17 发挥其作用。

方法: 利用具有长期作用效果的 miR-SP 方法, 通过慢病毒介导产生 microRNA-122 海绵 (miR-122-SP), 并于 Huh7 肝癌细胞系和 U2OS 骨肉瘤细胞系中鉴定其沉默作用。通过细胞增殖, 克隆形成, 半胱天冬酶-3/7 活性实验, 细胞侵袭和细胞划痕实验来检测 miR-122-SP 处理后细胞的增殖, 侵袭和转移能力。并将感染 Huh7-ctrl 或 Huh7-miR-122-SP 慢病毒的细胞皮下接种到雌性无胸腺裸鼠 (3-4 周龄) 体内, 每 4 天用游标卡尺测量植入的肿瘤体积, 在接种 4 周后通过颈椎脱臼处死小鼠, 对肿瘤进行称重。

结果: miR-122-SP 有效地阻断异位 miR-122 并恢复靶向 CCNG1, Bcl-w 和解聚素和金属蛋白酶 10 的 miR-122 的表达。此外, miR-122-SP 过表达在 Huh7 人肝癌细胞, U2OS 骨肉瘤细胞中拯救了



异位 miR-122 抑制增殖,抑制细胞迁移和侵袭,抑制 G1 期细胞周期和激活半胱天冬酶-3 / 7 的作用。同时, miR-122-SP 还敲低 Huh7 中内源性 miR-122 的表达并促进体内肿瘤发生。

结论: 总之,我们设计的 miR-122-SP 可以在体内外成功沉默 miR-122 抑制肿瘤发生的作用,表明在低表达 miR-122 的肝癌模型中可通过 miR-122-SP 研究 miR-122 在肝脏发育和肿瘤发生方面的功能。

关键词: microRNA

444. DNA 免疫技术制备人 CLDN18.2 单克隆抗体

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目的: 应用 DNA 免疫技术制备 CLDN18.2 特异性单克隆抗体并对其特性和在免疫检测中的应用进行鉴定,为 CLDN18.2 的抗体药物研发奠定基础。

方法: 将体内转染试剂和 pcDNA3.1-CLDN18.2 质粒在体外混合后经尾静脉注射免疫小鼠两次,用细胞 ELISA 筛选效价较高的小鼠经过杂交瘤融合技术和单克隆筛选,制备 CLDN18.2 的特异性单克隆抗体。获得杂交瘤后,通过制备小鼠腹水纯化获得抗体。然后,对获得的单克隆抗体的亲和力和特异性及其在细胞 ELISA,流式细胞术,细胞免疫荧光和免疫沉淀等实验中的应用进行鉴定。

结果: 通过 DNA 免疫技术,获得了 15 株有较好特异性的 CLDN18.2 单克隆抗体,它们与 CLDN18.2 结合的 EC₅₀ 均在纳摩尔或亚纳摩尔级;它们可在 ELISA,免疫沉淀,流式细胞术和细胞免疫荧光实验中用于对 CLDN18.2 的特异检测,但它们均不能用于 Western blot 实验。

结论: 成功制备并获得了 15 株可识别蛋白天然构象,亲和力高,特异性好的小鼠抗人 CLDN18.2 单克隆抗体,为 CLDN18.2 抗体药物的研发奠定了重要基础。

关键词: CLDN18.2; DNA 免疫; 单克隆抗体

445. 病理技师在日常工作中应掌握肿瘤标志物的应用

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在病理学诊断研究中,免疫组织化学技术的作用和意义非常重要,它可以确定细胞类型,辨认细胞产物,了解分化程度,研究肿瘤起源或分化表型,确定肿瘤分期,发现微小转移灶,鉴定病变性质,指导治疗和预后,辅助病理诊断和分类,寻找感染病因。我们病理技师在日常的工作中,既要熟练掌握免疫组化技术,同时还要熟悉肿瘤标志物在病理诊断中的应用,这不仅能够提高



我们正确观察组化结果的判断能力，同时对于免疫组化质量的控制也起到了重要作用。以下我们就肿瘤标志物在病理诊断中的应用做一些探讨。

关键词：病理技师；肿瘤标志物；应用

446. 免疫组织化学标准化的探讨

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免疫组织化学在当今病理诊断中的作用已经得到广泛的认同，具有特异性强、敏感性高、程序相对一致等特点，并且已成为病理诊断中不可或缺的重要辅助技术。尽管免疫组化的理论相对简单，但方法与步骤比较繁琐，在实际应用中还存在不少问题，直接或间接地影响了最终的病理诊断。要想得到可靠的实验结果，最重要的是将免疫组化技术的全部程序包括：标本固定、包埋切片、烤片、脱蜡、抗原修复、抗原抗体孵育时间、DAB显色、苏木素衬染、封片等形成标准化。

关键词：免疫组织化学；标准化

447. RNA demethylase ALKBH5 prevents colon adenocarcinoma progression by posttranscriptional activation of PER1 in an m6A-YTHDF2-dependent manner

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Abstract

Background: N6-methyladenosine (m6A) is the most abundant reversible methylation modification of eukaryotic mRNA, and it plays vital roles in tumorigenesis. This study aimed to explore the role of the m6A demethylase ALKBH5 in colon adenocarcinoma (COAD).

Methods: The expression of ALKBH5 and its clinicopathological impact were evaluated in COAD cohorts. The effects of ALKBH5 on the biological characteristics of COAD cells were investigated on the basis of gain-of-function and loss-of-function analyses. Subcutaneous and orthotopic models further uncovered the role of ALKBH5 in tumour growth. mRNA and m6A sequencing and assays of m6A methylated RNA immunoprecipitation-qPCR (MeRIP-qPCR) were performed to identify the targeted effect of ALKBH5 on PER1. P53-binding sites in the ALKBH5 promoter were investigated by ChIP and luciferase assays to reveal the interplay between ALKBH5 and PER1-activated ATM-CHEK2-P53/CDC25C signalling.



Results: ALKBH5 loss characterized the occurrence and poor clinicopathological manifestations in patients with COAD. Overexpression of ALKBH5 reduced tumoural proliferative, migrative, invasive activities in vitro and ameliorated tumour growth in vivo, whereas ALKBH5 knockdown facilitated COAD progression. Mechanistically, ALKBH5 posttranscriptionally activated PER1 by m6A demethylation in an m6A-YTHDF2-dependent manner. PER1 upregulation led to the reactivation of ATM-CHK2-P53/CDC25C signaling, which inhibited cell growth. P53-induced activation of ALKBH5 transcription acted as a feedback loop regulating the m6A modifications in COAD.

Conclusion: ALKBH5 serves as a COAD suppressor by regulating the posttranscriptional activation of PER1 through m6A abolishment, which may highlight a demethylation-based approach for COAD diagnosis and therapy.

Key words: colon adenocarcinoma; m6A; ALKBH5; PER1

448. Concordance Analysis of Mismatch Repair System and Microsatellite Instability

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Purpose: To evaluate the consistency of the results about immunohistochemistry (IHC) testing in mismatch repair system and microsatellite instability (MSI).

Methods: Forty-five in patients with cancer who were tested for mismatch repair protein (MMR) and microsatellite instability (MSI) at the same time in our hospital from October 2019 to June 2021 were selected. The mismatch repair proteins MLH1, PMS2, MSH2 and MSH6 were detected by IHC, and the changes of MSI gene level were detected by PCR and capillary electrophoresis. The consistency of MMR and MSI was analyzed and compared.

Results: Tumor cell mismatch repair protein (dMMR) was expressed in 35 cases and normal in 10 cases. There were 30 cases of highly unstable MSI-H and 15 cases of microsatellite-stabilized MSI-L or MSS. The consistency of MMR and MSI was 85.71% (30/35). Among the 5 cases of inconsistency, the expression of MMR was PMS2(-) in 3 cases and MSH2(-) in 2 cases.

Discussion: The mismatch repair system is highly correlated with the microsatellite system, but it is not equal, and can not be diagnosed by a single detection result. The expression of the mismatch repair proteins MLH1, PMS2, MSH2 and MSH6 in tumor tissues can be combined with the level of MSI gene to diagnose, judge the prognosis, and guide drug use.

Key words: Mismatched Repair system; Microsatellite Instability; MSI-H; Consistency



449. A novel nomogram to predict mortality in patients with stroke: a survival analysis based on the MIMIC-III clinical database

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Background: Stroke is a procedure of sudden cerebral ischemia, which is the second largest cause of death around the world. We aim to develop and validate a nomogram model to predict the mortality in ICU patients, suffering from stroke.

Methods: All data involved in this study was extracted from the Medical Information Mart for Intensive Care III database (MIMIC-III). Based on the multivariate Cox regression, the data was analyzed and then the performance of the novel nomogram that assessed the patient's overall survival at 30, 180, and 360 days after a stroke was evaluated, using Harrell's concordance index (C-index) and the area under the receiver operating characteristic curve (AUC). Calibration curve and decision curve (DCA), meanwhile, were introduced to test the clinical value and effectiveness of our prediction model.

Results: A total of 767 patients with stroke were randomly split into a derivation (n=536) and validation (n=231) cohort at a 7:3 ratio. Multivariate Cox regression showed that eleven independent predictors including age, weight, ventilation, cardiac arrhythmia, cancer, OASIS score, DiasBP, bicarbonate, chloride, RBC and WBC played a significant role in the survival of stroke individuals. The nomogram model was validated basing on C-indexes, calibration plots and DCA.

Conclusions: The plotted nomogram performed a quite accurate ability of predicting the stroke ending, which were equipped with the potential contributing to clinical decision-making and treatment, as well as providing consultation services for patients.

Key words: stroke; nomogram; MIMIC-III; mortality

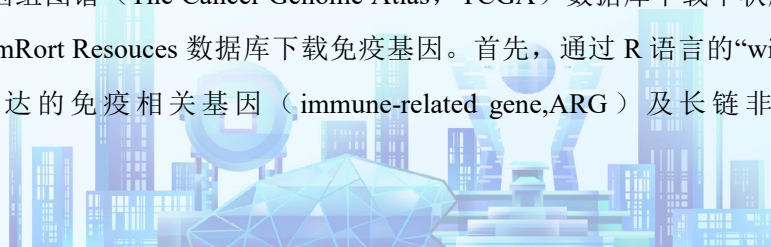
450. 基于生物信息学方法构建甲状腺癌免疫相关 lncRNA 预后评估模型

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目的: 基于 TCGA 数据库筛选出预测甲状腺癌患者预后的免疫相关长链非编码 RNA 并构建预后评估模型。

方法: 从肿瘤基因组图谱 (The Cancer Genome Atlas, TCGA) 数据库下载甲状腺癌临床及转录组数据, 从 ImmPort Resources 数据库下载免疫基因。首先, 通过 R 语言的“wilcox.test”分析甲状腺癌差异表达的免疫相关基因 (immune-related gene, ARG) 及长链非编码 RNA (long



noncoding RNA ,lncRNA),其次, Spearman 相关性分析筛选出与差异表达的免疫相关 lncRNA 并通过单因素及多因素 COX 分析筛选独立预后因子并构建预后评估模型。最后, 分析该模型与甲状腺癌患者临床病理特征及预后的相关性。

结果: 共筛选出 128 个在甲状腺癌中差异表达的免疫相关 lncRNA ($P<0.05$), 通过单因素 COX 分析进一步筛选出 26 个免疫相关 lncRNA 与预后相关 ($P<0.05$), 多因素 Cox 分析得到了 7 个作为独立预后因子的免疫相关 lncRNA (LINC01614,AC121757.1, LINC02861,FAM111A-DT,AC006058.1,LINC02454) 并构建了预后评估模型。基于模型风险评分将患者分为高、低风险组, 高风险组患者 10 年总生存期 (overall survival,OS) 为 99.8%, 低风险组患者 10 年 OS 为 73.5%。且该预后评估模型具有较高准确性 (AUC=0.997)。基于该模型及临床病理特征的 COX 分析结果显示, 预后评估模型风险评分是 OS 的独立预测因子 ($P<0.05$), 高风险评分是患者 OS 不良的危险因素。

结论: 基于 7 个独立预后因子 (LINC01614,AC121757.1, LINC02861,FAM111A-DT,AC006058.1 及 LINC02454) 构建的免疫相关 lncRNA 预后评估模型,有助于临床医生对患者个体化预后的评估, 筛选出高危人群, 同时为甲状腺癌的免疫相关 lncRNA 的机制研究提供理论基础。

关键词: 甲状腺癌; 预后评估模型; 生物信息学

451. 生物标志物在甲状腺癌免疫微环境的作用再认识

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目前, 甲状腺癌 (TC) 是发病率最高的内分泌恶性肿瘤, 既往 TC 发病机制的研究主要集中在肿瘤细胞突变方面, 而忽视肿瘤微环境对 TC 发生发展的影响。近年来, 随着甲状腺癌免疫微环境深入研究, 甲状腺癌细胞, 免疫细胞, 可溶性分子相互作用关系备受广泛关注。本文重点介绍 TC 免疫微环境中的免疫细胞, 生物标志物包括可溶性介质, 免疫检查点, 酶类, 免疫相关分子相互调节关系, 以及 TC 细胞免疫逃避的机制和治疗策略。有助于深入认识甲状腺癌免疫调控微环境。

关键词: 甲状腺癌; 免疫微环境; 免疫逃避; 生物标志物

452. Intratumoral CD8+ T Cell as a Potential Positive Predictor for Treatment of Chemo-immunotherapy in PD-L1 Negative Advanced Gastric Cancer Patients

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Background: As a positive therapeutic indicator, PDL1 has been studied in several types of malignancies.

It was demonstrated that CPS PDL1 positive patients of advanced gastric cancer (GC) could benefit from specific immune checkpoint inhibitors (ICI) for first-line, and second-line or subsequent therapy. However, whether the application of ICI could lead to better clinical outcome in advanced GC patients who were negative for PDL1 remains further explore.

Method: We retrospectively enrolled 26 advanced GC patients who were treated by chemoimmunotherapy in Shenzhen Hospital of Peking University and evaluated for clinical characteristics. Peritumoral and intratumoral Tumour-infiltrating lymphocytes (TIL) were detected by mIHF among these patients. The correlation between PFS and clinical characteristics including TIL was analyzed by univariate survival analysis and multivariate Cox proportional hazards analysis.

Result: In 26 patients, 5 patients (19.2%) experienced complete response (CR), 9 patients (34.6%) experienced partial response (PR), while 7 patients (26.9%) experienced stable disease (SD). Compared with non-responders, higher intratumoral infiltrating CD8⁺ T cells instead of other subtypes were detected in CPS PDL1 negative Patients who respond to chemoimmunotherapy. Further analysis revealed that CD8⁺ TIL was a predictive biomarker for PFS to chemo-immunotherapy in CPS PDL1 negative patients.

Conclusion: For CPS PDL1 negative advanced GC patients, intratumoral CD8⁺ TIL may be a potential positive predictor for treatment of chemo-immunotherapy.

Key words: Advanced Gastric Cancer; PDL1; chemo-immunotherapy; biomarker

453. 合理预测 HCC 患者半肝切除术安全性的研究

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目的: 寻找能够有效预测肝细胞肝癌患者行半肝切除术后预后不良的危险因素及方法,并评估其应用价值。

方法: 对南通大学附属南通第三人民医院 2016 年 1 月至 2020 年 8 月行半肝切除术并符合本研究纳入标准的 35 例 HCC 患者的临床病例资料进行回顾性分析,利用术前 CT 及术中排水法测算标准残肝体积 (SRLV),肝脏瞬时弹性成像技术测定患者的肝硬度值 (LSM),根据术后患者有无发生肝功能不全分组,采用 χ^2 检验和多因素 Logistic 回归对包括 SRLV 和 LSM 在内的 25 个因素进行术后肝功能不全的相关因素分析;采用 MedCalc 19.0.4 工作特征曲线 (ROC) 对半肝术后不同肝纤维化分期 SRLV 临界值和半肝术后发生肝功能不全 SRLV 临界值进行比较分析;尝试结合 Child-Pugh 评分构建新型肝储备评估模型,并评估其预测肝功能代偿的应用价值。



结果：相关因素分析显示 LSM,SRLV 与患者术后肝功能不全相关 ($t=-3.020, 3.176; P<0.01$)。多因素 Logistic 回归分析显示, $LSM\geq 25kPa, SRLV\leq 290mL/m^2$ 为术后肝功能不全发生的独立危险因素 ($OR=6.254, 5.686; P<0.05$)；术后 S2~S3 及 S4 期肝纤维化的患者的 SRLV 临界值分别为 $0.25734L/m^2$ 和 $0.31092L/m^2$ ；而术后肝功能不全 S2~S3 及 S4 期肝纤维化患者的 SRLV 临界值均为 $0.28542L/m^2$ ；此外, 分析显示, 新型肝储备评估模型在预测患者术后肝功能良好及不良的准确率分别为 100%及 91.3%, 均高于 Child-Pugh 评分对患者术后肝功能的预测 (54.8% 及 $25\%, P<0.05$)。

结论：对于伴中、重度肝纤维化的患者, 当预计的 $SRLV>0.31092L/m^2$, 应用新肝储备评估模型预测术后肝功能代偿良好的, 行半肝切除是安全的；而 $SRLV\leq 0.28542L/m^2$ 时, 新肝储备评估模型预测术后肝功能代偿不良的, 半肝切除术后发生肝功能不全的几率较大, SRLV 和 LSM 可作为评估 HCC 行半肝切除安全指标, 新型肝储备评估模型在对半肝手术患者肝脏储备功能的评估方面具有良好前景。

关键词：肝细胞癌；半肝切除术；预后；标准残肝体积；肝硬度值

454. Identification of potential core genes in colorectal cancer using bioinformatics analysis

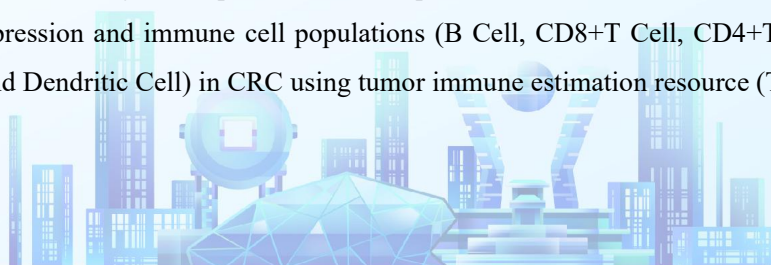
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Background: Colorectal cancer (CRC) is a common human malignancy worldwide. The tumorigenesis mechanism in CRC is unclear.

Materials and methods: To explore potential therapeutic targets for CRC, we analyzed 3 microarray datasets (GSE20347, GSE38129, and GSE67269) derived from the gene expression omnibus (GEO) database. Then, the GEO2R tool was used to screen out differently expressed genes (DEGs) between CRC and normal tissue. Gene ontology function and kyoto encyclopedia of genes and genomes pathway enrichment analysis were performed using the database for annotation, visualization and integrated discovery to identify the pathways and functional annotation of DEGs. Protein-protein interaction of these DEGs was analyzed based on the search tool for the retrieval of interacting genes database and visualized by Cytoscape software. In addition, we used encyclopedia of RNA interactomes (ENCORI), gene expression profiling interactive analysis (GEPIA), and the human protein atlas to confirm the expression of hub genes in CRC. Finally, GEPIA was used to evaluate the prognostic value of hub genes expression in CRC patients and we estimated the associations between hub genes expression and immune cell populations (B Cell, CD8+T Cell, CD4+T Cell, Macrophage, Neutrophil, and Dendritic Cell) in CRC using tumor immune estimation resource (TIMER).



Results: In this study, 707 DEGs (including 385 upregulated genes and 322 downregulated genes) and 6 hub genes (cyclin B1 [CCNB1], cyclin dependent kinase 1 [CDK1], aurora kinase A [AURKA], ubiquitin conjugating enzyme E2C [UBE2C], cyclin A2 [CCNA2], and cell division cycle 20 [CDC20]) were identified. All of the 6 hub genes were highly expressed in CRC tissues. Among of them, only CCNB1 and CDC20 were associated with stage of CRC and all of them were not associated with survival time of patients.

Conclusion: DEGs and hub genes were confirmed in our study, providing a thorough, scientific and comprehensive research goals for the pathogenesis of CRC.

Key words: colorectal cancer; hub genes; expression profiling data; bioinformatics analysis; differently expressed genes

455. 以外泌体为基础的液体活检在胰腺癌诊断中的研究现状与进展

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摘要: 胰腺癌是一种恶性程度极高的消化系统肿瘤,因缺乏敏感有效的检测标志物,多数患者就诊时已处于晚期,治疗手段有限,预后极差,因此早期诊断是患者能及时治疗,改善预后的最有效途径。外泌体是由细胞分泌的细胞外囊泡,具有脂质双分子膜结构保证内含的大量生物活性物质稳定存在,可确切反映亲代细胞特征,并且广泛存在于各种体液中可无创,方便,实时提取,具有成为肿瘤早期诊断标志物的潜力。既往研究表明,与传统的诊断方法相比,外泌体在各类癌症的早期诊断中表现出更高的敏感性和特异性。本文就外泌体在胰腺癌早期诊断中的研究现状和进展作一综述。

关键词: 胰腺癌; 外泌体; 诊断; 液体活检

456. ELERA 疗复杂 HAE 单中心诊疗经验

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目的: 总结离体肝切除联合自体肝移植 (Ex vivo Liver Resection and Autotransplantation, ELRA) 治疗终末期肝泡型包虫病 (Hepatic alveolar echinococcosis, HAE) 的单中心诊疗经验。

方法: 回顾性分析青海大学附属医院自 2015 年 1 月份至 2020 年 12 月 1 日期间收治的 13 例应用自体肝移植术治疗肝泡型包虫病患者的临床资料及随访资料。



结果：13 例患者成功行全离体/半离体肝切除联合自体肝移植术，术中无死亡。标准肝体积中位数 1118（991-1336）ml；残肝体积中位数 634（441-1338）ml；预留肝质量 520-1355g，平均 865.4g；手术时间 9.7-18.5h，平均 14.15h；无肝期 226~365min，平均为 289.23min；术中失血量中位数 1900（300-4000）mL；输入红细胞悬液中位数 7.5（3-20）u，住院时间中位数 32（9-77）d；术后发生并发症 9 例，Clavien-Dindo 分级在Ⅲ级及以上者 7 例；术后死亡 4 例。术后 9 例患者获访，随访时间为 2-63 个月，中位随访时间为 43 个月。1 例患者手术后第 8 个月反复出现腹胀并大量胸腹水和凝血功能障碍，考虑小肝综合征可能，于术后第 13 个月给予肝右叶胆管 PTCD 穿刺引流，肝左静脉-下腔静脉血管支架植入后，上述症状逐渐缓解。随访期间 1 例患者出现 HAE 复发，考虑为术中切口种植。

结论：自体肝移植是治疗终末期复杂肝泡型包虫病最有价值的一项治疗措施，术前精确的肝脏功能评估，术中个体化的管道重建，术后病情精确的管理，可取得较好的治疗效果。

关键词：自体肝移植术；棘球蚴病；预后；并发症

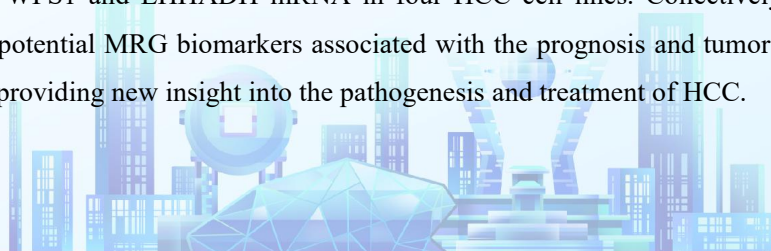
457. Multi-omics analyses of the expression and prognostic signatures of metabolism-related genes in hepatocellular carcinoma

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Hepatocellular carcinoma (HCC) is a common malignant tumor with relatively high malignancy and rapid disease progression. Metabolism-related genes (MRGs) are involved in the pathogenesis of HCC. This study explored potential key MRGs and their effect on T-cell immune function in the tumor immune microenvironment to provide new insight for the treatment of HCC. Of 456 differentially expressed MRGs identified from TCGA database, 21 were screened by MCODE and cytoHubba algorithms. From the key module, GAD1, SPP1, WFS1, GOT2, EHHADH, and APOA1 were selected for validation. The six MRGs were closely correlated with survival outcomes and clinicopathological characteristics in HCC. Receiver operating characteristics analysis and Kaplan-Meier plots showed that these genes had good prognostic value for HCC. Gene set enrichment analysis of the six MRGs indicated that they were associated with HCC development. TIMER and GEPIA databases revealed that WFS1 was significantly positively correlated and EHHADH was negatively correlated with tumor immune cell infiltration and immune checkpoint expression. Finally, qRT-PCR confirmed the expression of WFS1 and EHHADH mRNA in four HCC cell lines. Collectively, the present study identified six potential MRG biomarkers associated with the prognosis and tumor immune infiltration of HCC, thus providing new insight into the pathogenesis and treatment of HCC.



Key words: hepatocellular carcinoma; Metabolism-related genes; Prognosis; immune checkpoint; tumor infiltrating

458. FAT4-Hippo 信号通路下调长链非编码 RNA ZFH4-AS1 抑制卵巢癌的侵袭及转移

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目的: 卵巢癌是女性最致命的恶性肿瘤之一。越来越多的证据表明, 长链非编码 RNA (long non-coding RNAs, lncRNAs)通过调控肿瘤发生和发展的关键通路参与了人类肿瘤的发生。本研究旨在探讨 lncRNA ZFH4-AS1 在卵巢癌中与 Hippo 信号通路相关的调控机制。

方法: 首先进入 GEO 数据库进行微阵列分析, 筛选与卵巢癌相关的差异 lncRNA。通过异位表达, 敲除和记录分析实验, 确定 lncRNA ZFH4-AS1 在卵巢癌中的功能作用。检测 lncRNA ZFH4-AS1,YAP 的表达情况, 验证 lncRNA ZFH4-AS1 与 TAF4 的靶向关系。检测细胞增殖, 侵袭,迁移,细胞周期,凋亡情况。用肿瘤异种移植裸鼠检测肿瘤的生长和转移情况。

结果: lncRNA ZFH4-AS1 在卵巢癌组织中高表达, 而 FAT4 在卵巢癌组织中低表达。FAT4 是 lncRNA ZFH4-AS1 的靶基因, 沉默 lncRNA ZFH4-AS1 增加了 FAT4 的表达, 降低了 YAP 的表达。此外, 敲除 lncRNA ZFH4-AS1 可以抑制卵巢癌细胞的增殖,迁移,侵袭和肿瘤的生长, 阻断细胞周期的进入, 同时通过抑制 Hippo 信号通路促进细胞凋亡。

结论: 综上所述, 我们的研究结果表明 lncRNA ZFH4-AS1 沉默通过抑制 TAF4 激活 Hippo 信号通路, 从而抑制卵巢癌的发生发展。

关键词: FAT4-Hippo 信号通路; 卵巢癌; ZFH4-AS1

459. Clinical implications of XPO1 mutations in NSCLC patients with immunotherapy

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Introduction: The nuclear export protein exportin 1 (XPO1) regulates the export of a range of cargoes from the nucleus to the cytoplasm, and plays an important role in the maintenance of cellular homeostasis. Previous studies indicated that non-small-cell lung cancer (NSCLC) patients with XPO1 mutations were associated with poorer survival. However, up to now, the approaches for XPO1-inhibitors are still challenging, and the definite efficacy for XPO1 blockade is still undetermined in

several cancer types including NSCLC. Therefore, finding novel strategies is urgently needed to improve the survival for XPO1-mutant NSCLC patients. Interestingly, NSCLC patients with XPO1 mutations were more likely to have high tumor mutational burden (TMB), which suggested that immune checkpoint inhibitors (ICIs) could serve as an option for these patients. Nonetheless, as far as we known, there is no study investigate the efficacy of ICIs in NSCLC patients with XPO1 mutations.

Methods: We integrated the MSK-TMB, POPLAR and OAK cohorts to evaluate the association between XPO1 mutation and the survival of NSCLC patients. A total of 350 ICI-treated NSCLC patients from the MSK-TMB cohort and 429 atezolizumab-treated NSCLC patients with available genomic sequencing data (biomarker evaluable population) from the POPLAR and OAK cohorts were included in this study. Importantly, XPO1 mutations were defined as any nonsynonymous or fusion mutations.

Results: The incidence of XPO1 mutations was 1.2 % (9 of 779) in the entire cohort. Detailly, most of patients were non-squamous (6 of 9, 66.7 %), were male (7 of 9, 77.8 %), had missense mutation type for XPO1 gene (7 of 9, 77.8 %) and exhibited high TMB scores (above 10 mutations/Mb) (7 of 9, 77.8 %). At first, we analyzed the overall survival (OS) in NSCLC patients with XPO1 mutations and their wild type counterparts. Unfortunately, we found patients harboring XPO1 mutations had comparable OS compared with those without the mutation (median OS, 19 months versus 12 months, $P = 0.186$). Considering the inferior impact of STK11/KEAP1 mutations on the efficacy of ICIs, which was already disclosed both in our cohorts and other studies, we further divided patients into pure XPO1-mutant, wild type and XPO1-STK11/KEAP1 mutant groups. Surprisingly, NSCLC patients with pure XPO1 mutations had significantly longer OS than wild type and XPO1-STK11/KEAP1 mutant cohorts (median OS, not reached versus 12 months versus 4 months, $P = 0.039$).

Conclusions: Collectively, for the first time, we investigated the role of XPO1 mutations in NSCLC patients with ICIs treatment. Our results suggested that there was no significant difference in the efficacy of ICIs therapy between NSCLC patients with and without XPO1 mutations. However, considering the comutation status of STK11/KEAP1, we demonstrated that patients with pure XPO1 mutations were correlated with longer survival and could serve as a favorable prognostic biomarker in NSCLC. Nevertheless, the small sample of XPO1-mutant NSCLC patients should not neglect, and further studies will be necessary to verify our results.

Key words: XPO1, NSCLC; Immunotherapy

460. Alstonine inhibits proliferation of osteosarcoma cells in vitro and tumor growth *in vivo* through AMPK-activation and PGC-1 α /TFAM up-regulation

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Osteosarcoma, a leading malignant tumor of bones is diagnosed mostly in adolescents and young adults worldwide. The present study investigated alstonine as anti-osteosarcoma agent in vitro as well as in vivo and evaluated the under mechanism. Treatment with alstonine led to a significant ($P<0.05$) reduction in MG63 and U-2OS cell viability. Alstonine treatment of MG63 and U-2OS cells caused a significant reduction in colony formation compared to the control cells. Viability of osteoblasts was not affected by alstonine treatment in 1.25 to 20 μM concentration range. In alstonine treated MG63 and U-2OS cells apoptotic cells increased significantly ($P<0.05$) compared to the control cells. Moreover, in MG63 and U-2OS cells treatment with alstonine caused a prominent increase in expression of cleaved caspase-9, caspase-3 and PARP. Treatment of MG63 and U-2OS cells with alstonine caused a prominent increase in AMPK α (Thr172) phosphorylation and elevated count of mtDNA copies compared to the untreated cells. Alstonine treatment of the cells caused a remarkable increase in expression of PGC-1 α and TFAM proteins. Treatment of the mice with alstonine at 5 and 10 mg/kg doses for 30 days caused a significant ($P<0.05$) reduction in xenograft growth. Expression of PGC-1 α and TFAM proteins in tumor tissues of the mice treated with alstonine was significantly ($P<0.05$) raised compared to the control group. Thus, alstonine inhibits osteosarcoma cell growth and activates apoptosis through AMPK dependent pathway. Therefore, alstonine may be considered for treatment of osteosarcoma as it effectively arrests tumor growth in mice.

Key words: Alstonine; Osteosarcoma; Mitochondrial biogenesis; Chemotherapy; Alkaloids

461. Significance of Tumor Mutation Burden in Immune Infiltration and Prognosis in Adrenal Cortical Carcinoma

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Objective: Adrenal cortical carcinoma (ACC) is a rare endocrine malignant tumor, and its incidence peaks in children under 10 years old and adults between 40 and 50 years old. Tumor mutation burden (TMB) and immune infiltration have been reported to predict the response to immunotherapy. In this study, we aimed to explore the association of TMB with immune infiltration and prognosis in adrenal cortical carcinoma.

Material and methods: The data of adrenal cortical carcinoma used for analyses was downloaded from The Cancer Genome Atlas (TCGA) database. The mutation data was sorted using “maftools” R package. TMB was estimated and then patients were divided into two groups based on TMB. The association of TMB with prognosis and clinical characteristics was explored. Differential analysis between two TMB groups was performed using “DESeq2” R package to identify differentially expressed genes (DEGs). The function enrichment analyses of DEGs were conducted to screen critical pathways. Besides, DEGs were further filtered to identify two hub genes, based on which a risk score model and nomogram for predicting prognosis were conducted, and the validation was performed using three

datasets from Gene Expression Omnibus (GEO) database. Finally, CIBERSORT algorithm and TIMER database were used to assess the effect of TMB and hub genes on immune infiltration.

Results: C>T mutation was the most common. TTN, TP53, MUC4, MUC16, CTNNB1, PKHD1, NF1, CNTNAP5, PCDH15 and ASXL3 were the top 10 genes with mutation frequency. The overall survival (OS) of patients in the high TMB group was significantly worse than that in the low TMB group ($P < 0.001$). Functional enrichment analysis indicated that the high TMB group was significantly enriched in many immune-related pathways. The risk scoring model was verified by receiver operating characteristic (ROC) curve and calibration curve, which showed high predictive ability. Among the differentially expressed genes, 34 key genes related to immunity were screened out by the ImmPort database. Through survival analysis, we obtained 6 immune-related differentially expressed genes associated with survival. In terms of immune infiltration, activated CD4⁺ memory T cells ($P = 0.048$) in the high TMB group were more infiltrated than those in the low TMB group, while non-activated CD4⁺ memory T cells ($P = 0.042$) and activated natural killer cells ($P = 0.013$) were more infiltrated in the low TMB group than in the high TMB group.

Conclusion: In adrenal cortical carcinomas, TMB was associated with prognosis. The risk score models can better predict prognosis. The immune-related differentially expressed genes (TMSB15A, MMP9, TNFAIP3, BIRC5, LTBP1 and AMH), which were negatively correlated with prognosis in ACC patients. The association between TMB with immune infiltration can help improve the predicting methods for the response to immunotherapy.

Key words: adrenal cortical carcinoma; tumor mutation load; immune infiltration; prognosis

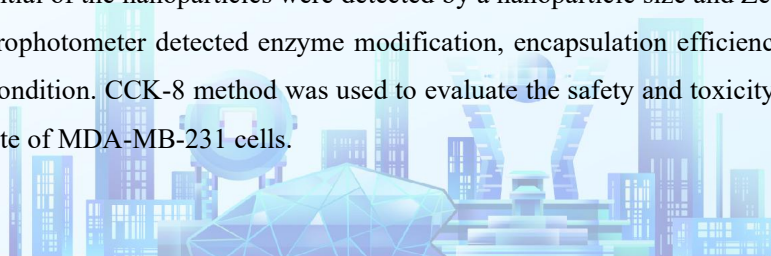
462. Hyaluronidase-modified pH-Responsive Nanomicelles to Enhance the Efficiency of Photodynamic Therapy

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Objective: Poor permeability is a major obstacle of nanoparticle-based photodynamic therapy. Hyaluronidase has been confirmed to enhance the penetration of nanoparticles in tumors. In this study, hyaluronidase-modified pH-responsive nanomicelle has been designed to enhance the diffusion in solid tumors for photodynamic therapy to improve the therapeutic efficiency.

Methods: The pH-responsive IR780-loaded nanomicelles were prepared by nanoprecipitation method, and the Recombinant Human Hyaluronidase (PH20) was modified on the surface of drug-loaded micelles. Subsequently, PEG protective layer was added to pH-responsive nanomicelles modified by PH20. The morphology and size of the nanoparticles were observed by transmission electron microscopy. DLS and Zeta potential of the nanoparticles were detected by a nanoparticle size and Zeta potential analyzer. UV-Vis spectrophotometer detected enzyme modification, encapsulation efficiency, drug loading and drug release condition. CCK-8 method was used to evaluate the safety and toxicity of nanoparticles on the survival rate of MDA-MB-231 cells.



Results: The pH-responsive nanomicelles modified with hyaluronidase prepared in this study were uniform spheres under TEM, with a DLS of (89 ± 2.84) nm and a Zeta potential of (18.62 ± 1.09) mV. UV-Vis spectrophotometer results showed that hyaluronidase was successfully modified on the surface of nanoparticles, the encapsulation rate was (81 ± 3.01) %, and the drug loading was (1.75 ± 0.39) %. Compared with the pH=7.4 system, the prepared nanoparticles released more in the pH=5.5 system. Meanwhile, the results of CCK-8 showed that the pH-responsive nanomicelles modified by hyaluronidase were significantly more damaging to MDA-MB-231 cells than free IR780 and IR780-loaded nanomicelles.

Conclusion: The hyaluronidase-modified pH-responsive nanomicelle prepared in this study represents a novel approach to enhance the efficiency of photodynamic therapy.

Key words: Photodynamic Therapy; Breast Cancer; Hyaluronidase; pH-Responsive Nanomicelle

463. Clinical efficacy and prognostic indicators of ICIs combined with anti-angiogenesis therapy in patients in advanced non-small cell lung cancer patients

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Objective: The objective of this study was to explore the real-world efficacy and prognostic indications of immune checkpoint inhibitors (ICIs) combined with anti-angiogenesis therapy in patients with advanced non-small cell lung cancer (NSCLC).

Methods: First, the effect of vascular endothelial growth factor A (VEGFA) on clinical prognosis was analyzed with the data from TCGA database. Then, we retrospectively collected hematological data and medical records of 190 eligible patients with advanced NSCLC. The included patients were divided into ICIs combined with anti-angiogenesis therapy group (the treatment group, $n=96$) and ICIs without anti-angiogenesis therapy group (the control group, $n=94$). The peripheral blood indexes of interest were neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), albumin (ALB), and lactate dehydrogenase (LDH). Objective response rate (ORR), disease control rate (DCR), and progression-free survival (PFS) and overall survival (OS) were assessed.

Results: Negative correlation was found between the expression of VEGFA and OS through analysis of TCGA database ($P=0.007$). Besides, the results showed that VEGFA was negatively correlated with B-lineage cells, CD8 T cells, myeloid dendritic cells (MDCs) and monocytic -lineage cells, while positively correlated with endothelial cells and mast cells. We then found that the median PFS of the treatment group was 9.7 months, and that of the control group was 8.6 months ($P=0.101$). Subgroup analysis showed that the difference in PFS among first-line treatment patients was statistically significant ($P=0.038$), but not among other lines treatment patients ($P=0.519$). Moreover, we found that the PFS of patients with brain metastases (BM) in the treatment group was significantly higher

than the control group ($P=0.028$), while there was no difference in patients without BM ($P=0.207$). In the treatment group, we observed that the decreased NLR and PLR at 6 week were associated with a higher ORR ($P=0.011$; $P=0.001$) and the decreased NLR at 6 week ($P=0.002$) or 12 week ($P=0.042$) was related to a greater DCR. In addition, patients whose NLR decreased at week 6 or 12 post-treatment tended to have longer PFS ($P=0.012$; $P=0.014$), and similar results were found in those with decreased PLR ($P=0.019$; $P=0.013$). However, the dynamic changes of ALB ($P=0.759$) and LDH ($P=0.127$) was not correlated with PFS. In addition, we found that the adverse events (AEs) were mainly grade 1-2 thrombocytopenia (38.5%) and fatigue (45.8%).

Conclusion: The administration of ICIs combined with anti-angiogenesis therapy presented a good therapeutic effect and safety in real-world advanced NSCLC patients. Patients may benefit more from immunotherapy with first-line combination of anti-angiogenesis therapy, especially those with BM. More importantly, revealing whether there is hypervascularization in tumor tissues may help clinicians to clarify the adoption of anti-angiogenesis and ICIs combination therapy or not. In addition, Post-treatment NLR and PLR changes are suggestive indicators for the prognosis of advanced NSCLC patients after ICIs combined with anti-angiogenesis therapy.

Key words: Non-small cell lung cancer; Immune checkpoint inhibitors; Anti-angiogenesis; Efficacy; Prognosis

464. 基于 GEO 数据挖掘肝癌脂代谢相关基因及茯苓多糖干预机制

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前言: 肝癌是我国常见的恶性肿瘤之一，是与癌症相关死亡的第二大主要原因，其发病率呈逐年上升趋势，但对于肝癌的研究始终面临难以攻克的壁垒。随着生物信息学的发展，人们对寻找各种疾病枢纽基因的关注日益增加，收集到的枢纽基因信息可为疾病尤其是肿瘤防治提供新手段。现代病机研究从宏观视角和微观角度明确了“痰”是肝癌产生的物质基础，是肿瘤微环境的重要组成部分。痰浊和血脂的代谢异常之间含有一定关系。茯苓是我国传统中药材，其主要成分茯苓多糖可达到茯苓干重的 80%，具有保护肝、抗肿瘤、抗炎、抗病毒等药理作用，具有一定化痰祛瘀的功效。本研究根据生物信息学分析方法筛选肝癌脂代谢相关差异表达基因及信号通路，并对其给予中药单体茯苓多糖进行 CCK-8 和实时荧光定量 PCR 实验验证，探讨茯苓多糖对血脂异常肝癌的影响。以期对肝癌的早期筛查、诊断以及后期治疗提供新的思路与方法。

目的: 利用生物信息学分析方法筛选肝癌胆固醇代谢通路相关差异表达基因，探讨肝癌的发病机制，并探寻化痰中药茯苓提取物茯苓多糖干预脂质代谢途径化痰抑癌的分子机制。



方法：从 GEO 公共数据库中下载基因芯片 GSE84402 数据集矩阵数据，并用其分析工具 GEO2R analysis 对数据进行初步分析，运用 UNIPROT 数据库对基因进行标准化。分别应用 DAVID 在线数据库和 GSEA 数据库进行分析，运用 R 语言 ggplot2 做出 BP 和 KEGG 的气泡图，筛选出与脂代谢相关差异表达基因，运用 STRING 数据库构建差异表达基因的蛋白质相互作用网络，筛选出参与肝癌脂代谢的核心基因。应用 Venny diagram 在线绘制网站筛选 DAVID 和 GSEA 数据库肝癌脂代谢基因的共表达基因，运用 Cytoscape 软件绘制蛋白互作网络。应用 GEPIA 数据库进一步筛选，得到胆固醇代谢通路上的核心差异基因 2 个。用茯苓多糖作用于 HepG2 肝癌细胞株，观察其对细胞的抑制作用，并对以上筛选出的核心基因进行实验验证。

结果：一：筛选肝癌差异表达基因：通过 GEO2R 分析 GSE84402 数据集并对其基因在 UNIPROT 数据库中进行标准化，获得 448 个差异表达基因，其中包括 178 个上调基因及 274 个下调基因。GO 分析和 KEGG 通路富集分析脂代谢相关信号通路，发现差异表达基因在代谢方面富集，其中胆固醇代谢过程、脂质运输等方面显著。二：筛选肝癌脂代谢差异表达基因：DAVID 筛出脂代谢相关基因 37 个，GSEA 筛出脂代谢相关基因 50 个，韦恩图绘制得到交集基因 22 个，应用 STRING 数据库和 Cytoscape 软件构建差异表达基因的蛋白互作网络，最终得到差异表达基因 22 个。其中与胆固醇代谢相关差异表达基因 6 个：EPHX2, ApoC2, ApoA5, PON1, SQLE, SOAT2。三：DEGs 在肝癌组织和正常组织中的表达情况：通过 GEPIA 数据库验证 DEGs 在肝细胞癌和正常样本中 RNA 表达差异数据，进一步筛选出 2 个 DEGs：ApoA5, SQLE。四：实验验证（一）不同浓度茯苓多糖对 HepG2 细胞抑制率的影响：经过 24 h, 48 h, 72 h 三个不同时间给予茯苓多糖干预后，肝癌细胞 HepG2 有明显差异变化。其中 800 $\mu\text{g/mL}$ 茯苓多糖干预 48H 后，细胞抑制效果最好。（二）RT-qPCR 检测肝癌脂代谢差异表达基因 mRNA 的表达：与对照组相比，ApoA5 mRNA 表达显著上升；SQLE mRNA 表达显著下降

结论：茯苓多糖对血脂异常肝癌有一定影响作用，且 APOA5、SQLE 基因有望成为血脂异常肝癌患者的潜在治疗靶点。我们未来努力的方向，以血脂异常为突破口，用现代科学技术探究肝癌血脂异常的关系，为临床诊断治疗和实验研究提供理论基础。

关键词：肝癌；GEO 数据库；脂质代谢；茯苓多糖；qPCR

465. Olaparib resistant NSCLCs with ARID1A deficiency are specifically sensitive to proton radiation versus X-ray radiation

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Background: Homologous recombination repair (HRR) deficient tumor cells are well known to be synthetic lethal to olaparib therapy. It has also been reported to be linked to increased proton relative biological effectiveness (RBE) versus X-ray radiation. However, to our present knowledge, there are no reports directly studying the relationship between olaparib response and proton radiotherapy in tumors, especially in non-small cell lung cancers (NSCLCs) which greatly benefit from proton therapy to reduce toxicities to the surrounded organs of tumors because of its unique characteristic Spread Out Bragg Peak (SOBP) versus X-ray radiotherapy.

Methods and Results: We screened the olaparib IC₅₀ of twelve NSCLC cell lines which had also been tested for proton RBE at 10% survival level (termed RBE_{0.1} hereafter), taking X-ray as a reference. The Pearson correlation analysis revealed that the cells with higher olaparib IC₅₀ were prone to be more sensitive to proton radiotherapy versus X-ray radiation, illustrated by higher proton RBE_{0.1}. Then the genomics related to olaparib response from genomics of drug sensitivity in cancer (GDSC) database suggested that ARID1A mutation (Mut) was the only factor significantly associated with olaparib resistance in lung adenocarcinoma (LUAD) cells. Although ARID1A deficiency has been reported to be lethal to poly (ADP-ribose) polymerase inhibitors (PARPi) including olaparib, rucaparib, niraparib in vitro and in vivo, our further screening data showed that the proton RBE_{0.1} was dramatically higher in ARID1A mutated NSCLC cells, supporting our above findings. Besides, loss of ARID1A protein expression has been suggested as a surrogate biomarker for ARID1A mutation, we further found that the proton RBE_{0.1} was higher in ARID1A truncated cells (81% vs 19%). Subsequently, the proton RBE_{0.1} from ARID1A deficient olaparib sensitive cells, innate resistant cells and acquired resistant cells confirmed our hypothesis. To develop practical biomarkers stratifying specific tumor patients to proton radiotherapy, we found that deficiency of RAD51 foci, which has been proposed to be a functional biomarker predicting olaparib response, greatly predicted the olaparib resistance in NSCLCs.

Conclusions: Collectively, our data fully support that ARID1A deficiency in both olaparib primary and acquired resistant cells which can be efficiently predicted by RAD51 foci is a promising genomic biomarker used to specifically predict the proton sensitive patients with NSCLCs versus X-ray radiation. Besides, genetically and pharmacologically targeting ARID1A in olaparib resistant cells without ARID1A deficiency is an alternative strategy to sensitize NSCLC patients to proton radiation.

Key words: Proton radiation, RBE; NSCLC, RAD51 foci; ARID1A truncation; genomic biomarker

466. 体检机构鼻咽癌早筛项目标准化建议稿

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华东疗养院

男性鼻咽癌的发病率是女性的 2-3 倍。对于高风险人群, 发病高峰在 50-60 岁[5]。早期鼻咽癌对放疗非常敏感, 单纯放疗可取得较满意的疗效, 5 年生存率高达 95%[6], 但中期和晚期患者需放

化疗联合治疗可取得一定效果，但治疗精准性和特异性欠佳，易产生较强的副作用，复发风险较大，总体生存时间骤减。鉴于鼻咽癌在特定地区和某些家族中的高发病率以及早期鼻咽癌的高治愈率，对鼻咽癌高危人群进行筛查可以大大提高鼻咽癌的早期发现率，降低死亡率，可以提高患者生存率,改善患者预后，并从而减轻社会医疗负荷[7]。筛查是恶性肿瘤二级预防的主要手段，它主要通过某些检查手段，对无症状的高危人群进行定期监测，从而达到早发现,早治疗的目的。加强健康体检中鼻咽癌早期筛查的重要性及必要性不容置疑，为进一步规范社会健检机构的鼻咽癌早期筛查标准，本机构参考中国《健康体检基本项目专家共识》（2014版）[9],《CSCO 鼻咽癌诊疗指南》（2021版）[10]等标准化文件，制定健检机构鼻咽癌早筛项目标准化建议稿，以期为从事鼻咽癌早诊早治的相关健检从业人员提供指导。本建议稿共五个章节：一,鼻咽癌个性化早筛项目推荐；二,鼻咽癌早筛标准流程；三,鼻咽癌早筛标准诊断；四,鼻咽癌早筛健康教育；五,鼻咽癌早筛健康管理。其中关于鼻咽癌的生物指标，利用血清学指标检测鼻咽癌高发地区人群 EB 病毒感染状况,可有效地筛查出患癌高危群体,而高危人群经影像学及病理活检确诊,有利于及时发现和治疗早癌,提高患者生存率和生活质量[12]。目前较为常用的抗体有很多，本建议稿选取了 3 种抗体，其中 VCA-IgA 的灵敏度最高，达到 93%左右，但其阳性预测值仍不够理想，国内已有单独检测易发生漏诊,误诊的报道。而 Rta-IgG 的诊断效能尽管不是最优，然而其能大大提高各项抗体联合检测的特异度及阳性预测值；抗体联合检测在一定程度上明显提高了灵敏度,特异度及阳性预测值。

这个三联检方案的好处是做到了 EBV 基因谱全覆盖，理论上将大大提高检测鼻咽癌的灵敏度和特异性，适宜大规模的鼻咽癌筛查。近期研究成果显示：Rta-IgG,VCA-IgA,EA-IgA 三项联检鼻咽癌的灵敏度高达 94.1%，特异性达到 98.9%[22-27]。

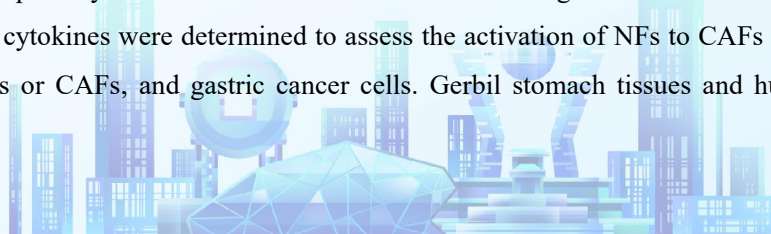
关键词：鼻咽癌；EB 病毒；血清学检测

467. Crosstalk of *Helicobacter pylori*, fibroblasts, and cancer cells induces fibroblast activation and Serpin E1 expression to promote gastric tumorigenesis

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H. pylori can disrupt the tight junctions between gastric epithelial cells and penetrate the intercellular spaces acting on epithelial cells, normal fibroblasts (NFs), and cancer-associated fibroblasts (CAFs), but the roles of their interplay in gastric cancer tumorigenesis and progression have not been explored. In this study, primary CAFs and NFs were isolated from gastric adenocarcinoma tissues. FAP, Lumican, and cytokines were determined to assess the activation of NFs to CAFs in the co-cultures of *H. pylori*, NFs or CAFs, and gastric cancer cells. Gerbil stomach tissues and human gastric cancer



cells were used to evaluate the influence of *H. pylori* infection and CAFs on Serpin E1 expression. The migration, invasion, and tumor formation of gastric cancer cells overexpressing Serpin E1 were detected. The clinical significance of Serpin E1 was analyzed using the TCGA-STAD database and gastric cancer sample. Gastric CAFs are inflammatory CAFs with α -SMA^{low}FAP^{high} lumican^{high}. The interplay of *H. pylori*, fibroblasts, and cancer cells promotes the transition of NFs to CAFs by inducing cytokines release. *H. pylori* infection and CAFs together induce Serpin E1 expression in gerbil gastric epithelial cells and human gastric cancer cells. Serpin E1 overexpression enhances cell migration, invasion, and tumor formation in vitro and in vivo. Serpin E1 is highly expressed in human gastric cancer tissues, and its high expression is negatively associated with the ten-years overall survival of patients. Targeting Serpin E will provide a promising therapeutic strategy for gastric cancer by disrupting the interaction between *H. pylori*, CAFs, and gastric cancer cells.

Key words: *Helicobacter pylori*; gastric cancer; fibroblasts; Serpin E1

468. The long noncoding RNA SNHG3 regulates breast cancer cell growth through miR-142-5p and CCND1

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Background: Emerging studies suggest that long non-coding RNAs (lncRNAs) have regulatory functions in breast cancer (BRCA), providing numerous potential diagnostic biomarkers, prognostic biomarkers, and therapeutic targets.

Methods: The expressions of SNHG3/miR-142-5p/CCND1 in BRCA were analyzed by RNA-sequencing, quantitative reverse transcription polymerase chain reaction (qRT-PCR) and western blot. The effects of SNHG3 on breast cancer were investigated through in vitro and in vivo assays (colony formation assay, EdU assay, wound healing assay, flow cytometry assay, transwell assay, and xenograft model). Bioinformatics analysis, RNA fluorescence in situ hybridization and luciferase reporter assay were utilized to explore the mechanism of action of SNHG3.

Results: SNHG3 was found to be strongly elevated in human breast cancer tissues and cell lines, and high SNHG3 expression was associated with reduced patient survival. Functional studies showed that SNHG3 promoted growth, migration, and invasion and inhibits apoptosis of BRCA cells both in vitro and in vivo. Mechanistically, we found that SNHG3 expressed predominantly in the cytoplasm. SNHG3 was verified as a competing endogenous RNA (ceRNA) via negative regulation of miR-142-5p and regulate their common target CCND1.

Conclusions: This study elucidated that SNHG3 acted as an oncogene in BRCA, suggesting new biomarkers and therapeutic targets in BRCA.

Key words: lncRNASNHG3; breast cancer; miR-142-5p; CCND1



469. 局部晚期乳腺癌保乳手术的流行病学现状与影响因素研究进展

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乳腺癌近年来发病率显著增加,已成为女性最常见的恶性肿瘤。随着患者诊治意识的提高和医疗手段的进步,乳腺癌的早期检出率随之增加;但仍有部分患者就诊时即已为局部晚期乳腺癌。早期乳腺癌可选择保留乳房的根治性手术,即乳腺癌保乳手术。随着目前综合治疗手段的不断发展,局部晚期乳腺癌患者通过全身治疗达到良好局部缓解和疾病控制后,部分患者也可采取保乳手术提高生存和生活质量。本文综述了局部晚期乳腺癌保乳手术的流行病学现状及影响因素,以为临床局部晚期乳腺癌保乳手术提供决策思路和依据。

关键词: 局部晚期乳腺癌; 手术治疗; 保留乳房; 危险因素; 生存质量

470. Glypican-3 肿瘤靶向穿透肽构建及功能评价

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目的: 肿瘤靶向穿透肽是一类兼具有肿瘤标志物特异性结合能力及肿瘤组织穿透能力的多肽,为获取针对肝癌标志物——磷脂酰肌醇蛋白聚糖-3 (Glypican-3, GPC-3) 的肿瘤靶向穿透肽,本研究将 GPC-3 靶向结构域与 C 末端法则 (C-end Rule, CendR) 介导的肿瘤穿透结构域融合表达,并对该融合多肽进行肿瘤特异性结合及穿透功能评价。

材料与方法: 通过多肽固相合成方法,制备 GPC-3 靶向结构域与肿瘤穿透结构域融合多肽 (Glypican-3 Binding and Penetrating Peptide, GBPP), 并进行荧光标记。利用细胞荧光实验,免疫组织化学染色,组织荧光染色等,在肿瘤细胞及组织中验证 GBPP 的特异性结合肿瘤能力;利用 HUVEC 细胞二维培养模型进行融合多肽穿透功能评价,并探究 uPA 介导的酶切机制。进一步地,利用 HepG-2 肿瘤细胞三维培养模型,通过共聚焦成像技术,评价 GPC-3 肿瘤靶向穿透肽在肿瘤细胞球中穿透能力。

结果: 在肿瘤特异性结合能力评价方面,细胞荧光实验显示,GPC-3 肿瘤靶向穿透肽 GBPP 可特异性结合 GPC-3 阳性的 HepG-2 细胞,而对阴性的 PC-3 细胞无明显结合;组织学染色显示,对于 GPC-3 阳性表达的临床组织样本,GBPP 可显著特异性结合肿瘤组织。在肿瘤穿透能力评价方面,HUVEC 二维细胞穿透实验显示,GBPP 中包含的 uPA 酶切位点可特异性响应外源性 uPA,并通过 CendR 功能域介导实现细胞穿透;此外,HepG-2 肿瘤细胞球成像显示,GBPP 可向细胞球深部渗入。



结论: 本研究成功构建了针对肝癌标志物 GPC-3 的肿瘤靶向穿透肽, 细胞学及组织学实验显示出该融合多肽具备良好的肿瘤特异性结合能力及穿透能力。基于该肿瘤靶向穿透肽可设计针对肿瘤标志物 GPC-3 的药物递送新体系, 可增强药物在肿瘤组织深部特异性聚集, 有望进一步应用于临床诊疗中。

关键词: 磷脂酰肌醇蛋白聚糖-3; 肿瘤靶向穿透肽; 肿瘤标志物

471. Preoperative Serum Iron Represents a Prognostic Factor in Patients with Oral Cancer

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Objectives: There is an urgent need to find blood circulation indicators to ameliorate the prognosis of patients with oral cancer. The purpose of this study was to investigate the relationship between the level of preoperative serum iron and the prognosis in patients with oral cancer.

Methods: The study was conducted in a cohort of 698 oral cancer patients in the Department of Oral and Maxillofacial Surgery of the First Affiliated Hospital of Fujian Medical University from September 2007 to July 2019. X-tile program was utilized to determine the optimal cut-off value for preoperative serum iron. Chi-square test was used to compare categorical patient characteristics. Our primary endpoint is overall survival (OS); secondary endpoint is disease-free survival (DFS). Survival analysis was done using Kaplan-Meier method and long rank test. Univariate Cox regression and Multivariate Cox regression analysis was performed to evaluate the prognostic relevance of preoperative serum iron. A web-based dynamic nomogram was then established based on the identified independent prognostic factors.

Results: According to the optimal cut-off values of preoperative serum iron, patients were divided into low serum iron ($\leq 8.9 \mu\text{mol/L}$), median serum iron and high serum iron ($\geq 15 \mu\text{mol/L}$) groups. There were more males, smokers, drinkers and surgical patients in the high serum iron group, but no differences in age, BMI, tumor differentiation, tumor size and TNM stage were observed. After a median follow-up of 44.9 months, median overall survival (OS) and disease-free survival (DFS) were 170.5 months and 102.5 months, respectively. Kaplan-Meier analysis showed that the oral cancer patients with high level of serum iron had better OS ($P < 0.001$), whereas a significant association in serum iron level and DFS was not detected. Through univariate analysis, patients with high serum iron level were shown to have

better prognosis in terms of OS ($HR=0.48$, $CI: 0.33-0.69$) and DFS ($HR=0.57$, $CI: 0.40-0.82$). Meanwhile, the univariate analysis also suggested a correlation between age, treatment, tumor size, and TNM stage and survival of oral cancer patients. In Cox regression analyses, adjusted for multiple clinical and general variables including age, gender, treatment, tumor size and TNM stage, serum iron level was independently associated with OS ($HR_{adj}=0.61$, $CI: 0.42-0.89$) and DFS ($HR_{adj}=0.66$, $CI: 0.46-0.95$). In addition, multivariable analysis confirmed that older age, no surgical treatment and high TNM stage were independent prognostic factors of survival (all $P < 0.001$). The dynamic nomogram (https://fanyi.shinyapps.io/Dynamic_nomogram/) was further constructed with age, gender, drinking, surgical treatment, TNM stage and tumor size as prognostic parameters to predict the 1, 3, and 5-year OS probability (Eg, for a 57-year-old female patient with low serum iron level, TNM I-II stage, tumor size ≤ 2 cm, no surgical treatment, no smoking and drinking habits, the probability of 1, 3, and 5-year OS was about 82.0%, 57.0% and 43.0%, respectively.), which may show more convenience in clinical prediction of oral cancer patients survival.

Conclusion: The preoperative serum iron level seems to represent an independent prognostic factor for OS and DFS in patients with oral cancer, patients with high serum iron have better prognosis. Additional large-scale prospective studies are warranted to confirm and extend our findings.

Key words: Keywords: Serum iron; Oral cancer; Overall survival; Disease-free survival

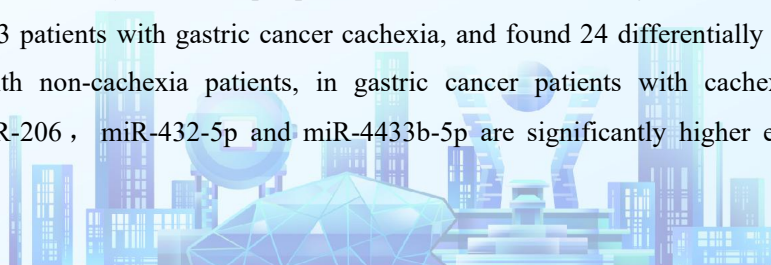
472. Study on the mechanism and clinical diagnostic value of gastric cancer cell-derived exosomal miRNA inducing cachexia

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Cachexia is a multifactorial metabolic syndrome characterized by weight loss and progressive bone wasting.

Among them, cachexia caused by tumors is the most common, which is called tumor cachexia. Currently, the diagnosis of cachexia by weight alone has great limitations, which is not conducive to the early detection and diagnosis of the disease. As major members of liquid biopsy, exosomes have the advantages of high concentration, stability, easy for collection and rich in tumor genomes and mutation characteristics, thus, are expected to be novel targets of predicting and treating gastric cancer cachexia. As signaling molecules, exosomes could be transferred to recipient cells and consequently altering their function. Furthermore, exosomes participate in tumor growth, migration, immune escape, angiogenesis, chemoresistance and so on. Here, we performed high-throughput sequencing analysis and bioinformatics analysis on the peripheral blood exosomes of 2 gastric cancer patients with no-cachexia and 3 patients with gastric cancer cachexia, and found 24 differentially expressed miRNAs. Compared with non-cachexia patients, in gastric cancer patients with cachexia, we found that exosomes miR-206, miR-432-5p and miR-4433b-5p are significantly higher expression. Through



enlarging samples, our research confirmed this conclusion. Results showed that miR-206 (** $P < 0.001$), miR-432-5p (** $P < 0.001$) and miR-4433b-5p (* $P < 0.05$) were up-regulated in patients with gastric cancer cachexia. According to the further analysis of the high-throughput sequencing results, our study predicted the target genes of the differentially expressed miRNAs. The results of the GO classification of the differentially expressed miRNA target genes between samples were counted, and it was found that the differentially expressed miRNA target genes were mainly concentrated in the processes of cell processes, biological regulation, metabolism, and tumors. In KEGG enrichment, differential genes are mainly enriched in various cancer development pathways such as PI3K-Akt signaling pathway, MAPK signaling pathway, TNF signaling pathway, and cell cycle-related signaling pathways. In general, regarding the early diagnosis of gastric cancer, we first studied the exosomes miR-206, miR-432-5p and miR-4433b-5p related to gastric cancer cachexia, and confirmed their clinical significance in the pathogenesis of gastric cancer. It can be used as an important reference index for early diagnosis of gastric cancer cachexia and provide clinical value for the treatment and prognosis of gastric cancer.

Key words: cachexia; gastric cancer; miRNA; diagnosis

473. Identification and verification cancer-associated fibroblasts-related prognostic signature based on scRNA-seq and bulk-seq in colorectal cancer

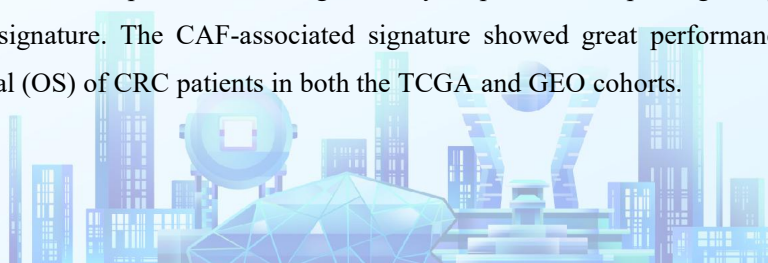
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Background: The tumor microenvironment was considered a vital factor for the tumor development of colorectal cancer (CRC). Cancer-associated fibroblasts (CAFs), a particular form of fibroblasts in the tumor, play a considerable role in the CRC progression. However, the various subtypes of CAFs may have different, even opposite functions, and related researches are warranted.

Methods: Single-cell RNA-sequencing (scRNA-seq) data and Bulk-seq data from Gene Expression Omnibus (GEO) database and The Cancer Genome Atlas (TCGA) were obtained and analyzed. R package Seurat was used to identify the subtypes of CAFs. R package iTALK was applied for cell communication analysis in different subtypes of CAFs. The signature based on receptor-ligand pairs was constructed and verified by LASSO COX regression analysis.

Results: Totally, scRNA-seq data from 23 patients and bulk-seq data from 452 patients were collected in the current study. 6 subtypes of CAFs were identified. CAF1 and CAF5 were found associated with the prognosis of CRC patients. 825 significantly expressed receptor-ligand pairs were used to build up the signature. The CAF-associated signature showed great performance in predicting the overall survival (OS) of CRC patients in both the TCGA and GEO cohorts.



Conclusion: Our study introduced an accurate classification of CAFs in CRC based on scRNA-seq. A robust CAF-associated signature was established for prediction of OS in CRC patients.

Key words: scRNA-seq; TCGA; CRC; prognosis; signature

474. 846 例孕晚期妇女 B 族链球菌感染检测及妊娠结局分析

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目的: 了解咸阳地区孕妇感染 B 族链球菌 (GBS) 与年龄、妊娠情况及妊娠结局等因素的相关性, 为孕晚期妇女防治 B 族链球菌感染提供建议。

方法: 选取 2019 年 9 月至 2021 年 3 月在陕西中医药大学附属医院产科进行 B 族链球菌检测的 846 名孕妇作为研究对象, 采用实时荧光定量聚合酶链反应 (PCR) 的方法检测 B 族链球菌, 按照患者年龄、妊娠情况及妊娠结局对检测结果进行分析。

结果: 846 例妊娠孕妇 GBS 阳性率为 7.40%。其中 82.54% (52/63) GBS 阳性孕妇伴有不良妊娠症状, 脐带绕颈症状占比 66.67% (42/63) 有统计学意义。21~25 岁孕妇感染 GBS 的阳性率为 12.12%, 26~30 岁孕妇感染 GBS 的阳性率为 6.97%, 31~35 岁孕妇感染 GBS 的阳性率为 7.86%, <20 岁和 ≥36 岁孕妇的 GBS 阳性率为 0%。**结论:** 年龄在 21~25 岁的孕妇易感染 B 族链球菌, 感染 GBS 阳性孕妇的胎儿易发生脐带绕颈现象。

关键词: B 族链球菌; 实时荧光定量聚合酶链反应; 妊娠结局

475. miR-370-3p 靶向调控 FBLN5 在乳腺癌中的作用机制及临床诊断研究

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目的: 乳腺癌作为女性最常见恶性肿瘤, 其传统肿瘤标志物诊断效能较低, 且病理诊断具有创伤性, 诊断周期长, 因而需找到一种新型非侵入性诊断标志物。本文旨在探讨 miR-370-3p 在乳腺癌中的生物学作用及分子机制并探讨其作为乳腺癌诊断标志物的可行性及临床应用价值。

方法: ①构建高、低表达 miR-370-3p 的乳腺癌细胞, 体外采用克隆形成及 transwell 迁移实验检测增殖转移作用, Western blot 测定增殖转移相关蛋白表达水平; 体内构建裸鼠皮下成瘤模型, 检测形成肿块体积及重量。②TargetScan 和 PicTar 预测并用双荧光素酶报告基因实验验证靶基因; Western blot 测定靶基因及信号通路蛋白的表达。③定量 PCR 检测乳腺癌组织, 血清以及血清

外泌体中 miR-370-3p 表达量。ROC 曲线分析诊断效能。结合临床病理资料评价 miR-370-3p 在乳腺癌诊断中的价值及临床意义。

结果：①miR-370-3p 高表达细胞迁移及克隆数显著增加，E-cadherin 表达量明显降低，N-cadherin, Vimentin, PCNA 表达量明显增加；反之结果相反。②miR-370-3p 高表达细胞体内形成肿瘤体积，重量大于对照组，反之结果相反。③miR-370-3p 靶向负调控 FBLN5 且促进 NF- κ B P65 表达。④miR-370-3p 在乳腺癌组织，血清及 exosome 表达量显著增加。血清中的 miR-370-3p 与淋巴结的转移程度，TNM 分期成正相关；exosome 中 miR-370-3p 与肿瘤直径大小，淋巴结的转移程度，TNM 分期成正相关。

结论：①miR-370-3p 促进乳腺癌增殖与转移。②miR-370-3p 靶向负调控 FBLN5, 活化 NF- κ B 信号通路。③miR-370-3p 是乳腺癌诊断的潜在新型非创伤性分子标志物，具有重要的临床应用价值。

讨论：本文主要采用细胞，分子生物功能学，体内动物模型以及临床标本研究了 miR-370-3p 在乳腺癌进展中的作用机制以及临床应用价值。结果显示 miR-370-3p 是一种乳腺癌致癌基因，其能促进乳腺癌增殖转移。miR-370-3p 可通过靶向 FBLN5，异常活化 NF- κ B 信号通路，从而促进乳腺癌发展。乳腺癌组织 miR-370-3p 对乳腺癌有较高的诊断效能，检测敏感性和特异性。与临床病理资料结合分析后发现乳腺癌血清高表达 miR-370-3p，其表达水平与淋巴结转移程度以及 TNM 分期正相关。乳腺癌血清外泌体高表达的 miR-370-3p 与乳腺癌肿瘤直径大小，淋巴结转移程度以及 TNM 分期正相关。本研究为 miR-370-3p 在乳腺癌进展中的作用提供了新的分子机制，具有重要的意义。

关键词：miR-370-3p；乳腺癌；外泌体；FBLN5；诊疗

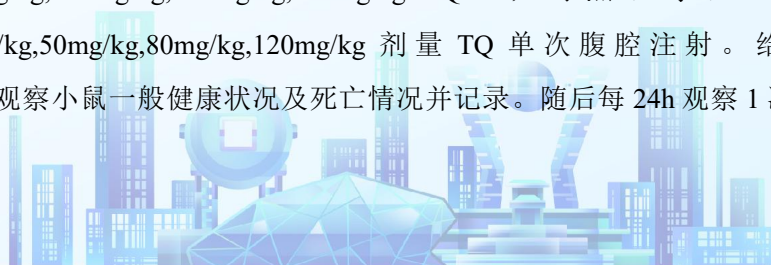
476. 百里醌新型衍生物 TQFL12 的小鼠急性毒性研究及其调控机制的探索

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目的：百里醌(TQ)是一种来自天然产物黑种草籽的有效成分，研究证明其具有抗肿瘤, 抗炎症, 抗氧化等多种作用。由我们实验室设计合成的一种百里醌新型衍生物 TQFL12，已经被证明，其抗肿瘤作用优于 TQ，因此研究它在体内的毒性作用是有必要的。本文旨在检测百里醌新型衍生物（TQFL12）在小鼠体内的急性毒性作用并初步研究其调控机制。

方法：1. 选取 8w 左右的 BALB/c 小鼠（约 20g），雌雄各半，将其分组，实验组每组 10 只，分别予以 0, 50mg/kg, 100mg/kg, 200mg/kg, 250mg/kg TQ-12；对照组每组 8 只，分别予以 0mg/kg, 25mg/kg, 50mg/kg, 80mg/kg, 120mg/kg 剂量 TQ 单次腹腔注射。给药首日分别于 2h, 6h, 9h, 24h 观察小鼠一般健康状况及死亡情况并记录。随后每 24h 观察 1 次，收集数据。分



别于给药第五日和给药第二日取高剂量组小鼠肝、肾组织与正常小鼠肝、肾组织进行对比。2. 应用 bless 法，将收集的死亡数据导入 SPSS 软件，分别计算出 TQFL12 与 TQ 的半数致死量（LD50）。3. 新鲜组织取下后固定于 4%多聚甲醛（>24h），经包埋、切片后 HE 染色，观察与正常组织相比，给药后两种组织是否有病理改变及改变程度。4. 取部分提取组织蛋白，WB 检测 AMPK α 信号通路 AMPK、p-AMPK、p-ACC 等蛋白改变情况。

结果：TQ 组各浓度梯度小鼠在 48h 内全部死亡，期间出现不同程度的活动减少、驼背、行走不稳、呼吸困难等表现，24h 内各剂量组死亡率分别为 0、25%、87.5%、87.5%、100%呈浓度依赖性升高；而 TQFL12 组小鼠高剂量组在一周内未全部死亡，其余组死亡率呈浓度依赖性升高，一周内死亡率分别为 0、30%、60%、80%、90%。经计算，TQ 24h 半数致死量（LD50）为 33.758mg/kg，TQFL12 第 7 天的半数致死量（LD50）为 81.405mg/kg。HE 染色结果显示，与正常小鼠相比，TQ 组肾脏组织出现较为严重的肾小管上皮变薄、间质肿胀和明显的血管内皮肿胀、管腔变窄、血管充血、出血，有少量的炎细胞浸润；而 TQFL12 组出现上述改变情况较 TQ 组程度明显减轻。Western blot 结果，TQFL12 组小鼠较正常小鼠 AMPK、p-AMPK 表达增加；其它下游靶标蛋白是否有改变，目前正在实验中。

结论：TQ 新型衍生物（TQFL12）在小鼠体内的毒性明显低于 TQ，可能有一定的药物开发价值，它抗毒性的机制可能是通过 AMPK 信号通路进行的。

关键词：TQFL12；百里醌；毒性实验；小鼠；AMPK

477. Crowberry (*Empetrum nigrum* var. *japonicum*) inhibits cell proliferation and migration by targeting DEK via the Akt signaling pathway in cholangiocarcinoma cells

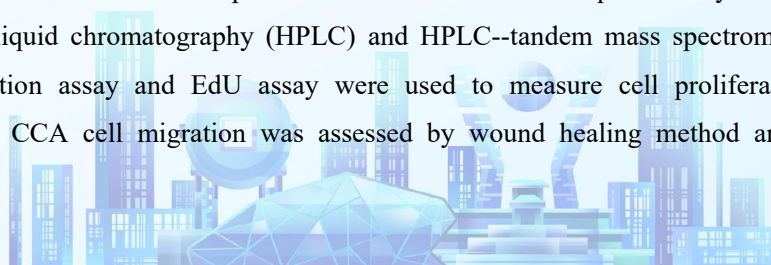
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YANBIAN University

Background: Cholangiocarcinoma (CCA) is a rare biliary adenocarcinoma related with poor clinical prognosis. Crowberry is used as herbal medicine to control inflammatory diseases and repair cellular antioxidant enzyme activity. Although crowberry has shown significant therapeutic efficacy about the treatment of various tumors and diseases, its anti-cancer results and specific molecular mechanisms in CCA remain poorly understood.

Aim of the study: The main purpose of this study is to survey the effects of crowberry on the biological behavior of CCA cells.

Materials and Methods: Chemical profiles of the extract were qualitatively analyzed using high-performance liquid chromatography (HPLC) and HPLC--tandem mass spectrometry. MTT method, colony formation assay and EdU assay were used to measure cell proliferation. The effect of crowberry on CCA cell migration was assessed by wound healing method and migration assay.



Moreover, hocheist assays and flow cytometry were used to assessed the cell apoptosis. Western blotting was used to assess the protein expression levels of key factors associated with apoptosis, the Akt signaling pathway, and epithelial-mesenchymal transition. Xenograft model, immunohistochemistry staining and H&E staining were used to assessed the effect of crowberry in vivo.

Results: Crowberry clearly inhibited the proliferation and migration of CCA cells in a dose-dependent manner and induced apoptosis. Furthermore, crowberry targeted the PI3K/Akt signaling pathway by obviously altering the expression levels/activation of several key mediators and reducing the expression of the proto-oncogene DEK in vivo and vitro.

Conclusion: Crowberry inhibits the proliferation and migration of CCA cells by downregulating DEK through the Akt signaling pathway.

Key words: Cholangiocarcinoma; Empetrum nigrum var; japonicum; Proliferation; Migration; DEK

478. 基于 GEO 数据神经母细胞瘤 miRNA 的生物信息学分析

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目的: 基于神经母细胞瘤 (Neuroblastoma, NB) miRNA 表达的差异, 分析下游基因,信号通路和蛋白的改变。

方法: 从 GEO 下载 GSE128004 二代测序表达数据, 利用 R 语言的 limma 包分析差异表达, 并绘制火山图和热图; 使用 miWalk 网页工具找出差异 miRNA 对应的靶基因, 并进行 GO 和 KEGG 分析, 对差异表达进行功能富集分析, 并使用 STRING 数据库进行 PPI 分析, 找出关键基因并在 TCGA 数据库中进行验证。

结果: 筛选出 34 个差异表达 miRNA, 其中 22 个上调的 miRNA 预测出靶基因 1163 个, 12 个下调的 miRNA 预测出靶基因 1474 个。靶基因经过 KEGG 富集分析, 得到 FoxO 信号通路,mTOR 信号通路,AMPK 信号通路等; 经过 GO 分析, 得到轴突形成,化学突触递质的调节,神经突触的调节,跨突触信号的调节等生理过程; PPI 分析得到 16 个关键基因, 在 TCGA 数据库中验证得到 TP53,ATM 两个基因的生存分析有统计学意义。

结论: 34 个差异 miRNA 可能与 NB 疾病的发生发展有关, TP53,ATM 在 NB 的预后中有关, 其在 NB 中的作用及机制有待进一步验证。

关键词: 神经母细胞瘤; miRNA; 生物信息学

479. Prognostic value of preoperative albumin to globulin ratio in urolog-ical cancer: what should we expect from a meta-analysis?



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Background: Current studies have shown that the albumin to globulin ratio (AGR) can be used as a prognostic marker for a variety of cancers. The purpose of this study was to further systematically investigate the relationship between preoperative AGR and clinical outcomes of urinary cancers.

Methods: A computer search was conducted for relevant articles published before January 1, 2021 in PubMed, Embase and Web of Science. Two independent researchers searched for relevant articles in PubMed, Embase and Web of Science. The included literatures were analyzed by MATA with RevMan 5.0 statistical software, and the main outcome indicators were OS, CSS and PFS.

Results: The pooled results showed that a low AGR significantly correlated with poor OS (HR: 0.53, 95% CI: 0.33–0.73, $P < 0.001$), worse cancer specific survival (CSS) (HR: 0.36, 95% CI: 0.22–0.50, $P < 0.001$) and lower progression free survival (PFS) (HR: 1.26, 95% CI: 1.17–1.34, $P < 0.001$) in urologic cancers.

Conclusion: Low preoperative AGR may be an influential factor for poor prognosis after surgery for urinary tumors, and preoperative AGR may be a cheap and valuable prognostic biomarker after surgery for urinary tumors.

关键词: albumin-to-globulin ratio; urologic cancer; prognosis

480. EPOR 在 LUAD 中高表达作为潜在的预后标志物

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目的: 肺腺癌 (LUAD) 作为非小细胞肺癌最常见的的组织学亚型, 其预后成为关注的热点。促红细胞生成素 (EPO) 对 LUAD 患者预后的影响一直是研究的重点领域, EPOR 作为 EPO 的受体, 其对 LUAD 患者预后的影响也十分值得探讨。

方法: EPOR mRNA 水平的表达通过 TIMER, Oncomine, UALCAN 等数据库获取, EPOR 蛋白质水平的表达通过免疫组织化学法检测; muTarget 数据库用于探索影响 EPOR 表达的基因突变; GeneMANIA, String 数据库用于探索 EPOR 互作的基因和蛋白; GEPIA 数据库用于挖掘 EPOR 共表达基因并分析 EPOR 与免疫检查点的相关性; cBioPortal 数据库探索了 EPOR 的遗传学改变; GO 和 KEGG 富集分析和基因集富集分析 (GSEA) 对 EPOR 的差异表达基因的潜在生物学功能进行了探索。此外, 通过 UALCAN 数据库还分析了 EPOR 的表达与临床参数的相关性。最后, 通过 Kaplan-Meier Plotter, PrognScan 数据库并结合患者临床资料进行了预后分析, 通过 Cox 风险回归分析以检测 EPOR 作为预后因素的独立性, 通过构建列线图及校准曲线以评估 EPOR 的预测能力。



结果: EPOR 在 LUAD 中相比正常组织表达下调。DDX60L,LGR6,POTEB3,RIF1,SOX5 5 种基因突变会导致 EPOR 表达下调。EPOR 在不同年龄,性别,肿瘤分期,淋巴转移组的表达水平无显著差异。EPO,CCDC150 和 CFAP161 等基因以及 EPO,JAK2 和 STAT5B 等蛋白与 EPOR 互相作用,RGL3,DOCK6 和 HOOK2 等为 EPOR 共表达基因。EPOR 在 LUAD 中的遗传变异发生率不及 1%,其中 Deep Deletion 是较为常见的类型。EPOR 表达水平与肿瘤纯度和巨噬细胞,中性粒细胞,树突状细胞的浸润无明显相关性,与 CD8⁺ T 细胞的浸润呈负相关,与 B 细胞和 CD4⁺ T 细胞的浸润呈正相关;与 B cell,M1,Neutrophils,NK,DC,Th1,Th2,Th17,Tfh,Treg,Tem 和 NKT 的部分基因标志物具有相关性,其中与 CD19 (B cell),CD11c (DC),STAT6 (Th2),BCL6 (Tfh) 和 TGFB1 (Treg) 的相关性超过 0.2,但总体显示 LUAD 中 EPOR 的表达与免疫细胞标志物有较弱的相关性。富集分析结果显示,在神经系统和配体-受体相互作用方面,MAPK 以及 PI3K/Akt 信号通路,癌症通路等显著富集。KM Plotter 结果显示,LUAD 中 EPOR 基因高表达的患者 OS 较好。在 GSE13213,GSE31210 队列中,EPOR 的高表达与较好的 OS 显著相关。Cox 风险回归分析显示 EPOR 是 OS 的独立保护因素。在 1 年和 3 年生存率中和预测值有较好的一致性。

结论: LUAD 中 EPOR 的表达与肿瘤进展和转移无显著相关性,高表达的 EPOR 与较好的 OS 相关,EPOR 有望成为 LUAD 潜在的新的阳性预后标志物。

关键词: 肺腺癌;促红细胞生成素受体;预后

481. Up-regulation of YY1 Associates with Proliferation and Glutamine Metabolism in Esophageal carcinoma

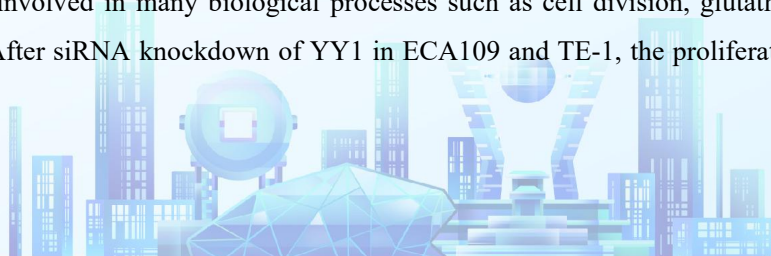
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Affiliated Hospital of North Sichuan Medical College

Objective: To investigate the expression of YinYang-1 in Esophageal carcinoma (ESCA) and its effect on glutamine metabolism in ESCA.

Methods: The expression and roles of YY1 in ESCA were investigated using a series of bioinformatics databases and tools. The expression of YY1 between ESCA with the corresponding adjacent tissues was validated using Real-time PCR, Western Blotting and Immunohistochemical staining method. Furthermore, the effects of YY1 on ESCC cell proliferation were examined using CCK8. The correlation between the YY1 and glutamine metabolism was evaluated by Western Blotting.

Results: YY1 gene was highly conserved in evolution and up-regulated in ESCA tissues and ESCC cell lines. In addition, YY1 can affect the level of immune cell infiltration and promote tumor cell immune escape. YY1 involved in many biological processes such as cell division, glutathione and glutamine metabolism. After siRNA knockdown of YY1 in ECA109 and TE-1, the proliferation of ECA109 and



TE-1 were suppressed. The glutamine consumption and glutamate production was significantly decreased. The protein expression of GLS and GLUD1 was significantly down-regulated.

Conclusion: YY1 is highly expressed in ESCC, promotes glutamine metabolism of ESCC cells, and may be as a diagnostic biomarker for ESCC.

Key words: Esophageal carcinoma; YinYang-1; Expression; Proliferation; Glutamine metabolism

482. Radiomic models trained with machine learning approach in FOWARC trial for accurate prediction of pathological response and survival after rectal cancer treatment

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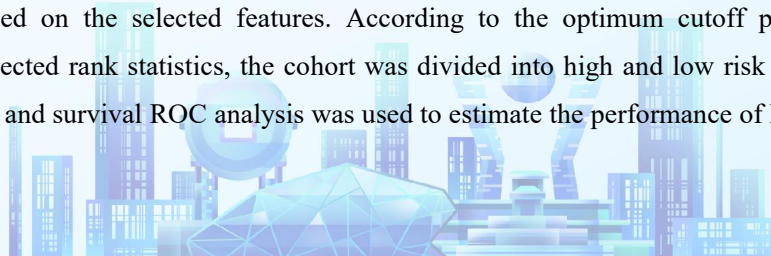
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Purpose: We aimed to develop radiomic models based on pre-treatment computed tomography (CT) to predict the pathological complete response (pCR) after neoadjuvant treatment and long-term prognosis in rectal cancer.

Material and Methods: Data collection and radiomic features extraction: This was a secondary analysis of the FOWARC randomized controlled trial. Radiomic features were extracted from pre-treatment portal venous-phase contrast-enhanced CT images of 177 patients with rectal cancer. Patients were divided into two different response groups: pCR group (TRG 0, no viable residual tumor cells) and non-pCR group (TRG 1–4, varying from rare residual cancer cells to extensive residual cancer cells). The region of interest (ROI) covering the whole tumor was manually outlined along the margin of tumors and a total of 1218 radiomic features were preprocessed and extracted.

Development of pCR prediction model: We applied multi-step pipeline including correlation matrix and the least absolute shrinkage and selection operator (LASSO) method to eliminate the potential redundancy and identify the pCR-associated radiomic features. Finally, the radiomic signature, termed as Rad-pCR, of each patient was constructed. Three models were applied to integrate Rad-pCR with clinicopathological predictors, including logistic regression, support vector machine (SVM) and gradient boosting machine (GBM). The performance of different models were compared by receiver operator characteristic (ROC) curve analysis. **Development of prognosis prediction model:** A univariate screen by Cox proportional hazard model for each radiomic feature was performed and features with $P < 0.1$ were included in the LASSO Cox model to examine their independently predictive value for overall survival (OS). The radiomic risk signatures (termed as Rad-OS) were then generated based on the selected features. According to the optimum cutoff point determined by maximally selected rank statistics, the cohort was divided into high and low risk group. The Kaplan-Meier method and survival ROC analysis was used to estimate the performance of Rad-OS.



Results: pCR prediction model: 14 features were finally selected to build the Rad-pCR. The Rad-pCRs of the pCR group were significantly higher than those in the non-pCR group in both the primary ($P<0.001$) and validation ($P<0.001$) cohort (**Fig.1 A, C**). After integrated with clinicopathological predictors, the SVM model and GBM model had better predictive performance than the logistic model (**Fig.1 B, D**). The SVM model had an AUC of 0.961 [95% CI, 0.909–1.000] and 0.811 [95% CI, 0.672–0.950] in the primary and validation cohort, respectively, while the GBM model yielded the highest AUCs of 0.997 [95% CI 0.990–1.000] in the primary cohort and 0.822 [95% CI, 0.649–0.995] in the validation cohort. Moreover, the GBM model had the best accuracies, sensitivities, and specificities in both cohorts.

Prognosis prediction model: Four features were finally selected to independently predict OS of patients and the Rad-OS was constructed. Significantly worse survival was observed in patients with high Rad-OSs compared to those with low Rad-Oss (**Fig.2 A**). As the risk score elevating, the survival time of patients decreased with the radiomic features changing (**Fig.2 B**). The AUC of 1-year and 3-year survival ROC curve were 0.748 and 0.768 (**Fig.2 C, D**).

Conclusion: The CT-based radiomic models we constructed may provide a useful and reliable tool to predict pCR after neoadjuvant treatment and long-term prognosis, which may help clinical decision making.

Key words: Radiomics; Computed tomography; Machine learning; Rectal cancer

483. Analysis of Hypoxia-Inducible Factor-1 α Expression and its Effects on glycolysis of esophageal carcinoma

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Objective: To investigate the regulatory effects of HIF-1 α on glycolysis metabolism in Esophageal cancer (ESCA).

Methods: A series of bioinformatics databases and tools were performed to investigate the expression and role of HIF-1 α in ESCA. The expression of HIF-1 α in ESCA tissues and corresponding adjacent tissues was validated by Real-time PCR. After silencing the HIF-1 α in ESCC cells using siRNA, the changes of cell proliferation was further detected by CCK-8. The expression of HIF-1 α and glycolytic enzymes were investigated by Real-time PCR and western blotting.

Results: The expression level of HIF-1 α in ESCA patients was significantly higher than that in normal subjects, and was related to the clinicopathological parameters of the patients. The expression level of HIF-1 α in ESCA tissues was significantly higher than that in paracancerous tissues, which was validated by Real-time PCR. The expression of HIF-1 α was significantly correlated with the abundance of ESCA immune cells and the expression of immune markers. There was a relationship between ESCA gene promoter methylation and HIF-1 α expression. Functional enrichment analysis of HIF-1 α related gene showed that they were mainly concentrated in HIF-1 α signal pathway, glycolysis

signal pathway and so on. The expression of HIF-1 α in Eca109 and KYSE150 cells increased significantly under hypoxia. The glucose uptake and lactate production under hypoxia were higher than those under normoxia. The expression levels of HK2 and PDK1 were most significantly increased. After siRNA knockdown of HIF-1 α in Eca109 and KYSE150, the proliferation of Eca109 and KYSE150 were suppressed. The glucose uptake and lactate production was significantly decreased under hypoxia. The mRNA and protein expression of HK2 and PDK1 was significantly down-regulated.

Conclusions: HIF-1 α promotes glycolysis of ESCA cells by up-regulating the expression of HK2 and PDK1 under hypoxia.

Key words: Esophageal cancer; Bioinformatics analysis; Hypoxia; HIF-1 α ; Glycolysis

484. LRRN4CL 在甲状腺癌中的预后价值和免疫学作用

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研究目的: 通过生物信息学的方法鉴定 LRRN4CL 在甲状腺癌中的表达谱和预后价值, 探讨 LRRN4CL 与免疫浸润之间的关系和潜在分子机制。

材料与方法: LRRN4CL 是一种新基因, 其功能尚未确定。最近有研究表明细胞表面蛋白 LRRN4CL 在黑色素瘤细胞中的表达上调导致肺转移性定植增强, 并且 LRRN4CL 的高表达水平与黑色素瘤患者存活率降低相关。目前尚不清楚 LRRN4CL 在甲状腺癌中的作用, 值得进一步探索。使用癌症基因组图谱 (TCGA) 数据库获取甲状腺癌的 RNA 测序数据和临床数据。使用 R 软件分析肿瘤和正常组织中 LRRN4CL 表达的差异。使用 Kaplan-Meier 生存曲线和 COX 分析分析了 LRRN4CL 与预后之间的关联。使用 ESTIMATE 算法和 CIBERSORT 分析了 LRRN4CL 表达与免疫浸润之间的关系。使用基因集富集分析 (GSEA4.1.0) 进行基因功能富集, 用于探索 LRRN4CL 的潜在分子机制。

结果: 与正常组织相比, LRRN4CL 在甲状腺癌组织中低表达。LRRN4CL 表达降低的甲状腺癌患者存活率降低, 临床分期更差。LRRN4CL 表达与甲状腺癌的基质评分和免疫评分之间存在相关性。LRRN4CL 表达与多种免疫细胞相关, 包括浆细胞, $\gamma\delta$ T 细胞, 未活化的 NK 细胞, 活化的 NK 细胞, 未活化的树突细胞。基因集富集分析结果显示, LRRN4CL 的表达水平与 NK 细胞介导的细胞毒性, 肿瘤相关信号通路, 自身免疫性甲状腺炎, 白细胞内皮迁移, T 细胞受体信号通路, 产生 IgA 的肠道免疫网络等信号通路有关。

结论: LRRN4CL 是一种具有前景的甲状腺癌的预后标志物, 并且在甲状腺癌的肿瘤免疫浸润中发挥重要作用, 值得通过实验进一步探索。

关键词: 生物信息学; 甲状腺癌; 预后; 免疫浸润; 自然杀伤细胞



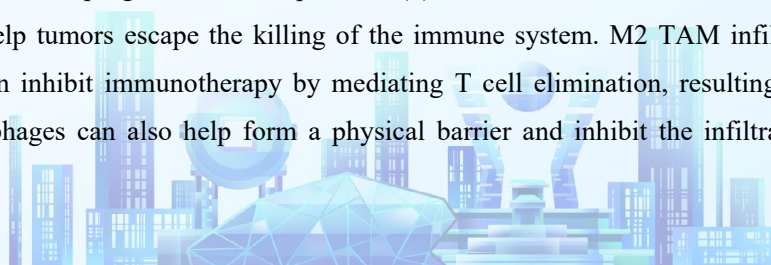
485. Effect and mechanism of pexidartinib combined with chemotherapy in the treatment of KRAS and BRAF mutant MSS colorectal cancer

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Introduction: Colorectal cancer (CRC) is one of the most common malignant tumors, and its incidence rate is third of all malignant tumors. The number of deaths due to CRC has risen to the second place. Chemotherapy is one of the standard treatment schemes for metastatic colorectal cancer (mCRC). The commonly used chemotherapy schemes are dual or triple drug schemes based on 5-fluorouracil (5-FU), oxaliplatin or irinotecan, but the toxicity is very difficult to tolerate, and the overall survival time of chemotherapy is difficult to prolong. Monoclonal antibodies targeting EGFR have low toxic and side effects, but are only used to treat KRAS and BRAF wild-type CRC, and the long-term use of cetuximab will accumulate rare drug-resistant subclones that cannot be detected at first. PD1 / PD-L1 immunotherapy brings the hope of complete tumor remission to many patients, but only MCRC with defective mismatch repair (dMMR) and microsatellite instability- high (MSI) respond to it. Only a few patients (about 5%) responded to the epidemic treatment, while the proportion of microsatellite stability (MSS) and positive mismatch repair (pMMR) reached 95%. Generally, tumors with abundant T cell infiltration are often called "hot tumors", which respond well to immunotherapy regulating T cell function (such as PD-1 / PD-L1 antibody); On the contrary, tumors with less T cell infiltration and more myeloid cell infiltration such as macrophages are "cold tumors", which are resistant to PD-1 / PD-L1 antibody therapy. KRAS / BRAF mutant MSS subtype MCRC, which accounts for about 30-50% of the total mCRC, is a typical "cold tumor", which is the most difficult to treat and has the worst prognosis.

The dense matrix of CRC solid tumors is rich in activated fibroblasts and tumor- associated macrophages (TAMs) which can be divided into M1 and M2. The main role of M1 TAM is to drive the response of type 1 T helper cells (Th1), which has cytotoxic activity to tumor cells; On the contrary, M2 TAM can not only participate in anti-inflammatory response, tumor angiogenesis and extracellular matrix remodeling by secreting anti-inflammatory cytokines, but also control inflammatory response by inhibiting M1 TAM mediated function and adaptive immunity, so as to occupy a dominant position in tumor microenvironment and promote tumor progression[4]. The infiltration number of M2 TAM is closely related to the prognosis of CRC patients: (1) M2 TAM can inhibit the tumor killing activity of T cells and help tumors escape the killing of the immune system. M2 TAM infiltrated in CRC liver metastases can inhibit immunotherapy by mediating T cell elimination, resulting in poor prognosis. These macrophages can also help form a physical barrier and inhibit the infiltration of T cells. (2)



TAM in CRC tumor microenvironment also makes tumor cells insensitive to chemotherapeutic drugs. Based on the important role of TAM in CRC, KRAS / BRAF mutant MSS CRC insensitive to EGFR targeting inhibitor and PD1 / PD-L1 is likely to become a new immunotherapy for the effective treatment of this kind of CRC.

As a specific drug, pexidartinib, a CSF-1R inhibitor, was approved by FDA in 2019 for the clinical treatment of Tenosynovial giant cell tumour(TGCT) , with good curative effect and low toxicity and side effects, but there is no report on the application of this drug in the treatment of CRC.

Results: Pexidartinib significantly inhibited the proliferation of CT26 subcutaneous transplanted tumor in vivo, a cell line with KRAS (G12D) mutation and MSS CRC, and combined with 5-FU, had a synergistic effect. CD206+cells, a marker of M2 TAM, decreased significantly in tumor tissues; Interestingly, iNOS+M1 TAM cells increased significantly. Moreover, Pexidartinib can selectively kill KRAS / BRAF mutant MSS CRC cells, such as SW480 (KRAS G12V mutant MSS subtype), T84 (KRAS G13D mutant MSS subtype) and HT29 (BRAF V600E mutant MSS subtype). Its activity was equivalent to that of 5-FU, but it was less sensitive to KRAS / BRAF wild-type MSS cells (Caco2) and KRAS / BRAF wild-type MSI cells (SW48).

Discussion: To sum up, we speculate that pexidartinib may kill KRAS / BRAF mutant MSS CRC cells through other unknown pathways and propose a scientific hypothesis: pexidartinib eliminates M2 TAM in tumor tissue microenvironment by targeted inhibition of CSF-1R, stimulates M1 TAM proliferation, increases M1 Tam infiltration, up regulates M1 / M2 ratio and inhibits CRC malignant progression; On the other hand, KRAS / BRAF mutant MSS type CRC cells were directly and selectively killed.

Key words: pexidartinib; tumor- associated macrophages (TAMs); KRAS / BRAF mutant MSS CRC

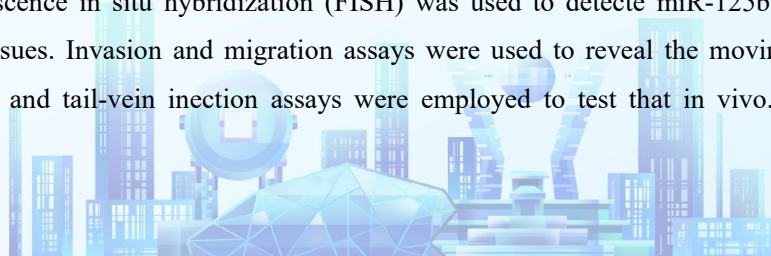
486. miR-125b promotes colorectal cancer migration and invasion by dual-targeting CFTR and CGN

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Aims: Metastasis contributes to the poor prognosis of colorectal cancer (CRC), the causative factor of which is not fully understood. Previously, we found that miR-125b contributed to cetuximab resistance in CRC. Here, we like to define the role it played in CRC metastasis.

Methods: Fluorescence in situ hybridization (FISH) was used to detect miR-125b expression level in microarray tissues. Invasion and migration assays were used to reveal the moving capacity of CRC cells in vitro, and tail-vein injection assays were employed to test that in vivo. What more, Dual-



luciferase reporter assay was used to verify the existence of binding structure between miR-125b and the 3'UTR of target genes.

Results: In this study, we identified a novel mechanism by which miR-125b enhances metastasis by targeting cystic fibrosis transmembrane conductance regulator (CFTR) and the tight junction-associated adaptor cingulin (CGN) in CRC. We found that miR-125b expression was upregulated in primary CRC tumors and metastatic sites compared with adjacent normal tissues. Overexpression of miR-125b in CRC cells enhanced migration capacity, while knockdown of miR-125b decreased migration and invasion. RNA-seq and dual-luciferase reporter assays identified CFTR and CGN as the target genes of miR-125b, and the inhibitory impact of CFTR and CGN on metastasis was further verified both in vitro and in vivo. Moreover, we found that miR-125b facilitated the epithelial-mesenchymal transition (EMT) process and the expression and secretion of uPA by targeting CFTR and enhanced RhoA/ROCK pathway activity by targeting CGN.

Conclusions: Together, these findings suggest miR-125b as a key functional molecule in CRC and a promising biomarker for the diagnosis and treatment of CRC.

Key words: Colorectal cancer; migration; invasion; metastasis; miRNA

487. 循环肿瘤细胞监测在极低危险度乳腺癌患者复查中的应用价值

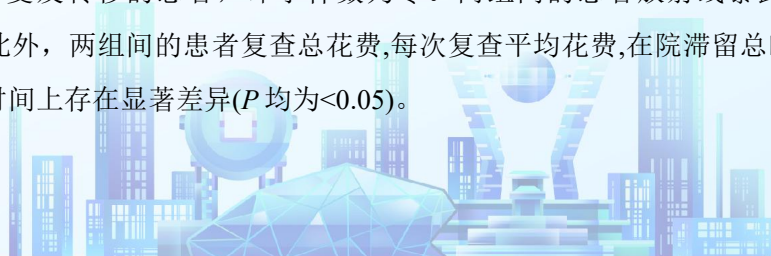
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背景: 无淋巴结转移的管腔 A 型乳腺癌患者预后明显优于其他亚型及其他分期。然而, 根据乳腺癌治疗指南, 患者的术后复查项目繁多且间隔较短。临床上亟需一种简单便捷、高敏感度的方法, 在这部分患者中替代复杂繁琐的影像学检查, 进而在保证复查有效性的基础上节省医疗成本。与影像学检查相比, 循环肿瘤细胞可以提前 4-6 个月提示异常。此外, 本团队既往研究表明循环肿瘤细胞监测可以在早期管腔 A 型乳腺癌中部分替代常规影像学复查。因此, 本研究探讨周期性循环肿瘤细胞监测能否完全替代无淋巴结转移的管腔 A 型乳腺癌患者的术后常规影像学复查。

方法: 131 例无淋巴结转移的管腔 A 型乳腺癌患者随机分为循环肿瘤细胞监测组(64 例采用循环肿瘤细胞监测)和对照组(67 例进行常规影像学复查)。记录两组患者的事件数, 在院滞留总时间, 患者复查总花费及放射线暴露剂量。

结果: 两组均没有复发转移的患者, 即事件数为零。两组间的患者放射线暴露剂量有显著差异($P < 0.001$)。此外, 两组间的患者复查总花费, 每次复查平均花费, 在院滞留总时间及每次复查在院滞留平均时间上存在显著差异(P 均为 < 0.05)。



结论:在无淋巴结转移的管腔 A 型乳腺癌患者中, 循环肿瘤细胞监测可以完全替代常规影像学复查, 在保证复查有效性的前提下, 极大地节省了医疗成本, 减少该部分患者不必要的放射线暴露。

关键词: 循环肿瘤细胞; 管腔 A 型乳腺癌

488. Prognostic and Clinicopathological Significance of upregulated circRNAs in Pancreatic cancer: a meta-analysis

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Abstract Background: Circ RNA is a type of RNA with a covalently closed configuration, which play important role in the development and progression of malignancies. This study aimed to evaluate the prognosis and clinicopathological significance of upregulated circ RNAs in pancreatic cancer.

Methods: Literature retrieval was conducted on PubMed, Embase, CNKI. The included studies were observational studies on the relationship between circRNA expression and prognosis in patients with pancreatic cancer. Pooled hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated to assess the association between circRNA expression, and overall survival (OS) and clinical parameters. Meta-analysis of total HR was performed using RevMan 5.3 software.

Results: A total of 15 eligible observational studies (979 cases of pancreatic cancer) were included. Meta-analysis for overall survival shows that the combined HR value is 1.91, 95%CI is 1.65-2.20, and the p-value is $p < 0.00001$. That the high expression of circRNA in pancreatic cancer is significantly associated with a poor prognosis of pancreatic cancer. Meta-analysis for clinicopathological parameters shows tumor differentiate (1.74, 95%CI 1.20-2.54), TNM stage (2.22, 95%CI 1.51-3.25), lymph node metastasis (2.42, 95%CI 1.60-3.65), distant metastasis (2.11, 95%CI 1.61-2.76) indicate unfavorable clinical features.

Conclusion: Upregulated circRNA expression is associated with poor prognosis in patients with pancreatic cancer, circRNA might be a useful prognostic biomarker in pancreatic cancer.

Key words: circular RNA; pancreatic cancer; prognosis

489. Transcriptomic N6-methyladenosine methylation loss in genes related to cell differentiation conferred by ALKBH5 misregulation is a hallmark of colorectal malignancy

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Background: N6-methyladenosine (m6A) modification is an emerging epigenetic regulatory mechanism in tumorigenesis. Considering that AlkB homolog 5 (ALKBH5) is a well-described m6A demethylase in previous enzyme assays, we aimed to investigate the role of m6A methylation alteration conferred by disturbed ALKBH5 in colorectal cancer (CRC) development.

Methods: Expression of ALKBH5 and its correlation with clinicopathological characteristics of CRC were evaluated using the prospectively maintained institutional database program of colorectal disease (IDPCD). The biological functions and underlying mechanisms of ALKBH5 were explored using in vitro and in vivo experiments. Moreover, methylated RNA immunoprecipitation (MeRIP), RNA-seq and m6A dot blot assay were applied to identify the target genes that were regulated by ALKBH5-induced m6A methylation change.

Results: ALKBH5 expression was significantly upregulated in CRC tissues compared to their adjacent normal tissues. Highly expressed ALKBH5 was found to be independently associated with worse overall survival (adjusted HR 1.63, 95% CI: 1.09-2.43; $P = 0.017$) after corrected by multiple clinicopathological risk factors. Next, we verified that ALKBH5 could promote CRC cells proliferation, migration and invasion in in-vitro assays, whereas its knockdown produced the opposite effects. Then, we determined the global m6A level of RNA in the scramble and ALKBH5-knockdown group through m6A dot blot assay. As expected, m6A levels were obviously increased after ALKBH5 was silenced in CRC cells. The integrating analysis of MeRIP-seq and RNA-seq for ALKBH5-silenced cells found a group of ALKBH5-target genes that were potentially regulated by RNA m6A modification. Gene Set Enrichment Analysis (GSEA) and Gene ontology (GO) analysis revealed that ALKBH5-target genes were mostly involved in cell differentiation (including ITGAX, TACSTD2, DPEP1, PTP4A1 and IFIT2).

Conclusions: The m6A methylation loss in cell differentiation-related gene mRNA is a hallmark in colorectal cancers. This hallmark is conferred by aberrant upregulation of ALKBH5, which could facilitate tumor development and serve as a valuable biomarker for colorectal malignancy.

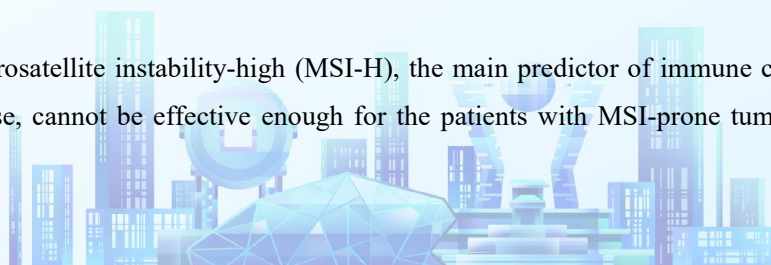
Key words: ALKBH5; Colorectal cancer; m6A modification; Hallmark

490. ATRX mutations as predictive biomarker for immune checkpoint inhibitors in female patients with MSI-prone tumors

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Background: Microsatellite instability-high (MSI-H), the main predictor of immune checkpoint inhibitors (ICIs) response, cannot be effective enough for the patients with MSI-prone tumors. It still needs to



identify other predictive biomarkers of ICI response in MSI-prone tumors. Studies have confirmed the association of homologous recombination (HR) defects with improved ICIs efficacy. ATRX plays an important role in HR repair. A previous study reported female-biased injury caused by loss of ATRX. Therefore, we hypothesize that ATRX mutations may be associated with ICIs efficacy in female patients with MSI-prone tumors.

Methods: The genomic, transcriptomic and clinical data were extracted from two published ICIs-treated cohorts and The Cancer Genome Atlas (TCGA). We integrated multiple immunotherapy-related indicators to explore the association of ATRX mutations with anti-tumor immunity and tumor microenvironment. The indicators of anti-tumor immunity included tumor mutation burden (TMB), tumor neoantigen level, cytolytic activity score, inflammation signature score, immunologic constant of rejection score, IFN- γ signaling score, TGF- β pathway score and expression of eight immune checkpoint genes. The tumor microenvironment was characterized by 29 knowledge-based functional gene expression signatures with conserved immunotherapeutic predictive function and the abundance of tumor-infiltrating lymphocytes. We further made MSI-stratified analyses to investigate the independent role of ATRX mutation in anti-tumor immunity and tumor microenvironment. The prediction of chemotherapy and anti-PD1/anti-CTLA4 therapy sensitivity was performed by pRRophetic R package and method of subclass mapping, respectively.

Results: We found that ATRX mutations were correlated with better response and survival benefits from ICIs treatment in exclusively female patient. Only female ATRX mutated patients (ATRX-mt) showed enhanced anti-tumor immunity and inflamed tumor microenvironment. MSI-stratified analyses suggested that female ATRX-mt patients appeared the immune activation features in both MSI-H and non-MSI-H population. The enhancement of ICIs-related immune properties did not depend on MSI status. There might exist synergistic effect between ATRX mutations and MSI-H in female patients. Furthermore, female ATRX-mt patients were more sensitive to both anti-PD1 therapy and chemotherapy.

Conclusions: Our work suggested the correlation of ATRX mutations with ICIs efficacy in female patients with MSI-prone tumors. ATRX mutations might serve as the potential biomarker for ICIs response in both MSI-H and non-MSI-H population. The combination use of ATRX mutations and MSI-H might be of clinical utility to better identify female responders of ICIs.

Key words: ATRX mutations; biomarker; immune checkpoint inhibitor; female patients; MSI

491. TCTN2 在脑胶质瘤患者中的表达及其临床预测价值

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目的: 分析 TCTN2 在多种肿瘤中的表达情况, 分析其在胶质瘤患者中的表达与生存预后的相关性, 探究 TCTN2 在肿瘤免疫微环境之中的作用。



材料与方法：采用 TCGA 及 GTEx 数据库 TCTN2 在不同肿瘤之中的表达情况，及具有表达差异的肿瘤患者总生存期。通过 STRING 数据库获得 TCTN2 的蛋白互作网络。再通过 TCGA 及 CGGA 数据库所得到的胶质瘤患者临床数据，采用单因素和多因素 COX 回归分析建立临床预测模型。

结果：通过 TCGA 数据库联合 GTEx 数据库对 33 种癌症进行泛癌分析发现，TCTN2 在肾上腺皮质癌（ACC），弥漫性大 B 细胞淋巴瘤（DLBC），胶质母细胞（GBM），肾乳头状细胞癌（KIRP），低级别胶质瘤（LGG），胸腺癌（THYM）中表达水平明显高于其对应的正常组织。通过对 TCGA 数据库中胶质瘤患者的临床数据进行分析发现，在 LGG 组,GBM 组,GBMLGG 组中，TCTN2 高表达患者的生存期明显低于低表达的患者。（LGG 组： $P<0.0001$ ，GBM 组： $P=0.0085$ ，GBMLGG 组： $P<0.0001$ ）。而在 CGGA 数据库额分析中发现，TCTN2 在所有级别胶质瘤患者数据的分析中，高表达患者生存期低于低表达组（ $P<0.0001$ ），在 WHO II 级中及在 WHO III 级中存在统计学差异（WHO II $P=0.023$;WHO III $P=0.0041$ ），但在 WHO IV 级中无统计学差异（ $P=0.46$ ）。然而有趣的是，CGGA 数据库中分析发现，TCTN2 的表达与胶质瘤患者的 WHO 分级有关（ $P<0.0001$ ），男女性表达水平也存在一定的差异（ $P=0.014$ ），其中在 WHO IV 及中，男女性表达差异最为明显（ $P=0.027$ ）。此外我们还研究了 TCTN2 在免疫浸润中的作用，我们分析发现，TCTN2 与巨噬细胞,中性粒细胞,Th2 细胞,细胞毒性细胞水平具有正相关性，提示其可能在肿瘤微环境中发挥作用。

结论：TCTN2 的表达水平在多种肿瘤组织中明显增高。其表达水平的高低与胶质瘤患者分级及生存期具有统计学意义。且 TCTN2 还与免疫浸润相关，提示 TCTN2 可能为脑胶质瘤免疫治疗中的潜在靶点。

关键词：TCTN2；泛癌；预后分析；免疫浸润

492. h-BN 纳米片/Au@Ag 纳米颗粒基底用于比率型 SERS 检测 乳腺癌细胞来源外泌体

张琪*,张滢之,徐章润

东北大学

外泌体作为细胞分泌的产物，其来源广泛且携带有丰富的遗传物质，可以为癌症早期诊断提供重要信息，是极具潜力的肿瘤生物标志物[1]。然而，外泌体的异质性使其难以通过单个表面蛋白标志物准确鉴别癌症类型[2]。二维六方氮化硼纳米片（hexagonal boron nitride nanosheets, h-BNNSs）是一种无机石墨烯类似物，具有优异的稳定性和高比表面积，可通过 π - π 相互作用将 DNA 链自组装到其表面用于生物传感[3,4]。本工作中，基于双适配体识别和比率型表面增强拉曼光谱（surface-enhanced Raman scattering, SERS）策略，提出了以 h-BNNSs 包覆 Au@Ag

纳米颗粒 (Au@Ag nanoparticles, Au@Ag NPs) 作为增强基底的 SERS 传感器。通过一段标记 Cy3 的互补 DNA 将 EpCAM 适配体和 HER2 适配体连接, 构建得到部分互补双链 DNA 探针。h-BNNSs 表面吸附构建的 DNA 探针, 用于特异性识别乳腺癌细胞来源的外泌体。当乳腺癌细胞来源的外泌体存在时, 将 DNA 探针从 h-BNNSs 表面分离, 使得标记 Cy3 的互补 DNA 远离基底, SERS 信号随着外泌体浓度的增加而降低。修饰在 Au@Ag NPs 表面的 4-巯基苯甲酸用作内标, 实现外泌体的比率型 SERS 检测。实验结果表明, Cy3 的 SERS 强度随外泌体浓度的增加而降低, 4-巯基苯甲酸的 SERS 强度保持不变。本文所提出的比率型 SERS 传感策略具有良好的灵敏度, 可为外泌体的精准识别和癌症的早期诊断提供新路径。

关键词: h-BNNSs/Au@Ag NPs; 比率型 SERS; 外泌体; 双适配体识别

493. 肿瘤相关性低磷性骨软化症一例报告

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华中科技大学协和深圳医院

目的: 探讨肿瘤相关性低磷性骨软化症(Tumor induced osteomalacia, TIO)的临床特点及诊治要点, 减少误诊和漏诊。

方法: 回顾性分析我院收治的 1 例 TIO 患者的临床资料, 并复习相关文献。

结果: 本例因双下肢无力, 疼痛 1 年余, 加重伴全身痛 3 月就诊。曾于外院及我院住院治疗, 查血无机磷 0.40 mmol/L, 结合髋部、腰椎骨密度测定及股骨颈 MRI, 考虑严重骨质疏松及股骨颈不完全性骨折, 予对症治疗后效果不佳。入院后行血清 FGF23 因子检测, PET-CT 及手术病理检查确诊为 TIO, 予卧床, 补磷, 补钙, 止痛, 抗骨质疏松等对症治疗, 复查血无机磷 1.21 mmol/L, 已能扶拐行走, 双髋关节疼痛减轻, 全身骨骼疼痛明显缓解后出院, 嘱定期复查血磷, 预防复发。

结论: 接诊低血磷, 全身不明原因的骨痛和肌无力患者要考虑到 TIO 可能, 完善相关医技检查, 避免或减少误诊和漏诊。

关键词: 肿瘤相关性低磷性骨软化症; 低磷血症; 血清成纤维细胞生长因子

494. LINC01559/MYH9 axis promotes the growth of gastric cancer via Wnt/ β -catenin signaling pathway

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Research purposes: Gastric cancer (GC) is one of the most common malignant tumors of the digestive system. The etiology of GC is complex, and much more attention should be paid to genetic factors. The present study aimed to determine the potential functions and the molecular mechanisms of long intergenic non-protein coding RNA 1559 (LINC01559) underlying progression of gastric cancer (GC).

Materials and methods: A quantitative reverse transcriptase-polymerase chain reaction (qRT-PCR) was used to measure the expression of LINC01559 in GC cell lines and normal cells. After silencing LINC01559 in GC cells, a cell counting kit-8 assay monitored the viability of the cells. qRT-PCR and western blot documented the EMT key genes in response to LINC01559 change. In order to explore the role of LINC01559 in vivo, we subcutaneous inoculated or injected through the tail vein with AGS cells stably knocking down LINC01559 or control cells to establish xenograft tumor growth model or lung metastasis model. Mechanistically, chromatin immunoprecipitation, luciferase reporter, RNA pulldown, mass spectrum, RNA immunoprecipitation and fluorescence in situ hybridization assays were executed.

Results: LINC01559 was significantly upregulated in GC tissues from GEPIA database (Figure 1) and cells (Figure 2). Knockdown of LINC01559 strikingly inhibited the proliferation and invasion of GC cells in vitro (Figure 3-5). Further mechanistic research proved that LINC01559 can bind to myosin heavy chain 9 (MYH9) by RNA pull-down assay and mass spectrometry analysis (Figure 6). RNA immunoprecipitation (RIP) experiments confirm the binding of LINC01559 to MYH9 (Figure 7). Knocking down of LINC01559 could inhibit the expression of MYH9, and also influence the protein expression of β -catenin and p-GSK3 β (Figure 8), which are key molecules of the Wnt/ β -catenin signaling pathway. It suggested that abnormal expression of LINC01559 could influence aberrantly activation of the Wnt/ β -catenin signaling pathway and promoted tumor progression in GC. Furthermore, we found that upstream transcription factor ETS homologous factor (EHF) might promote the biogenesis of LINC01559. In vivo assay and further mechanism research are still in progress.

Conclusions: LINC01559 may promote the proliferation, invasion and the EMT process by binding MYH9 via Wnt/ β -catenin signaling, which indicates that LINC01559 /MYH9 might be an axis that could be further used as a biomarker to help with the diagnosis of GC.

Key words: LINC01559; gastric cancer; MYH9; β -catenin

495. Pan-cancer Analyses Reveal an Universal Gene Signature Associated with the Response to Immune Checkpoint Inhibitors

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Background: By exerting anti-tumor effects through augmenting adaptive immunity, immune checkpoint inhibitors (ICIs) have achieved remarkable survival improvement in multiple cancers. However, 60%-70% of patients showed primary resistance to anti-PD-1/PD-L1 agents, and the detailed underlying mechanisms remained to be elucidated. Many studies have tried to distinguish the potential responders from the vast majority of non-responders with promising biomarkers in each individual cancer type, but a universal marker panel for ICIs response prediction is still lack in the clinical setting of pan-cancer test.

Methods: The clinical and transcriptomic data are collected from 15 randomized controlled trials (RCT) studying ICIs in solid tumors (melanoma, urothelial cancer, non-small cell lung cancer, renal cell cancer, breast cancer, and esophageal cancer). A modified Z-score was used to standardize the expression data. Patients were randomly allocated to the training and validation cohort. The differential expression genes between ICIs responders and non-responders were identified as response-related genes (RRGs). Gene Set Enrichment Analysis (GSEA) and Gene Ontology (GO) analyses were performed. The identified RRGs were used to fit a LASSO regression model with the generated immune response score (IRS). The performance of the model was evaluated by receiver operator characteristic (ROC) curve analysis.

Results: 1286 patients were included, among which 426 were responders and 860 were non-responders. 900 and 386 patients were allocated to the training and validation cohort, respectively. Fifty genes with $FDR < 0.05$ were identified as RRGs by differential expression analyses in the training cohort. Multiple known immune response markers, such as CD8A, CD8B, FOXP3, NKG7, and CXCL9, were among the top-rank genes in the RRGs. In addition, the well-known immune exhaustion markers, such as PDCD1, IDO1, CTLA4, TIGIT, LAG3, and CD244, were top-ranked in the RRGs. In the GO analysis, the RRGs were annotated to be highly related to the immune system process, immune response, and lymphocyte activation. Moreover, the GSEA analysis indicated that the epithelial-mesenchymal transition might contribute to the response to ICIs. A total of 26 genes was finally included in the LASSO regression model, and the areas under curve (AUC) of ROC were 0.85 and 0.81 in the training and validation cohorts, respectively. The IRS was further found to be positively correlated with the mutation burden of crucial genes and the tumor immune infiltration density, which have been shown to effectively predict ICIs response in the previous studies.

Conclusions: By analyzing multiple RCT cohorts, we identified an universal gene signature that was associated with ICIs response across different cancer types and thus provided a valuable resource for exploring the common mechanism of ICIs response independent of tumor origin. The validated IRS serves well in predicting the response to ICIs. Our findings provide new insight into the ICIs treatment and may guide the clinical decision-making.

Key words: Cancer; Immune therapy; Biomarkers



496. m6A 诱导的 lncRNA FGD5-AS1 通过调控 wnt/ β -catenin 信号通路促进肝细胞癌的增殖,迁移和侵袭

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研究目的: 肝癌是在世界范围内最常见的恶性肿瘤之一,也是预后最差的肿瘤之一,其死亡率排在第五位,严重危害人类的生命健康。越来越多的证据表明,m6A 甲基化介导修饰的长链非编码 RNA(long non-coding RNA, lncRNA)参与多种生物学过程的调控,尤其在肿瘤中发挥了主要的调控角色。本研究以 lncRNA FGD5-AS1 为研究对象,从分子水平上揭示 m6A 诱导的 FGD5-AS1 调控肝细胞癌的发生机制,为肝细胞癌的治疗方案提供新的思路。

材料与方法: ①运用生物信息学分析目的基因的基本特征,评估 FGD5-AS1 与肝癌临床病理变量之间的相关性。②通过免疫组化在组织水平上验证 FGD5-AS1 在肝癌组织和癌旁组织的表达水平。③利用 CCK-8 实验,克隆形成实验来检测 FGD5-AS1 对肝细胞癌增殖的作用;利用划痕实验,transwell 实验来检测细胞转移,侵袭的作用;利用流式细胞仪的测定来检测细胞凋亡及周期。④通过 qRT-PCR,Western Blot 实验来验证 FGD5-AS1 及其调控蛋白对肝细胞癌表达和功能的影响。⑤FGD5-AS1 对肝细胞癌的影响通过异种移植裸鼠模型得到证实。

结果: 我们前期利用生物信息学方法,建立与 m6A 共表达的 lncRNAs,筛选并确定与肝癌密切相关的一个 m6A 介导的 lncRNA (FGD5-AS1),并评估其与临床病理特征,预后之间的关系。结果表明,FGD5-AS1 在肝癌组织和细胞中表达显著上调,高表达的 FGD5-AS1 可能有相对较差的预后。沉默 FGD5-AS1 抑制了肝癌细胞系的增殖,迁移和侵袭。而 FGD5-AS1 的过表达增加了 β -catenin 和细胞周期蛋白 D1 的 mRNA 和蛋白质水平。体内肿瘤生长试验表明,FGD5-AS1 通过激活 wnt/ β -catenin 通路加速肝癌的发展。

结论: FGD5-AS1 通过调控 wnt/ β -catenin 信号通路发挥癌基因的作用,从而促进肝细胞癌的增殖,迁移和侵袭。

关键词: m6A ; FGD5-AS1; 肝细胞癌; wnt/ β -catenin; 信号通路

497. 结肠腺癌 M6A 预后相关 lncRNA 特征分析

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目的: N6-甲基腺苷 (M6A) 是 RNA 中最普遍的表现遗传修饰,在结肠腺癌 (COAD) 的进展中起重要作用。近年来研究表明, lncRNA 在表现遗传调控,细胞周期调控和细胞分化调控等生理活



动中发挥重要作用。然而，m6A 相关的 lncRNA 在 COAD 中的预后作用尚未完全阐明。本研究旨在探讨 M6A 相关 lncRNA 信号在 COAD 中的生物学功能和预后作用。

方法: 收集 TCGA 数据库中 514 个 COAD 样本的 RNA-seq 及临床数据，采用 Pearson 相关性分析对样品中 m6A 相关 lncRNA 的表达进行分析；通过 m6A 相关 lncRNA 聚类分析将样本进行分型。采用生存分析，lasso 回归对样本进行独立预后模型的建立并运用 GEO 数据库样本进行模型验证。采用基因集富集分析(GSEA)方法进行 KEGG 和 GO 富集分析。

结果: 通过 Pearson 相关性分析筛选出 71 个 M6A 相关 lncRNA，并通过聚类分析将样本分为 cluster1, cluster2;对两组样本进行生存分析发现 cluster2 总体生存情况好于 cluster1 ($P<0.001$)。lasso 回归确定了与预后相关的 11 个 M6A 相关 lncRNA，并将样本分为高风险组与低风险组，结果显示低风险组总体生存情况好于高风险组 ($P<0.001$)。GEO 数据库模型验证显示 lncRNA 可以作为一个独立的预后因素来预测 COAD 的生存时间($P<0.001$)。GSEA 结果显示高风险组主要富集在细胞外基质受体相互作用,局部粘连和细胞因子-细胞因子受体相互作用途径，而低风险组则富集在碱基切除修复途径。同时，我们对 COAD 免疫微环境进行了分析发现低风险组的免疫细胞浸润情况要好于高风险组 ($P<0.001$)。最后我们对免疫检查点进行了分析发现免疫检查点抑制剂免疫疗法对低风险组可能更有效 ($P<0.01$)。

结论: m6A 相关的 lncRNA 可以独立预测 COAD 的生存时间，并有助于个性化免疫治疗策略的制定。

关键词: 结肠腺癌；N6-甲基腺苷；lncRNA；预后

498. TRIB2 regulates the expression of miR-33a-5p through the ERK/c-Fos pathway to affect the IM-resistance of CML cells

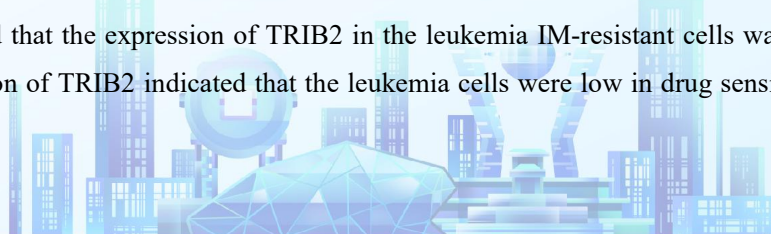
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Objective: To explore the molecular mechanism of TRIB2 mediating drug resistance in chronic myeloid leukemia (CML) cells through regulation of miR-33a-5p.

Methods: The expressions of TRIB2 and miR-33a-5p in leukemia K562 cells and IM-resistant cells were detected by RT-PCR. The growth of leukemia cells and IM-resistant cells and drug half inhibition rate (IC50) were evaluated by Cell Counting Kit-8 (CCK8) assay. Western blot, RT-PCR and luciferase assay were performed to determine how TRIB2 regulates miR-33a-5p. Immunoprecipitation (IP) and chromatin-immunoprecipitation (ChIP) were used to investigate the molecular mechanisms of c-Fos. The miR-33a-5p promoter was truncated to explore the specific fragment of TRIB2. The point mutation method was used to mutate the active site, and the role of the site was verified by luciferase assay. Blood cell count and blood smear were used to determine the success of model mice.

Results: We found that the expression of TRIB2 in the leukemia IM-resistant cells was increased, and the high expression of TRIB2 indicated that the leukemia cells were low in drug sensitivity. Functionally,



depletion of TRIB2 inhibits the proliferation of cancer cells and reduces the IC₅₀ value, while the overexpression of TRIB2 accelerates cell growth and promotes cell resistance. At the same time, in vivo experiments with tumor-bearing mice and mouse modeling also verified this result. Through the truncation experiment of miR-33a-5p promoter, it was found that c-Fos could play a role in the promoter-534~1124 fragment. Through IP and CHIP, it was found that the transcription factor c-Fos could inhibit the transcriptional activity of miR-33a-5p promoter. Further studies have shown that TRIB2 can regulate c-Fos through the ERK pathway and inhibit the expression of miR-33a-5p by enhancing the transcriptional activity of c-Fos. Overexpression of miR-33a-5p can inhibit cell growth and reduce the drug resistance of drug-resistant cells, knockdown of miR-33a-5p promotes cell proliferation and reduces the sensitivity of drug-resistant cells to drugs.

Conclusion: In conclusion, TRIB2 can regulate c-Fos expression through the ERK signaling pathway. Thus, it reduces the effect of miR-33a-5p expression on IM resistance in CML. Our study is promising for the clinical treatment of IM resistance in CML and can broaden the ideas of clinical treatment of IM resistance, and address the problem of clinical patient resistance.

Key words: TRIB2; CML; IM-resistance; c-Fos; miR-33a-5p

499. RFWD2 Knockdown as a Blocker to Reverse the Oncogenic Role of TRIB2 in Lung Adenocarcinoma

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RFWD2, an E3 ubiquitin ligase, is overexpressed in numerous human cancers. The roles of RFWD2 in cancer are related to the targeting of its substrates for ubiquitination and degradation. This study aimed to investigate the role of TRIB2 in relation to the regulation of protein degradation through RFWD2. inBio Discover™ results demonstrated that TRIB2 can perform its functions by interacting with RFWD2 or other factors. TRIB2 can interact with and regulate RFWD2, which further attends the proteasome-mediated degradation of the RFWD2 substrate p-IkB-a. TRIB2 colocalizes with RFWD2-related IkB-a to form a ternary complex and further affects the IkB-a degradation by regulating its phosphorylation. TRIB2 acts as an oncogene and promotes cancer cell proliferation and migration, whereas RFWD2 knockdown reversed the role of TRIB2 in promoting cancer cell growth and colony formation in vitro and in vivo. In summary, this study reveals that TRIB2 promotes the progression of cancer by affecting the proteasome-mediated degradation of proteins through the interaction with RFWD2.

Key words: RFWD2; proteasome-mediated degradation; TRIB2; cancer therapy; target gene



500. EGFR 基因 19del 和 L858R 突变的 IIIB/IV 期非小细胞肺癌 一线 TKI 疗效回顾及血清 lncRNAs 与 miRNAs 差异表达分 析

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研究目的：本研究拟从转录组层面探讨非小细胞肺癌 EGFR 基因 19 外显子的框架内缺失（19del）与第 858 位的 21 外显子的点突变（L858R 突变）之间的血清 lncRNAs 与 miRNAs 的差异表达。

材料与方法：研究收集了 2015 年 1 月至 2020 年 9 月本中心收治的 IIIB/IV 期不能手术的非小细胞肺癌患者共 96 例。入组患者均经基因检测确认为 EGFR 基因 19del 或 L858R 突变，且一线接受标准 EGFR-TKI 治疗，包括吉非替尼（250mg/d），厄罗替尼（150mg/d），埃克替尼（375mg/d）。根据基因突变类型，入组患者分为两组：EGFR 基因 19del 组和 L858R 突变组。应用生存曲线分析两组无进展生存之间的差异。本研究收集了 EGFR 基因 19del 与 L858R 突变的非小细胞肺癌血清各 3 例，采用 DNBSEQ 平台进行转录组测序，应用 Dr.Tom 系统进行基因的分析。

结果：入组患者中 49 例为 EGFR 基因 19del，47 例为 EGFR 基因 L858R 突变（表 1）。两组患者的年龄、性别、吸烟、饮酒、ECOG PS、临床分期等临床特征无显著差异。本中心回顾性分析显示 IIIB/IV 期非小细胞肺癌患者，EGFR 基因 19Del 组 PFS 较 L858R 突变组显著延长（324 天 vs 259 天, log-rank $P=0.03$ ）（图 1）。转录组测序显示，EGFR 基因 L858R 突变的三例血清中共同表达 lncRNAs 为 7309 个（图 2），共同表达 miRNAs 为 209 个（图 3）。EGFR 基因 19del 三例血清中共同表达的 lncRNAs 为 8099 个（图 4），共同表达 miRNAs 为 142 个（图 5）。lncRNAs 与 miRNAs 差异基因聚类热图（图 6，7），lncRNAs 的 GO 富集（图 8）及 KEGG 通路富集（图 9）。lncRNAs 测序组中，249 个显著上调，305 个显著下调。经关联转换（rnaplex max MFE=-100，max num=10），网络分析（rnaplex max MFE=-100），筛选出存在互作关系的 lncRNAs 共 44 个，其中上调的 23 个，下调的 21 个，互作关系如图（图 10）。通过位置关系（ $P<0.05$ 且 $|\log_2FC| \geq 2$ ），筛选出与 mRNA 存在位置关系互作的 lncRNAs 共 10 个，其中上调的 6 个，下调的 4 个（图 11）。miRNAs 测序组中，显著上调的 7 个，显著下调 13 个，经 targetscan，Miranda，rnahybrid 软件共同预测到 1890026 个靶基因（图 12）。

结论：本研究揭示了非小细胞肺癌 EGFR 基因 19del 与 L858R 突变两组之间的血清 lncRNAs 及 miRNAs 的差异表达，为探索 EGFR 突变状态的血清标记物提供了理论依据，为预测 EGFR-TKI 疗效的血清标记物提供了潜在线索。

关键词：非小细胞肺癌；EGFR 突变；血清；lncRNAmiRNA



501. LASS2 通过与 p62/CSNK2A1/HSP90/HSP70 互作介导 甲状腺未分化癌 8505c 细胞自噬与凋亡

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目的： 研究 LAG1 长寿保障基因 2(LAG1 longevity assurance homologue 2, LASS2)对甲状腺未分化癌(anaplastic thyroid cancer, ATC)细胞株 8505c 凋亡及自噬的影响及可能的分子机制。

方法： 采用重组腺病毒分别感染甲状腺未分化癌 8505c 细胞, 分为阴性对照组(NC 组),空载组(Adv-GFP 组),实验组(Adv-LASS2-GFP 组)。感染 48 h 后分别提取各组细胞总 RNA 和蛋白, 采用实时荧光定量 PCR(qRT-PCR),Western blot 检测 LASS2 mRNA,蛋白表达水平的变化; CCK-8,克隆形成实验评价各组细胞增殖能力的差异; TUNEL 染色评估各组细胞凋亡水平; 透射电子显微镜观察细胞微观结构的变化; Western blot 检测各组细胞凋亡及自噬相关蛋白(Cyto-c,A-casp-3,Bcl-2,Bax, p62,LC3A/B,Beclin-1) 的表达水平; co-IP/LC-MS 鉴定与 LASS2 互作的蛋白, 结合生信分析并经 co-IP Western blot 进一步验证互作关系。

结果： 与 NC 组,Adv-GFP 组相比, Adv-LASS2-GFP 组 LASS2 mRNA,蛋白表达水平均明显上调(均 $P<0.01$), 且随时间增殖能力明显抑制($P<0.01$),克隆形成能力降低($P<0.001$),细胞凋亡增加($P<0.001$); 透射电镜结果显示, 与 NC 组,Adv-GFP 组相比, Adv-LASS2-GFP 组细胞可见双层膜结构的自噬小体以及大量的自噬溶酶体; Western blot 结果显示 Adv-LASS2-GFP 组 Bcl-2,p62 蛋白相对表达水平较 NC 组,Adv-GFP 组均明显下调($P<0.01$), Bax,Cyto-c,A-casp-3,Beclin-1,LC3A/B 表达水平均明显上调($P<0.01$); 经 co-IP/LC-MS 鉴定与 LASS2 互作的蛋白, 并行 GO pathway,STRING 等生信分析, 结果提示 LASS2 与 p62/CSNK2A1/HSP90/HSP70 可能存在直接或间接互作关系。但 co-IP Western blot 分析结果提示 LASS2 与 p62 不存在结合, 提示两者可能存在中间蛋白参与互作。

结论： LASS2 可能通过与 p62/ CSNK2A1/HSP90/HSP70 互作介导分子伴侣自噬,进而促进 8505c 细胞凋亡, 在抑制 ATC 进程发挥一定作用。

关键词： LASS2; 甲状腺未分化癌; 自噬; 凋亡

502. PNI,GNRI,CONUT 评分系统对老年卵巢癌患者总生存期的预测价值

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目的：分析比较老年营养风险指数（geriatric nutritional risk index，GNRI），预后营养指数（prognostic nutritional index，PNI），营养控制状态评分（controlling nutritional status，CONUT）三种营养风险评估系统应用于卵巢癌患者预后的预测价值。

方法：选取了 2007 年 1 月 1 日至 2020 年 12 月 31 日期间在华中科技大学同济医学院附属同济医院妇产科接受治疗且年龄大于 50 岁的卵巢癌患者进行回顾性分析。通过使用 X-tile 确定 cutoff 值，根据各指标分组后 Kaplan-Meier 法绘制生存曲线，并进行 Log-rank 检验比较组间生存差异，Cox 回归模型进行多因素分析来探讨影响患者总生存期相关的预后因素。

结果：选取了 89 名患者，平均年龄为 63 ± 5.7 岁。我们根据 GNRI 评分分为高 GNRI (> 93.4 ; $n = 66$) 和低 GNRI (≤ 93.4 ; $n = 23$)，PNI 评分分为高 PNI (≥ 41.8 , $n = 63$) 和低 PNI (< 41.8 , $n = 26$)，CONUT 评分分为高 CONUT (> 6 , $n = 12$) 和低 CONUT (≤ 6 , $n = 77$) 进行分组，并评估两组之间的总生存期 (OS)。GNRI ≤ 93.4 , CONUT > 6 , PNI < 41.8 与患者总生存期下降有关，差异有统计学意义 (HR=5.738, 95% 置信区间: 1.646-20.00, $P=0.0002$; HR=0.1652, 95% 置信区间: 0.02455-1.111, $P=0.0001$; HR=4.534, 95% 置信区间: 1.406-14.62, $P=0.0015$)。在 Cox 回归风险模型多因素分析发现, 低 GNRI (OR:0.196(0.056-0.687), $P=0.011$) 和高 CONUT (OR:4.178(1.017-17.164), $P=0.047$) 是总生存期的危险因素。

结论：GNRI 评分, CONUT 评分系统可以作为有效预测老年卵巢癌患者预后的客观营养风险指标。

关键词：老年；卵巢癌；营养风险；预后

503. Aberrant ploidy in cancer

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Aberrant ploidy status is a prominent characteristic among malignant neoplasms. About 90% of solid tumors and 75% of hematopoietic malignancies show aneuploidy status while 40%-60% of tumors have undergone whole genome doubling, which indicates that the numerical chromosomal changes might be a prevalent and significant genomic aberration. Although the debate of whether the ploidy shifts are the affiliated byproduct or the primary trigger has not stopped, current studies still suggest that the abnormal ploidy cancer cells might be the dangerous minority in cancer development. The role of aberrant ploidy in cancer might experience dynamic variation, shaped by genomic context, tumor stage, tumor dissemination, tissues specificity and immune microenvironment in the whole process of tumor progression. With different traits from diploidy, aberrant ploidy cells are more prone to numerical and structural chromosomal changes or other genomic alterations accompanied with fitness coast and survival stress. Thus, abnormal ploidy status and ploidy shifts exert advantageous effects in selection evolution as well as the detrimental effects which can provide chances for targeted therapy.

In this paper, based on the current cancer studies related ploidy abnormalities, we reviewed some crucial definitions and the complicated reciprocity among diverse genomic alterations as well as their role in cancer. In addition, we also provide some thoughts about crucial issues for future ploidy researches including prognostic analyses, models and detection methods, and also potential alternatives of ploidy-selective targeting. Although the driver mutations and pathways are still the mainstream of cancer researches, increasingly accumulated evidences do show the mysterious charm of ploidy shifts in cancer therapy

Key words: Aneuploidy; Polyploidy; Chromosomal instability; Whole Genome Doubling; TP53 mutation; Cancer Development;

504. 利用常见血清肿瘤标志物构建肺癌病理分型的风险预测模型

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目的: 联合运用六种常见血清肿瘤标志物建立预测肺癌常见病理分型的风险模型。

方法: 回顾性分析新疆医科大学附属肿瘤医院 2012 年 5 月至 2013 年 5 月收治的 342 例肺癌患者和 91 例肺部影像学可疑并确诊非肺癌患者的临床资料。对六种肿瘤标志物进行热图分析, 得到肿瘤标志物和肺癌各病理亚型的关系。Logistic 回归分析筛选各病理亚型独立预测指标, 并构建预测模型。通过受试者工作特性 (ROC) 曲线下面积 (AUC) 评估各个模型的预测能力。运用 Bootstrap 重抽样法对模型的预测能力进行内部验证。

结果: 热图分析结果显示 Pro-GRP 和 NSE 预测小细胞肺癌, SCC 和 CYFRA21-1 预测肺鳞癌, CA125 和 CEA 预测肺腺癌的组合更好。小细胞肺癌、肺鳞癌和肺腺癌预测模型对应的 AUC 分别为 0.938, 0.965 和 0.965。模型预测能力的内部验证表明三个模型预测效果理想。

结论: 血清肿瘤标志物联合患者一般资料构建针对肺癌患者病理分型的风险预测模型预测效果较好, 未来进一步验证后可以展示在检验报告单上, 为临床医生进一步诊疗提供帮助。

关键词: 血清肿瘤标志物; 肺癌; 病理分型; 预测模型

505. 三阴性乳腺癌肿瘤干细胞的悬浮培养及干细胞表面标志物的研究进展

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研究目的: 通过悬浮培养法筛选出成球的干细胞, 同时综述最新研究发现的乳腺癌样细胞表面存在的特异性标志物。



材料与方法：将 MDA-MB-231 细胞以 1×10^4 个/ml 接种于超低粘附培养板，使用干细胞培养基进行培养。在超低粘附培养板的每个孔中加入约 2.0 ml 培养基，每 2~3 天补充 1/3 培养基，对细胞代谢产物进行稀释，培养约 7~14 天，可见乳腺癌细胞形成悬浮细胞球。

结果：乳腺癌是女性最常见的恶性肿瘤，在每年超过 92 万例新发癌症的女性中，乳腺癌约占所有确诊癌症的 30%，其发病率和死亡率均高居妇科肿瘤前列。目前常用的乳腺癌干细胞的特异性标志物主要为 CD29⁺,CD49f⁺,CD90⁺,CD133⁺,ALDH⁺,ESA⁺/CD44⁺/CD24⁻,CD44⁺/CD24⁻等。然而，最新研究发现，越来越多的乳腺癌干细胞靶点的出现为乳腺癌的靶向治疗提供了新的思路。蛋白 C 受体（PROCR）是乳腺中一个新的 Wnt 靶点。PROCR 阳性细胞定位于基底层，表现出上皮向间充质转化的特征，低水平表达基底角蛋白。PROCR 表达的细胞在移植实验中具有很高的再生能力，通过谱系追踪可以分化为所有的乳腺上皮细胞系。这些结果定义了一个新的多潜能乳腺干细胞群体，它可能在乳腺癌的发生中起重要作用。且约在 50% 的三阴性乳腺癌患者肿瘤细胞表面表达。最新研究发现，SGCE 可以影响乳腺癌干细胞的分化与更新。因此，针对 SGCE 的治疗可减少乳腺癌干细胞的自我更新与增值，从而达到抑制乳腺癌生长的目的。LSEctin 可以与 TNBC 细胞膜上的 BTX3A3 相互作用，可促进肿瘤干细胞的干性和促进肿瘤的发展，因此可称为乳腺癌的潜在治疗靶点。连接蛋白 Cx26 在肿瘤干细胞表面有较高水平表达，且该蛋白在肿瘤发展转移中起着重要的作用。

结论：乳腺癌干细胞的培养方式可成功筛选出乳腺癌干性细胞，为乳腺癌干细胞的研究提供了方法。同时，更多标志物的发现为乳腺癌的治疗提供了新的希望。

关键词：乳腺癌；干细胞；肿瘤标志物；悬浮培养法

506. 外周血 CTC 计数在肺结节良恶性筛查诊断中的作用探讨

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目的：通过对低剂量螺旋 CT 检出肺结节的患者采用外周血循环肿瘤细胞（CTC）光镜下计数诊断技术，结合随访脱落细胞病理学和或手术切除病变术中冰冻病理细胞形态及术后石蜡切片病理检查结果验证的方法，探讨外周血 CTC 细胞计数诊断技术在肺结节病变良恶性筛查诊断中的作用，以期指导临床精准分流肺结节良恶性病变患者。

材料及方法：收集 2019.12-2021.9 由低剂量螺旋 CT 检查发现肺结节且体检未发现其他脏器恶性肿瘤征象，未进行过放疗及化疗者按照技术规范要求使用 EDTA6.0 ml 抗凝真空采血管经由静脉采集 5ml 外周血，血液样本在 1h 内进行 CTCBIOPSY®异常细胞分离染色仪制片处理，制片后采用苏木素-伊红（HE）染色，树胶封片。具有丰富细胞学诊断经验的病理医师显微镜下观察细胞形态按照判读标准判读疑似 CTC,CTC,疑似 CTM 及 CTM，400 倍视野下血细胞分类计数器辅



助计数并采集图片，再由另一位病理医师复核，达成一致意见。结合随访痰和肺泡灌洗液细胞学、活检或单孔胸腔镜手术切除组织病理检查结果作为金标准验证，评估无创外周血 CTC 计数 HE 染色诊断技术的灵敏度与特异度。

结果：符合入组共 27 例，其中男 8 例，女 17 例，年龄 32-90 岁，结节大小 4-62mm；未查见 CTC/CTM 者 4 例，结节大小分别为 5mm、5.4mm、8mm 及 22mm，均无阳性病理发现且 CT 随诊 15-21 个月无进展；仅查见疑似 CTC 者 8 例，结节大小 6.2-62mm，1 例结节为 7mm 者术后病理结果为原位腺癌伴微浸润，2 例结节分别为 7mm 和 10mm 的术后病理结果为局灶肺泡间质纤维化，1 例肺多发实变者痰和肺泡灌洗液细胞查见异型细胞，1 年后 CT 随诊病灶吸收，考虑为炎症，1 例结节为 62mm 者临床拟诊中央型肺癌脑转移，无病理证实，余 3 例均无阳性病理发现且 CT 随诊 6-22 个月无进展；查见疑似 CTM 者 1 例，其结节大小为 45mm，临床拟诊为周围型肺癌骨转移，无病理证实；查见 CTC/CTM 者 14 例，结节大小 4mm-37mm，其中 1 例查见 CTC 同时查见疑似 CTM，结节大小为 27mm，术后病理为中央型鳞状细胞癌，脉管有累及且局部淋巴结有转移；有 2 例结节 6mm、8mm 术后病理诊断为原位腺癌伴微浸润，7 例结节 11mm-37mm 病理诊断为浸润性腺癌，有 2 例伴淋巴结转移；1 例 4mm 结节查见 3 个 CTC，痰和肺泡灌洗液细胞病理未见恶性肿瘤细胞，但纤维支气管镜活检示肺泡上皮小灶有不典型增生，1 年后 CT 随诊结节大小无变化；1 例 36mm 结节查见 7 个 CTC，有额部癌病史临床拟诊为肺转移瘤，肺无病理证实；1 例为 15mm 肺浸润性腺癌术后 1 年肺门淋巴结肿大，外周血查见大于 30 个 CTC，CT 随诊 12 个月双肺多发转移灶。总之，27 例肺结节病变者外周血中查见 CTC/CTM 者 14 例，其中有病理检查结果证实为恶性 13 例，未查见 CTC/CTM（包括疑似 CTC/CTM）者共 13 例，其中有病理检查结果证实为恶性 1 例，本组通过 CTC 计数判断肺结节良恶性的灵敏度 92.86%，特异度为 92.30%。

结论：由病理医生主导的无创外周血 CTC 计数 HE 染色诊断技术在筛查肺结节良恶性病变中的灵敏度及特异度均较高，虽然本组样本数较少，但其作为肺癌早期筛查的标志物具有较高的临床推广应用前景。

关键词：循环血肿瘤细胞（CTC）计数；HE 染色；肺结节；恶性；良性；低剂量螺旋 CT

507. 血浆外泌体来源的 hsa_circ_0003270 在结直肠癌中的差异表达及其作为诊断标志物的研究

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目的：探讨血浆外泌体来源的 hsa_circ_0003270 在结直肠癌患者中的差异表达，并分析其作为结直肠癌诊断标志物的潜能。



方法：选取 2019 年 9 月至 2020 年 8 月徐州医科大学附属医院经手术治疗且病理确诊为结直肠癌的患 78 例，选取同期于我院行健康检查的 78 例体检者作为非癌对照组，采用试剂盒方法提取结直肠癌及对照组血浆中的外泌体，并通过透射电子显微镜、蛋白免疫印迹分析及粒径分析鉴定提取的外泌体，应用实时荧光定量 PCR 方法检测 hsa_circ_0003270 的表达水平。通过绘制受试者工作特征曲线（ROC）判断 hsa_circ_0003270 诊断结直肠癌的效能。

结果：与对照组相比，hsa_circ_0003270 在结直肠癌患者血浆外泌体中显著高表达，hsa_circ_0003270 诊断 CRC 的灵敏度为 75.64%，特异度为 71.79%，ROC 曲线下面积为 0.7662。另外，与结直肠癌患者的临床病理资料相联系，高表达的 hsa_circ_0003270 与患者的淋巴结转移、TNM 分期呈正相关。

结论：高表达的 hsa_circ_0003270 有望作为结直肠癌的新型诊断标志物。

关键词：结直肠癌；环状 RNA；外泌体；诊断标志物

508. CD44 在骨肉瘤中的研究进展

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骨肉瘤是影响儿童和青少年的恶性骨肿瘤之一，骨肉瘤患者大多死于肺转移。虽然手术切除结合化疗延长了无转移骨肉瘤患者的无复发生存时间，但是已转移骨肉瘤患者的总体生存时间在近几十年并没有明显改善，所以急需寻求一种新的治疗方法。CD44 在肿瘤中是常见的干细胞标志物之一，在骨肉瘤中高表达。CD44 参与骨肉瘤的增殖、迁移和侵袭等肿瘤发展过程。miRNA 可以调节 CD44 的表达，CD44 是一种跨膜糖蛋白受体，配体也可以通过与 CD44 结合调节它的功能，主要配体是透明质酸。CD44 通过可变剪切可以形成 CD44Vs（CD44 Variants），CD44V6 在骨肉瘤中的表达较软骨肉瘤明显升高，CD44V6 的表达与骨肉瘤的转移和总生存率显著相关，CD44V6 有望成为骨肉瘤预后标志物。因此，本文主要对 CD44 在骨肉瘤中研究进展进行综述，希望对本领域的研究者有启发意义。

关键词：CD44；骨肉瘤；肿瘤；生物标志物

509. Cancer-associated fibroblast related gene signature predicts clinical outcomes and immune characters of gastric cancer

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Background: Cancer-associated fibroblasts (CAFs) play a key role in progression, immune evasion, and therapeutic resistance of gastric cancer (GC). Moreover, CAF associated genes have huge potential for prognosis evaluation, especially for predicting the efficacy of immunotherapy in GC.

Methods: A total of 1134 GC patients from TCGA-STAD, GSE62254, GSE84437 datasets and GC cohorts from Xijing hospital of digestive disease were included in this study. Firstly, we performed univariate COX regression analysis and Kaplan-Meier survival analysis to identify CAF associated prognostic genes. Subsequently, LASSO regression analysis was used to construct CAF gene signature (CAFGS) in TCGA-STAD training cohort. Then we evaluated the relationship between CAFGS and CAF infiltration. CAFGS's predictive value was evaluated in both the training and validation cohorts. The relationship between CAFGS and tumor microenvironment (TME) was investigated by ssGSEA, CIBERSORT and ESTIMATE. A nomogram of CAFGS was developed to predict the prognosis.

Results: 10 CAF associated genes were identified to develop CAFGS, which showed great predictive power in the training and validation sets. High CAFGS score could represent worse outcome for GC patients. We also found close relationship between CAFGS and immune cell infiltration. We showed that CAFs contribute to immune evasion and poor prognosis of GC patients by promoting the formation of immunosuppressive microenvironment. High level of CAF infiltration may attenuate the efficacy of immunotherapy. The nomogram based on CAFGS showed good ability in predicting prognosis and may deliver great clinical net benefits.

Conclusions: We developed a CAFGS model with great predictive value for GC prognosis evaluation. The model revealed a close relationship between CAFs and TME, and might be used to predict prognosis of GC in the future.

Key words: CAF; gastric cancer; tumor microenvironment; immunotherapy

510. 基于表观遗传学分析绘制肿瘤浸润免疫细胞图谱实现对肿瘤免疫特征的定量评估

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背景: 肿瘤浸润免疫细胞 (tumor-infiltrating immune cells, TIIC), 尤其是淋巴细胞 (tumor-infiltrating lymphocytes, TIL), 可用于预测化疗和免疫治疗的应答和生存结局。目前, 可通过组织病理学技术或转录组数据反卷积算法评估 TIIC。因此, 本研究旨在开发一项以 DNA 甲基化组学数据为基础的可以评估肿瘤微环境免疫特征的 TIIC 数字细胞分类计数器 (DNA methylation-based counter for TIIC, MeTIC)。

方法: MeTIC 数字细胞分类计数器是使用 Illumina 450K 甲基化芯片筛选的各类型免疫细胞特异的差异甲基化位点, 通过支持向量机机器学习的方法构建的。肿瘤微环境中的各种免疫细胞, 肿瘤细胞, 正常细胞, 其它细胞和两个肿瘤临床队列 (n=282 和 335) 被用于开发定量检测 DNA

甲基化的单碱基分辨率甲基化特异性 PCR (quantitative analysis of single-base methylation, QASM) 技术, 并用于验证 MeTIC 数字细胞分类计数器作为分子标志物的临床应用价值。

结果: 我们基于 DNA 甲基化芯片筛选出的各类免疫细胞特异的差异甲基化位点, 构建了 MeTIC 数字细胞分类计数器。MeTIC 可以特异地区分肿瘤微环境中的各类免疫细胞和肿瘤细胞。接下来, 我们开发了基于 QASM 的 MeTIC 数字细胞分类计数器, 能以一种完全定量, 准确和简单的方式定量评估 TIL。由 QASM 测定的 MeTIC-lymphocyte 评分与基于组织病理学评估的 TIL 计数和基于基因 mRNA 表达的 TIL 定量结果有很好的相关性。此外, MeTIC-lymphocyte 与肿瘤的高度微卫星不稳定状态相关, 并与更好的生存结局相关。

结论: 本研究开发了一种能在单碱基分辨率的表观遗传水平定量评估肿瘤微环境中各种免疫细胞的新型技术。这种方法有望广泛用于 TIL 的基础研究, 并有希望成为指导临床治疗 (包括肿瘤免疫治疗和化疗) 的生物标志物。

关键词: 甲基化标志物; 肿瘤微环境; 肿瘤浸润淋巴细胞; 免疫细胞; 免疫反应

壁报交流

511. 全身免疫炎症指数对胆囊癌术后生存的预测价值

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背景: 越来越多的证据表明, 全身免疫炎症指数(SII)可以预测各种实体肿瘤的预后。本研究的目的是探讨 SII 在胆囊癌根治术后, 预测患者预后的有效性。

方法: 回顾性分析了 93 例行根治性切除术的胆囊癌患者, 通过 ROC 曲线分析确定 SII 的 Cut off 值。采用 Pearsons χ^2 检验和 Fisher 精确检验分析 SII 与临床病理特征之间的关系。采用 Kaplan-Meier 法计算生存曲线。通过单因素分析来评估术前参数对预后的影响。采用多变量 Cox 回归比例风险模型评估变量在单变量分析中的显著性。

结果: 接受根治性切除术的胆囊癌患者的 Kaplan-Meier 生存分析和多因素分析显示 SII 能独立预测术后生存。单因素分析显示 TNM 分期, SII, CA19-9, ALP, 前白蛋白, NLR, MLR, 淋巴结转移, 组织病理学类型均与总生存率相关。在时间依赖性 ROC 分析中, SII-CA19-9 的 ROC 曲线下面积 (AUC) 高于术前 SII 或 CA19-9 用以预测术后生存的面积。

结论: 我们的结果表明, 高 SII 预示着接受根治性手术的胆囊癌患者长期预后不良。SII-CA19-9 分型可能对预测胆囊癌患者术后预后更有效。

关键词: SII; CA19-9; gallbladder carcinoma; prognosis

512. 评估细胞学, HR-HPV 在阴道镜拟诊中发生宫颈癌前病变的风险分层研究

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目的: 本研究旨在评估细胞学, 高危型人乳头瘤病毒 (high risk human papillomavirus, HR-HPV) 与阴道镜拟诊的不同组合发生宫颈上皮内瘤变 2 级及以上 (cervical intraepithelial neoplasia grade 2 or worse, CIN2+) 的风险, 并探讨细胞学和 HR-HPV 在阴道镜拟诊中的价值。

方法: 选取 2018 年 1 月至 12 月深圳市妇幼保健院阴道镜门诊数据库中 822 例患者的临床数据资料。根据患者三项检查结果 (细胞学, HR-HPV 以及阴道镜拟诊) 分为 18 个亚组, 比较不同组合发生 CIN2+ 风险的差异。

结果: 三项检查结果有两项及以上为高风险 (细胞学高度上皮内瘤变及以上 (high-grade squamous intraepithelial lesion or worse, HSIL+), HPV16/18+, 阴道镜拟诊高级别病变) 的亚组 CIN2+ 的风险均在 60% 以上; 三项结果均为高风险的亚组发生 CIN2+ 的风险为 97.1% (95%CI 85.1-99.9%)。

结论: 若三项检查结果中有两项及以上结果为高风险者, CIN2+ 的风险较高, 应予以重视, 减少不必要的误诊和漏诊。



关键词：细胞学检查；HR-HPV；阴道镜；宫颈癌；风险分层

513. 超声造影定量分析对乳腺癌新辅助治疗早期疗效评估的价值研究

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目的：探讨超声造影定量分析对乳腺癌新辅助治疗早期疗效评估的价值。

方法：回顾性分析乳腺癌新辅助治疗（Neoadjuvant Therapy, NAT）并行手术患者 60 例，均为单发病灶。治疗前，2 周期，4 周期及治疗结束后行超声造影检查，选择增强后病灶行定量分析，拟合生成时间-强度曲线（Time signal intensity curve, TIC），定量参数包括上升时间（Rise time, RT），峰值强度（Peak intensity, PI），平均渡越时间（Mean transit time, MTT），曲线下面积（Area under the curve, AUC），峰值半降时间（Time from peak to one half, TPH），流入斜率（Wash in slope, WIS），达峰时间（Time to peak, TTP）。以病理 MP 分级（1-3 级为无效，4-5 级为有效）为金标准，分析不同周期后定量参数的变化；以治疗前参数为基线，分别计算 2 周期, 4 周期及治疗结束后定量参数的差值及变化率，[差值（ Δ ）=治疗前参数-不同周期后参数；变化率（Rate of change, CRO）=（治疗前参数-不同周期后参数）/治疗前参数]，比较有效及无效组间的差值及变化率。

结果：60 例患者，治疗结束后有效者 27 例，无效者 33 例。与治疗前比较，在 2 周期，4 周期及治疗结束后 PI 降低，AUC 减少，WIS 减小，差异有统计学意义（ $P<0.05$ ）[1]。治疗结束后 PI, AUC, WIS 与病理分级呈负相关关系，差异有统计学意义（ $P<0.05$ ，即治疗结束后 PI, AUC, WIS 越小，术后病理 MP 分级越高，缓解程度越好）；以术后 MP 分级为金标准，在治疗结束后，有效组 PI, AUC, WIS 均低于无效组，差异有统计学意义（ $P<0.05$ ）；治疗 2 周期及治疗结束后有效组 Δ PI, Δ AUC, Δ WIS 高于无效组，有效组 CRO PI, CRO AUC, CRO WIS 高于无效组，差异有统计学意义（ $P<0.05$ ）

结论：乳腺癌新辅助治疗结束后有效组 PI, AUC, WIS 低于无效组，PI, AUC, WIS 的差值及变化率高于无效组，能有效评估治疗后疗效。2 周期后 PI, AUC, WIS 的差值及变化率高于无效组，对早期疗效预测有一定价值。

关键词：乳腺癌；超声造影；新辅助治疗

514. Plasma lipidomic profiles associated with precancerous gastric lesions and early gastric cancer



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Objective: Gastric cancer (GC) is one of the major gastrointestinal malignant tumors with multistep process of gastric carcinogenesis. The etiology of GC is yet to be clarified and biomarkers for the progression of precancerous gastric lesions and GC occurrence are very limited. Dysregulated lipid metabolism is a recognized feature of malignancy and has been reported for GC. However, no studies have comprehensively explored the lipid metabolism changes associated with the cascade of precancerous gastric lesions and GC. The aim of our study was to investigate the plasma lipidomic profiles and to define lipidomic signatures associated with the progression of precancerous gastric lesions and risk of early GC.

Methods: Based on a recognized high-risk population for GC in Linqi, Shandong Province of China, assays of targeted plasma lipidomics were conducted using ultra-high performance liquid chromatography-mass spectrometry, initially in a discovery set including a total of 200 subjects with superficial gastritis (SG), chronic atrophic gastritis (CAG), intestinal metaplasia (IM), low-grade intraepithelial neoplasia (LGIN), high-grade intraepithelial neoplasia (HGIN) and invasive GC. We then enrolled an independent validation set of additional 200 subjects of different gastric lesions (SG, CAG, IM, LGIN) and GC (HGIN or invasive GC), with prospective follow-up for subjects with gastric lesions, to validate the key findings identified in the discovery set.

Results: A clear distinction of lipidomic profiles was found for subjects with precancerous gastric lesions and GC. Compared with those of mild gastric lesions (SG or CAG), a total of 71 individual lipids were significantly associated with the risk of GC after correcting for multiple comparisons ($FDR < 0.05$) in the discovery stage. Among them, we validated the positive associations of PI36:2(18:1) and LBPA36:3(18:1) with risk of early GC, and the inverse associations between FFA18:3, PC38:6(20:4), LPI20:4, LPA18:3, PE32:2 and risk of early GC in the validation stage ($P < 0.05$). Taking advantage of the prospective follow-up of study subjects, we further found that FFA18:3 was significantly inversely associated with the progression of gastric lesion during the follow-up ($P < 0.05$).

Conclusion: Based on populations from a high-risk area for GC, we portrayed the distinct plasma lipidomic profiles and defined lipidomic signatures for precancerous gastric lesions and GC, which may serve as critical biomarkers for assessing high-risk populations and early diagnosis of gastric cancer.

Key words: Gastric cancer; Gastric lesions; Metabolomics; Biomarkers

515. 无 CO₂ 人工气胸辅助单肺通气在胸腔镜食管癌根治术中的临床应用



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目的: CO₂人工气胸法应用于食管癌微创治疗存在诸多弊端。作者尝试双腔气管插管结合开放性气胸而非 CO₂人工气胸进行单肺通气,在食管癌微创切除术中积累了宝贵的临床经验,并取得了积极的临床治疗效果。本文全面总结该麻醉方法及术式的临床资料,评价其安全性、可行性及肿瘤根治性。

方法: 回顾性分析 2013 年 6 月~2018 年 12 月在安阳肿瘤医院胸外科行胸腔镜食管癌切除术的 1015 例患者的临床资料,其中男性 578 例,女性 437 例,年龄 39~84 岁,平均(64.9±8.3)岁,食管上段 323 例,中段 591 例,下段 101 例,术后病理分期 0~I 期 183 例,II 期 343 例,III 期 356 例,IVA 期 133 例。手术均采用 McKeown 术式,麻醉采用双腔气管插管,非 CO₂气胸条件下左侧单肺通气,胸部操作采取左侧侧卧位,胸腔镜下食管癌切除,纵膈淋巴结清扫;腹部操作采用仰卧位,腹腔镜(23.4%, 238/1015)或开腹(76.6%, 777/1015)行胃游离,管状胃制作及腹腔淋巴结清扫;食管胃左颈部器械吻合。

结果: 中转开胸率 3.7%(38/1015),镜下 R0 切除率 96.5%(979/1015),术中无死亡事件发生。胸部手术时间,术中胸部出血量,术后 3 天内胸液量,术中主要并发症:出血 3.1%(31/1015),气管损伤 1.7%(17/1015),术后总并发症发生率为 38.5%(391/1015),其中肺部并发症发生率为 12.4%(126/1015),吻合口漏 3.2%(32/1015),乳糜胸 1.9%(19/1015),喉返神经损伤 22.0%(223/1015),残胃排空延迟 10.3%(103/1015)。术后 30 天死亡率为 1.2%(12/1015)。死亡归因: DIC 1 例,反流性误吸 2 例,呼吸衰竭 1 例,胸胃气管瘘 1 例,33.3%(4/12)。术后 1,3,5 年的生存率分别为 90.3%,65.4%和 48.7%。

结论: 非 CO₂气胸条件下单肺通气法行胸腔镜 McKeown 食管癌根治术安全、可靠,围手术期并发症及死亡率处于较低水平,值得推广应用。

关键词: 食管癌; CO₂; 人工气胸; 胸腔镜; 食管癌切除术

516. 结直肠癌 15 个基因预后标志物及评分系统的建立和单中心临床验证

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背景：结直肠癌是世界上发病率第三高的恶性肿瘤，尽管结直肠癌的诊治手段在不断进步，但是根据 2020 年世界癌症统计报告，该年内结直肠癌仍导致了超过 93 万名患者的死亡，在所有恶性肿瘤中位居第三。随着生物信息学技术的发展，高通量地获取肿瘤和外周组织的多维组学信息已经成为可能。通过多组学研究揭示结直肠癌的异质性并对其进行分子分型是实现结直肠癌精准治疗的重要途径。

目的：开发一套适用于结直肠癌预后标志物筛选鉴定的生物信息学算法，通过该方法鉴定出可以将结直肠癌患者进行预后结局分组的若干基因集并建立对应的评分系统。利用基于核酸分子杂交的石蜡标本基因表达水平检测技术在大规模的临床样本中验证预后评分系统的可靠性和独立性，探索其对于临床诊疗决策的指导价值。

方法：我们以多个独立的结直肠癌的公共数据库为基础，联合联合差异基因分析，单因素和多因素 Cox 回归以及 C-index，在多个独立的结直肠癌公共数据库中筛选了其中预测结直肠癌预后的最佳基因组合并建立评分系统。之后使用了 2 个结直肠癌公共数据库，比较了我们 15 个基因结直肠癌预后评分系统与临床现有的结直肠癌预后评价系统：*Oncotype DX Colon Recurrence Score* 在预后评价效能上的差异，进一步使用基于核酸分子杂交的石蜡标本基因表达水平检测技术在单中心 203 个结直肠癌石蜡标本中获取预后基因的表达水平。通过 Cox 生存回归和 Kaplan-Meier 生存分析验证其在临床标本中的评价效能。

结果：我们从 6 个独立的结直肠癌数据集中筛选出在肿瘤组织中稳定高表达或低表达的 738 个基因，筛选其中对结直肠癌预后影响较显著的 78 个基因 ($P<0.05$)。通过多因素 Cox 回归分析得到 78 个基因对预后影响显著性的大小，按从大到小逐个组合，并利用 C-index 筛选出 15 个最佳的预后基因集并建立评分。该评分在一个训练集 (373 个样本) 和两个独立验证集 (125 和 562 个样本) 中对预后风险均有显著区分能力， P 值分别为 0.0001, 0.0033, 0.00058。15 个基因预后评分系统的评价能力独立于现有的临床病理和分子亚型 ($P<0.0001$)。与现有的结直肠癌预后评分系统的比较中，“poor”组与“good”组的风险比分别为 2.32 倍和 1.58 倍。在单中心 203 个样本的临床验证中，三个预后分组差异显著 ($P<0.0001$)。

结论：我们开发了一套联合多种回归和验证模型的生物信息学算法。该算法可以在结直肠癌中准确筛选出最佳的预后基因集并以此为基础建立一套可靠的预后评分系统。我们的结直肠癌预后评分系统不仅独立于现有的结直肠癌分子亚型和临床病理因素，且在预后评价效能上优于已投入临床使用的 *Oncotype DX Colon Recurrence Score*。在单中心的 203 例结直肠癌石蜡标本中该评分系统的预测效能得到了临床验证。

关键词：结直肠癌；生物信息学算法；核酸分子杂交；化疗

517. 基于 DNA 甲基化谱和临床信息的胰腺癌分型及预后分析

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目的：胰腺癌是一种消化道恶性肿瘤，在全球范围内是癌症死亡的第七大原因，其早期诊断困难，预后状态差，不同患者对治疗的反应不同，但在临床实践中尚没有广泛应用的与胰腺癌预后相关的分子分型。研究表明，肿瘤的发生发展伴随着表观基因组的改变，DNA 甲基化作为表观遗传调控因子可参与调控基因的活性和细胞分化，许多肿瘤早期的表现之一就是肿瘤抑制基因甲基化水平提高，异常的 DNA 甲基化改变和特异甲基化模式可用作癌症的生物标志物。本文从 TCGA 数据库中获得了 194 例胰腺癌患者的临床信息和分子信息，包括 mRNA 表达谱和 DNA 甲基化数据并从 SEER 数据库收集了 205 389 例胰腺癌患者的临床数据，基于胰腺癌 DNA 甲基化数据，挖掘胰腺癌预后相关的特异性分子标记并构建胰腺癌分型预测模型。

方法：本文利用胰腺癌患者 DNA 甲基化谱，在癌症和癌旁样本间得到 1 235 个差异甲基化基因，构建单变量和多变量的 COX 比例风险回归模型从中筛得 78 个独立影响胰腺癌预后的甲基化分子标记，这些基因具有作为胰腺癌分子标志物和解释胰腺癌异质性的潜力。以这些基因为特征通过一致性聚类识别出 2 个胰腺癌亚型。生存分析和临床特征检验显示被命名为 cluster2 的亚型预后情况显著优于 cluster1 且两个亚型间在性别、临床肿瘤分期、T 分期和肿瘤分化程度上存在显著差异，挖掘每个亚型的特异临床特征组合，使用来自 SEER 的大样本进行验证，证明了基于 DNA 甲基化模式的亚型区分有着独特的临床特征和预后情况。结合转录组数据的研究表明，有 301 个癌症驱动基因在两个亚型间差异表达且免疫细胞浸润程度在亚型间存在显著差异。此外，本文在两个亚型间识别出表征亚型独特甲基化模式的 14 个特异性高/低甲基化基因，构建了基于贝叶斯网络的分型预后预测模型，模型在训练集中的准确性达 93.75%，AUC 值为 0.937，将模型应用于检验集，成功将样本分类为本研究得到的 2 个甲基化亚型，检验集的预后分析结果也与训练集相似。

结论：综上，本文利用 DNA 甲基化数据结合生物信息学算法，挖掘胰腺癌 DNA 甲基化分子标志物并识别与预后相关的胰腺癌 DNA 甲基化亚型，构建了胰腺癌分型预后预测模型，从表观遗传的角度解析了胰腺肿瘤的异质性并为胰腺癌患者的个性化治疗方案评估和精准医疗提供新思路新靶标。

关键词：胰腺癌；DNA 甲基化；预后；一致性聚类；肿瘤分型

518. 动态心电图监测 FOLFOX6 方案治疗结直肠癌相关心脏毒性的研究

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目的：研究 24 小时动态心电图（24h-DCG）在监测 FOLFOX6 方案治疗结直肠癌（CRC）相关心脏毒性中的效果。

方法：将 5 个肿瘤中心 2015 年 07 月至 2018 年 06 月接诊的,同意使用 FOLFOX6 化疗的中晚期 PLC 患者共 179 例。在每周期化疗前后,对患者分别使用 24h-DCG 及常规 12 导联心电图（ECG）监测心电图异常,对比两种方法在监测心脏毒性的发生率和严重程度。

结果：可评价 154 例,24h-DCG 的心电图异常发生率,I 级心脏毒性发生率均明显高于常规 ECG,差异有统计学意义 ($P<0.05$);而两种方法监测到 II 级,III 级,IV 级心脏毒性的发生率差异无统计学意义 ($P>0.05$)。

结论：24h-DCG 比 12 导联 ECG 检测 FOLFOX6 方案治疗中晚期 CRC 所致的心脏毒性更加灵敏,能更易,更早发现心脏毒性。

关键词：FOLFOX6; 结直肠癌; 心脏毒性; 动态心电图.

519. 服用虫草致 CA72-4 异常升高一例分析

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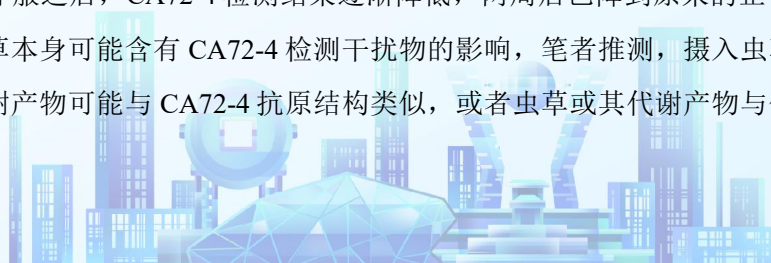
郑州安图生物工程股份有限公司

目的：笔者发现,一患者在服用虫草后,血清中 CA72-4 检测结果异常升高,停药一段时间后,CA72-4 检测结果又降低到原来的正常水平,现报道如下。

方法：患者在健康体检时发现,CA72-4 单项结果异常高 (286.31 U/ml),而前一年的体检结果还是正常的,且其他肿瘤标志物结果均正常。随后笔者查看了其胃镜,CT 等检查结果,均显示正常,且未发现肿瘤迹象。曾有文献报道服用灵芝孢子粉,螺旋藻等保健品后会导致 CA72-4 异常升高的案例,经仔细询问患者体检前的饮食史和病史发现,患者两个月前因生了一场病身体虚弱,后坚持每天用虫草煲汤以提高免疫力。于是,建议患者将煲汤中的虫草去掉,两周后再复查 CA72-4。

结果：患者停药虫草煲汤 7 天后,CA72-4 由原来的 286.31 U/ml 降到了 72.71 U/ml;停药虫草煲汤 15 天后,CA72-4 已经降低到 2.39 U/ml。考虑到虫草煲汤中可能含有 CA72-4 的交叉物,笔者将虫草磨成粉溶解到阴性血清中,CA72-4 检测结果和对照偏差 $<10\%$,体外实验无法重复出虫草对 CA72-4 检测结果的干扰。

结论：CA72-4 是一种消化道相关的肿瘤标志物。本例中的患者在服用虫草煲汤后 CA72-4 检测结果异常升高,停药之后,CA72-4 检测结果逐渐降低,两周后已降到原来的正常水平。体外实验可以排除虫草本身可能含有 CA72-4 检测干扰物的影响,笔者推测,摄入虫草之后,其在人体内的某种代谢产物可能与 CA72-4 抗原结构类似,或者虫草或其代谢产物与体内细胞相互作用



后可能会促进细胞过多表达 CA72-4 抗原。因此，临床上发现 CA72-4 异常升高时，应仔细询问患者饮食或用药史，确认是否是因为服用药物或保健品引起 CA72-4 异常升高的情况。以减少不必要的检查，减轻患者的经济负担和精神负担。

关键词：CA72-4； 虫草； 异常升高

520. Novel blood-based hypomethylation of DYRK4 is associated with very early stage lung cancer

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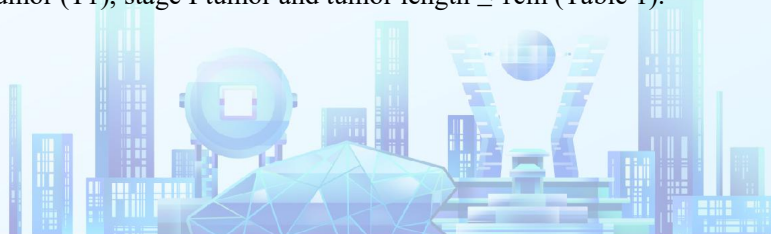
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Objective: Early detection is essential to improve the survival of lung cancer. The quantitative measurement of specific DNA methylation changes in the peripheral blood could provide an efficient strategy for the detection of early cancer. We applied a candidate approach and assess the association between blood-based DYRK4 methylation and the risk of lung cancer in a case-control study.

Methods: The methylation level of three CpG sites in the promoter of DYRK4 gene was quantitatively determined by mass spectrometry in 845 very early stage lung cancer patients (91.8% lung cancer at stage I) and 1000 healthy controls. The correlations between DNA methylation and the disease status were analyzed by binary logistic regression adjusted for possible co-founding effects of age, gender and different measurement batches. The comparisons between two or multiple groups were analyzed by non-parametric tests.

Results: All three investigated CpG sites in DYRK4 gene showed lower methylation levels in lung cancer cases than in control group (Figure 1A-1C), and decreased methylation of all these CpG loci showed significant association with lung cancer (odds ratio (ORs) per -10% methylation ranging from 1.17 to 1.43, $P < 0.00017$ for all, Figure 1D). Interquartile analysis showed that compared to the quartile with the highest methylation level (Q4), the three lower quartiles of methylation levels (Q1-Q3) of all three CpG loci were highly associated with an increased risk of lung cancer, and this association was especially pronounced in the lowest quartile (P trend < 0.001 for all, Figure 2). Further investigation disclosed that the hypomethylation of DYRK4 was associated with lung cancer with even larger ORs in the male group than that of the female group (OR per -10% methylation from 1.33 to 1.66, $P < 0.000088$ for all in males, Figure 3), which is in accordance with the fact the men have higher risk to lung cancer. The relationship between DYRK4 methylation and the clinical characteristics of 845 lung cancer demonstrated that the lung cancer cases with larger size (T2&T3), advanced stages (stage II and stage III), and larger length (> 1 cm) have lower methylation in CpG_2 than the patients with smaller tumor (T1), stage I tumor and tumor length ≤ 1 cm (Table 1).



Conclusion: Our study revealed an association between blood-based DYRK4 hypomethylation and very early stage lung cancer, which provides a novel support for the blood-based methylation signatures as a potential marker for the early detection of cancer.

Key words: lung cancer; DNA methylation; DYRK4 gene; early detection; peripheral blood

521. Urine metabolomics study of hepatocellular carcinoma patients

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Objective: The analysis of the small molecular metabolites in urine of patients with hepatocellular carcinoma and liver diseases aims to explore the characteristics of urinary metabolism for hepatocellular carcinoma and provide biomarkers on metabolic level for non-invasive diagnosis of hepatocellular carcinoma.

Methods: High throughput ultra-performance liquid chromatography-quadrupole time-of-flight mass spectrometry (UPLC-QTOFMS) was used to detect small molecular metabolites in urine of healthy control (Group A, n=10), patients with hepatic hemangioma (Group B, n=10) and patients with HCC (Group C, n=10). The orthogonal projections to latent structures-discriminant analysis (OPLS-DA) and hierarchical cluster analysis of multivariate analysis and univariate statistical analysis were used to analyze the differential metabolites of the three groups.

Results: The well distinguished metabolic profiles of the three groups showed that the total of 381 differential metabolites can be identified and divided into 96 up-regulated metabolites and 285 down-regulated metabolites. There were 55 specific urinary metabolites related to hepatocellular carcinoma. Among them, 21 metabolites were significantly up-regulated, including N-acetyl-leucine, alanine, aspartic acid, phenylalanine, histidine, arginine, etc. and 34 metabolites were significantly down-regulated, including selenocysteine, methionine, tryptophan, valsartan, oxoglutaric acid and so on. Kyoto encyclopedia of genes and genomes analysis showed that the differential metabolites were mainly enriched in glutamine/glutamate metabolism, lysine biosynthesis, tricarboxylic acid cycle and purine metabolism.

Conclusion: The analysis of the characteristic metabolic profile for the urine of hepatocellular carcinoma patients will provide metabolic basis for the non-invasive diagnosis and intervention of hepatocellular carcinoma.

Key words: hepatocellular carcinoma; urinary metabolism; non-invasive diagnosis; biomarker

522. USP7 及其抑制剂 P22077 对肝细胞肝癌发展进程的影响

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目的： 本研究主要探讨泛素特异性蛋白酶 7（USP7）抑制剂 P22077 对肝癌细胞的抑制与杀伤作用及机制，为肝癌的综合治疗,提高疗效提供理论基础。

方法： 1.利用免疫印迹检测 USP7 在 8 对肝癌组织以及癌旁组织和肝癌细胞系中的表达。免疫组化方法检测 100 例肝癌患者组织中 USP7 的表达及定位。卡方检验 USP7 与肝癌患者病例临床参数之间的关系。Kaplan-Meier 统计 USP7 与肝癌患者预后的关系。2.运用 CCK-8 法检测 USP7 抑制剂 P22077 对正常肝细胞和肝癌细胞增殖能力的影响；利用流式细胞仪分析经药物处理前后细胞凋亡数量的变化，平板克隆形成实验和悬浮克隆形成实验检测药物处理前后细胞克隆形成能力的变化，划痕试验验证药物处理前后细胞增殖迁移能力的改变，Transwell 实验验证药物对肝癌细胞侵袭能力的影响。3.选取对 P22077 敏感的细胞系（Huh7），利用 Shotgun 实验分析药物处理前后细胞中蛋白表达差异。4.经 Shotgun 实验分析后，组蛋白 3（H3）在药物处理前后差异性最为明显。处理后收蛋白，Western Blot 检测 H3 和 H3K4me2 表达变化，分析 H3 与 USP7 之间的关系。5.免疫印迹法检测 p53 磷酸化水平，明确 p53 磷酸化与 USP7 之间的关系。6.裸鼠成瘤实验。取 5×10^7 SK-Hep1 细胞注射到裸鼠皮下，同时腹腔注射 P22077（10 mg/kg），两周一次，观察裸鼠成瘤的能力。

结果： 1.免疫印迹和免疫组化结果表明，USP7 的表达在 HCC 组织和肝癌细胞系中显著上调，癌旁组织中表达很低或缺失。高表达的 USP7 与患者预后呈负相关。2.CCK-8 检测法显示 P22077 显著降低肝癌细胞活力；显微镜下发现 P22077 显著诱导肝癌细胞 Huh7,SK-Hep1 的死亡；流式细胞仪检测发现 P22077 诱导肝癌细胞的凋亡数量明显增加；克隆和划痕形成实验表明 P22077 几乎消除了 Huh7,SK-Hep1 的克隆形成能力；Transwell 实验证实 P22077 明显降低了肝癌细胞的侵袭能力。3.Shotgun 实验分析发现，将 Huh7 经过 P22077 处理，与未处理组相比，处理组中 H3 蛋白的表达具有明显差异。Western blot 检测验证，经过 P22077 处理后，H3 蛋白明显降低，且其甲基化形式 H3K4me2 蛋白也明显降低。4.经过 P22077 处理肝癌细胞，p53 蛋白在丝氨酸 392 位点的磷酸化降低，而在丝氨酸 15 号位点的磷酸化则升高，总 p53 蛋白无明显改变。5.裸鼠成瘤实验发现，P22077 明显抑制肝癌细胞移植瘤肿瘤的生长，显著增强 Dox 对肝癌细胞的毒性作用。

结论： 1.USP7 在 HCC 中高表达，且与肝癌患者的预后密切相关。2.USP7 抑制剂 P22077 明显诱导肝癌细胞的凋亡，并影响肝癌细胞的克隆形成和迁移能力。3.P22077 抑制肝癌细胞中 H3 的表达和 p53 的磷酸化水平。4.P22077 抑制肝癌细胞移植瘤的生长，提示 USP7 有望成为肝癌治疗的潜在靶点。

关键词： 肝癌；USP7；P22077

523. 醛酮还原酶 AKR1B1 调控胰腺癌外泌体分泌的机制研究



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目的: 初步研究醛酮还原酶 1 成员 B1 (AKR1B1) 调控外泌体分泌进而对胰腺癌转移侵袭的影响, 并对 AKR1B1 影响胰腺癌外泌体分泌的可能分子机制作初步探讨。

方法: 1. 分别采用免疫印迹法 (WB) 及 qRT-PCR 法检测 AKR1B1 在胰腺癌细胞系中的蛋白及 mRNA 表达水平。2. 采用 CRISPR-Cas9 技术构建 AKR1B1 的 SgRNA, 并在 AKR1B1 表达相对较高的 Capan2, CFPAC-1, hTERT-HPNE 细胞中构建敲除 AKR1B1 的稳转细胞株。WB 验证稳转细胞株是否构建成功。3. 细胞划痕和 Transwell 实验分别检测敲除及使用抑制剂抑制 AKR1B1 后对胰腺癌细胞迁移和侵袭能力的影响。CCK8 实验验证 AKR1B1 抑制剂依帕斯他 (epalrestat) 对细胞的活力影响。4. WB 检测敲除及抑制 AKR1B1 后 EMT 相关标志蛋白的表达情况。5. BCA 法检测敲除及抑制 AKR1B1 对外泌体蛋白浓度的影响。6. qRT-PCR 检测敲除及抑制 AKR1B1 对 Rab 家族分子表达情况的影响。

结果: 1. 与胰腺正常细胞系 hTERT-HPNE 相比, AKR1B1 在 CFPAC1, Capan2 细胞中表达相对较高, 在 Panc-1 和 Sw1990 细胞中表达较低。qRT-PCR 检测 AKR1B1 mRNA 在各细胞系表达的水平与 WB 结果一致。2. 在 Capan2 和 hTERT-HPNE 细胞中均成功敲除 AKR1B1, 与对照组比, AKR1B1 的表达明显下降。3. 在 AKR1B1 敲除的 Capan2 和 hTERT-HPNE 稳转细胞中, 与 Con-SgRNA 组相比, 细胞迁移和侵袭能力与对照组相比明显减弱。选用 50 $\mu\text{mol}/\mu\text{L}$, 100 $\mu\text{mol}/\mu\text{L}$ 分别作为 Capan2 和 CFPAC-1 的药物处理浓度处理细胞 48h 后, 对照组与各组之间有明显差异。在抑制 AKR1B1 的 Capan2 和 CFPAC-1 细胞中, 细胞迁移和侵袭能力与对照组相比明显减弱。4. 在 Capan2 稳转细胞中, 当 AKR1B1 被敲除后, E-cadherin 表达增高, N-cadherin 和 Vimentin 降低。然而, 在建成的 hTERT-HPNE 稳转细胞中, AKR1B1 敲除后对 EMT 相关标记蛋白的影响并不显著。用 epalrestat 分别处理 Capan2 细胞和 CFPAC-1 细胞 48h 后, 收集细胞蛋白, 进行 EMT 相关标记分子的检测。结果显示: 在 Capan2, CFPAC-1 细胞中, 使用 epalrestat 后, E-cadherin 表达显著增高, N-cadherin 和 Vimentin 表达显著降低。由此可见, AKR1B1 敲除的 Capan2 稳转细胞明显抑制了 EMT 的发生, 但对 hTERT-HPNE 稳转细胞没有很显著的作用。5. 在 AKR1B1 敲除的 Capan2 和 hTERT-HPNE 稳转细胞中, 敲除 AKR1B1 后所测外泌体蛋白浓度都明显降低。在经 epalrestat 处理的 Capan2 和 CFPAC-1 细胞中, 与对照组相比, 使用抑制剂后外泌体蛋白浓度降低。6. 在 Capan2 稳转细胞中, 与对照组相比, Rab27a 和 Rab27b 的 mRNA 水平明显降低; 在 hTERT-HPNE 稳转细胞中, 与对照组相比, Rab27b mRNA 水平明显下降。在经过 epalrestat 处理的 Capan2 中, 与对照组相比, Rab1a, Rab5b, Rab27a, Rab27b 的 mRNA 水平明显下降; 在经过 epalrestat 处理的 CFPAC-1 细胞中, 与对照组相比, Rab1a, Rab5a, Rab5b, Rab7a, Rab27a, Rab27b 的 mRNA 水平明显下降。



结论：1. AKR1B1 可通过调控 EMT 通路相关分子表达从而影响胰腺癌细胞的转移侵袭。
2. AKR1B1 可通过影响 Rab 家族相关分子调控外泌体分泌。3. Epalrestat 可能是胰腺癌新的潜在治疗药物。

关键词：AKR1B1；外泌体分泌；胰腺癌；Rab；转移侵袭

524. AMPK-mTOR 通路通过激活自噬促进休眠多倍体巨大肿瘤细胞的形成

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Dormant cancer cells that survive anti-cancer therapy can lead to cancer recurrence and disseminated metastases that ultimately prove fatal in the majority of cases. Recently, specific dormant polyploid giant cancer cells (PGCCs) have drawn our attention due to their association with the clinical risk of nasopharyngeal carcinoma (NPC) recurrence, as clarified by our clinical data. We reported their biological properties including mitochondrial alterations, and revealed that autophagy is a critical mechanism of PGCC induction, with the pharmacological or genetic inhibition of autophagy greatly impairing PGCC formation, significantly eliminating recurrence, metastasis, and improving survival in mouse model. Mechanistically, we observed that chemotherapeutic drugs partly damaged mitochondria, which then produced lower ATP levels and activated autophagy via the AMPK-mTOR pathway to promote PGCC formation. Transcriptional activated RIPK1 acts as a scaffold to promote PGCC survival by AMPK-mTOR pathway. Our findings suggest a therapeutic approach of targeting dormant PGCCs for cancer treatments.

关键词：autophagy; polyploid giant cancer cells; nasopharyngeal carcinoma; recurrence; metastasis

525. HAX-1 通过竞争性结合 Rab7a 阻断自噬通量参与鼻咽癌铂类耐药

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研究目的：鼻咽癌（Nasopharyngeal carcinoma, NPC）是头颈部最常见的恶性肿瘤，我国东南部为世界高发区。虽然放疗是 NPC 的主要治疗手段，但是铂类药物在 NPC 治疗中也是重要的治疗方式之一，铂类药物耐药性的产生严重影响着 NPC 的复发及转移，一旦复发或转移，预后极差。探索 NPC 患者铂类耐药（cisplatin resistance）的分子机制，对于提高患者预后，指导临床实践具有十分重要的意义。



研究方法：所在的耳鼻咽喉头颈外科研究所前期已验证 HAX-1 在 NPC 中高表达并与 NPC 的发生发展高度相关，且文献于 2016 年发表杂志，此课题为后续研究。通过 3D 成球,集落形成等细胞实验,流式细胞仪 procount 法以及裸鼠皮下成瘤等体内实验验证 HAX-1 与耐药的相关性。通过 RNA 转录组测序（RNA-seq）KEGG 分析,激光共聚焦显微镜观察（带有 GFP-LC3 以及 mCherry-GFP-LC3 慢病毒转染的 CNE2 鼻咽癌细胞系）,蛋白质印迹法（Western Blot）以及透射电镜分析验证 HAX-1 与自噬的关系。在实验组中增加自噬后期抑制剂 CQ（氯喹）组，通过蛋白质印迹法（Western Blot）以及 IHC（裸鼠皮下成瘤组织）进一步验证 HAX-1,自噬以及耐药三者的关系。通过 CO-IP 测序,蛋白质印迹法（Western Blot）以及免疫荧光法了解与 HAX-1 相结合的蛋白质，揭露 HAX-1 在蛋白质组学上的机制。通过 RNA-seq 找到 HAX-1 的下游分子，并使用放线菌素-D（Act-D）,CHX 以及 MG-132 验证 HAX-1 对下游分子 IGF2BP1 的具体作用机制。最后，通过蛋白质印迹法（Western Blot）,细胞实验（集落形成,3D 成球等）以及体内实验（裸鼠皮下成瘤,IHC）验证 IGF2BP1,HAX-1 以及 Rab7a 影响自噬的具体形式。

研究结果：（1）在鼻咽癌细胞 CNE2 中，HAX-1 与耐药高度相关，且 HAX-1 是通过影响自噬从而影响鼻咽癌细胞耐药。（2）Rab7a（RAS 家族的成员）是一个与自噬的全程发生高度相关的分子，通过 CO-IP seq 发现其是 HAX-1 的直接结合蛋白，并且 HAX-1 可以通过影响 Rab7a 的表达阻滞自噬流。（3）通过 RNA-seq 发现 IGF2BP1 是 HAX-1 的下游分子，并且 HAX-1 对该分子的影响是全方面的（翻译前后），IGF2BP1 作为 m6A 的 Reader,通过影响 HAX-1 mRNA 上的 m6A 水平影响 HAX-1 的表达，两者形成一个正反馈闭环相互影响。（4）IGF2BP1,HAX-1 以及 Rab7a 形成一条分子轴，通过影响鼻咽癌细胞自噬水平，从而调控鼻咽癌的耐药。

研究结论：（1）在正常鼻咽癌细胞株 CNE2 中，敲低 HAX-1 表达可以增强顺铂的治疗效果。高表达的 HAX-1 容易使 CNE2 细胞铂类耐药。（2）HAX-1 在鼻咽癌中抑制自噬的发生，促进肿瘤耐药。（3）HAX-1 与 Rab7a 竞争性结合 SNARE 复合体，阻滞自噬流，影响自噬后期。（4）HAX-1 与 IGF2BP1 形成一个正反馈闭环，互相影响其表达。（5）受 IGF2BP1 正反馈闭环调控的 HAX-1 通过竞争性结合 Rab7a 阻断自噬通量参与鼻咽癌铂类耐药。

关键词：鼻咽癌；HAX-1；自噬；铂类耐药；m6A

526. 肾透明细胞癌的新型分子分型和免疫表型及其与预后的相关性

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目的：旨在通过基因组和转录组测序，分析中国人群的肾透明细胞癌（ccRCC）分子特征，探索新型分子分型和免疫表型并评估患者预后。

方法：对 55 例 ccRCC 组织和 11 例正常肾脏组织进行基因组学和转录组学分析，检测基因表达、基因突变、基因融合以及肿瘤微环境中免疫标记物的表达。根据基因表达的差异，将患者队列分为三种分子分型，评估对应患者的预后。根据肿瘤微环境中肿瘤细胞的 66 个免疫标志物的表达差异，我们进一步将患者分为三种免疫表型，探讨免疫表型与患者的免疫治疗反应以及生存率之间的相关性。

结果：在中国人群 ccRCC 中，PBRM1 的突变频率为 11%，远低于 TCGA 所报道的白种人的突变频率（33%）。鉴定出 31 个融合基因，其中有 5 个融合基因在大于 1 个样本中重复出现，这些融合基因均与细胞凋亡、肿瘤抑制和转移相关。根据基因表达的差异，将患者队列分为三种分子分型：VEGF 通路相关基因表达增加者为第一种；细胞外基质相关基因表达增加者为第二种；VEGF 通路相关基因表达减低者为第三种。其中，第二种分子分型患者的生存率最低。此外，通过对 ccRCC 的 66 个免疫标志物分析，根据免疫标志物的表达差异，将患者进一步分为三种免疫表型，其中 17 个肿瘤样本具有较高的免疫标志物表达，被定义为免疫活性肿瘤；4 个样本免疫标志物的表达受到抑制，被定义为免疫非活性肿瘤；其余 34 个肿瘤样本的免疫标志物的表达介于两者之间，被定义为免疫耐受性肿瘤。在第二种分子分型患者中，免疫活性肿瘤和免疫耐受性肿瘤的患者存活率更低。另外，在这部分 ccRCC 患者肿瘤中，其巨噬细胞含量明显升高，CD4 阳性 T 细胞减少，表明巨噬细胞在免疫活性和免疫耐受性 ccRCC 中发挥重要作用，这部分患者可能在免疫治疗中受益。

结论：本研究明确了中国人群 ccRCC 基因组表达谱和免疫表型的特征。新型分子分型和免疫表型可改进患者人群分类，更好地评估患者预后，并为免疫治疗提供潜在的指导作用。

关键词：肾透明细胞癌；基因组分析；转录组分析；分子分型；免疫表型

527. 腹腔镜下微波消融联合肾部分切除术治疗囊性肾肿物的初步预后观察

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目的：探索腹腔镜下微波消融联合肾部分切除术治疗囊性肾肿物的安全性和有效性。

方法：回顾性分析 2017 年 11 月至 2019 年 12 月采用腹腔镜下微波消融联合肾部分切除术的 19 例囊性肾肿物患者的临床和预后资料。男性 13 例，女性 6 例。年龄 22~67 岁，平均年龄（46.2±13.1）岁。肿瘤位于左肾 7 例，右肾 12 例。肿瘤最大径 1.2~5.0 cm，平均最大径（2.8±1.3）cm。5 例患者的囊性肾脏病变为 Bosniak III 级，14 例为 Bosniak IV 级。按

R.E.N.A.L.评分标准,低难度(4~6分)11例,中难度(7~9分)7例,高难度(10~12分)1例。术前血肌酐中位值 $69\mu\text{mol/L}$ ($43\sim 87\mu\text{mol/L}$)。术后监测评估患者一般情况,有无手术相关并发症及肿瘤复发转移等预后情况。

结果:所有手术过程顺利。手术时间为 $60\sim 120\text{min}$,平均 $(84.0\pm 20.8)\text{min}$ 。术中出血量中位值为 20ml ($10\sim 50\text{ml}$)。术后 VAS 疼痛评分中位值为 1 分 ($0\sim 2$ 分)。术后复查血肌酐中位值 $74\mu\text{mol/L}$ ($41\sim 96\mu\text{mol/L}$),与术前相比差异无统计学意义 ($P=0.107$)。患者术后恢复良好,术后住院中位时间 3d ($2\sim 6\text{d}$)。根据术后病理将患者分为低危组和高危组。低危组包括乳头状腺瘤 1 例;肾血管平滑肌脂肪瘤 1 例;低度恶性潜能多房囊性肾肿瘤 1 例;肾嫌色细胞癌 1 例 (T1a)。高危组包括肾透明细胞癌 14 例,2 型乳头状肾细胞癌 1 例。术后中位随访 13 个月 ($5\sim 30$ 个月),19 例患者均存活,未见肿瘤复发或转移,常规化验未见明显异常。

结论:腹腔镜下微波消融联合肾部分切除术在囊性肾肿瘤治疗中的安全性和疗效良好,可预防囊性成分在术中分离切除过程中破裂导致的肿瘤种植播散。

关键词:微波消融;囊性肾肿瘤;腹腔镜;肾部分切除术;预后

528. 体外扩增肾癌循环肿瘤细胞的 PBRM1 突变可指导患者免疫治疗选择

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目的:PBRM1 基因突变的肾癌患者可从免疫检查点抑制剂中明显获益。循环肿瘤细胞 (CTCs) 是存在于外周血中数量极少且具有转移潜能的肿瘤细胞。以往体外 CTCs 培养成功率为 $6\sim 20\%$ 。本研究介绍一种 CTCs 体外培养新方法,并初步探究体外扩增的肾癌循环肿瘤细胞 PBRM1 表达突变与患者免疫治疗疗效的相关性。

方法:采集 10 例初诊转移性透明细胞性肾细胞癌 (mccRCC) 患者外周血, $15\text{ml}/\text{人}$,采用密度梯度离心法,悬浮培养条件和干细胞培养基,进行体外培养 30 天。通过免疫组化染色和全外显子组测序确定培养物的肿瘤源性和 PBRM1 基因突变情况。对其中使用免疫检查点抑制剂联合阿昔替尼治疗的 6 例 mccRCC 患者,在第 2 个治疗周期后通过 RECIST 标准评价治疗效果,并分析与 CTCs 培养物 PBRM1 基因突变情况的相关性。

结果:采用密度梯度离心法,悬浮培养条件和干细胞培养基培养初诊转移性肾癌 CTCs,成功率可达 70% 。接受靶向联合免疫检查点抑制剂治疗且出现部分缓解者,CTCs 中存在 PBRM1 基因双拷贝失活。



结论：采用密度梯度离心法,悬浮培养条件和干细胞培养基培养可提高肾癌 CTCs 培养成功率。

CTCs 源性 PBRM1 基因双拷贝失活与 mccRCC 靶向联合免疫检查点抑制剂治疗敏感性具有相关性,未来有望通过 CTCs 体外培养检测指导肾癌患者的治疗选择。

关键词：肾细胞癌；循环肿瘤细胞；悬浮培养；免疫治疗

529. Non-invasive detection of lymphoma with circulating tumor DNA features and plasma protein markers

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Introduction: The disease burden of lymphoid neoplasm has been rising in China over the last decade. But most patients manifest with advanced stage disease at initial diagnosis, and the prognosis is poor with a 5-year survival rate of 38.3%. Here we reported a novel multivariate cancer risk score (CRS) model which is used to detect early lymphoid neoplasm from the peripheral blood. It incorporates three cancer hallmarks, copy number aberrations (CNA) and fragment size (FS) via shallow whole genome sequencing (sWGS) from cell-free DNA (cfDNA), and a panel of seven tumor protein markers in a single blood draw (10ml).

Methods: 44 newly diagnosed and untreated stage I-IV lymphoid neoplasm patients and 247 healthy individuals with no cancer diagnosis were enrolled in this study. 10ml peripheral blood was collected from each participant after enrollment. cfDNA was extracted and subjected to sWGS whereas plasma was subjected to measure the levels of 7 PTMs. The cancer risk score (CRS) of a subject was calculated via an established CRS model[1].

Results: Firstly, genomic and epigenetic features were explored from cfDNA sWGS results. CNA is a ubiquitous genomic hallmark in a wide spectrum of cancers. In this study, 26 of the 44 (59.1%) lymphoid neoplasm patients had CNA in at least one genomic segment (>5Mb). FS feature of cfDNA bears the correspondence of the epigenetic landscapes of cells that give rise to those cfDNA fragments. When CNA was combined with FS, 29 (65.9%) patients were able to be detected by the CNA+FS classifier. On the other hand, 13 (29.5%) patients were tested positive by PTMs alone, indicating non-DNA molecular surrogates can also serve as cancer biomarkers with acceptable performance. When CNA, FS and PTM were incorporated into a multidimensional and multivariate CRS model, it achieved the best performance allowing 31 (70.0%) lymphoid neoplasm cases to be identified with a positive predictive value (PPV) of 86.1% at 98.0% specificity. The sensitivity of CRS model increases with the advances of disease with a sensitivity of 50.0% in early stage (stage I -II) and 90.0% in late stage (stage III-IV).



Conclusion: In summary, this study provides an efficient and non-invasive method to detect lymphoid neoplasm. Instead of relying only on one dimension of cancer markers, the multidimensional approach which incorporating CNA, fragment size and protein markers is plausible in early detection of lymphoid neoplasm with sufficient accuracy and robustness.

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Key words: lymphoid neoplasmmultidimensional; early detect

530. Association of cigarette smoking with plasma metabolomic profiles

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Objective: Limited studies have explored the metabolomic profiles associated with cigarette smoking. This study aimed to investigate the association between cigarette smoking and plasma metabolomic profiles, and to identify individual metabolites associated with cigarette smoking.

Methods: A total of 200 subjects were included based on the National Upper Gastrointestinal Cancer Early Detection Program in Linqu, Shandong Province of China. Information on cigarette smoking status and quantity of smoking (cigarettes/day) was collected using standardized questionnaires. Untargeted plasma metabolomic assay was performed using ultra-high performance liquid chromatography-mass spectrometry. We conducted unsupervised principal component analysis (PCA) to visualize metabolomic features comparing smokers and non-smokers. Associations between cigarette smoking and individual metabolites were examined using multiple linear regression models adjusting for age and sex.

Results: Among 200 subjects, 52 were smokers. Our study demonstrated distinct metabolomic profiles between subjects with and without smoking by the score plot of PCA. At individual metabolite level, a total of nine metabolites were identified differentially distributed between smokers and non-smokers after correcting for multiple comparisons (false discovery rate-adjusted q -values < 0.05), with six metabolites (theobromine, L-isoleucine, acetylcholine, isovalerylcarnitine, hydroxyphenyllactic acid and L-leucine) significantly upregulated and three (creatine, oleic acid and N1-methyl-2-pyridone-5-carboxamide) downregulated for smokers. Among them, two metabolites, including creatine and oleic acid were further significantly inversely associated with the quantity of cigarette smoking.

Conclusion: Our study observed apparent changes in plasma metabolic profiles and a set of individual metabolites associated with cigarette smoking, with two metabolites, including creatine and oleic acid inversely associated with cigarette smoking status and the quantity of smoking. These findings may

add to the knowledge of the molecular alterations caused by cigarette smoking and provide insights into understanding the biological mechanisms underlying the adverse effects of cigarette smoking.

Key words: Cigarette smoking; Metabolomics; Metabolite biomarkers

531. The gain-of-function mutation in DOT1L promotes lung cancer tumorigenesis and induces drug resistance via the MAPK/ERK signaling pathway

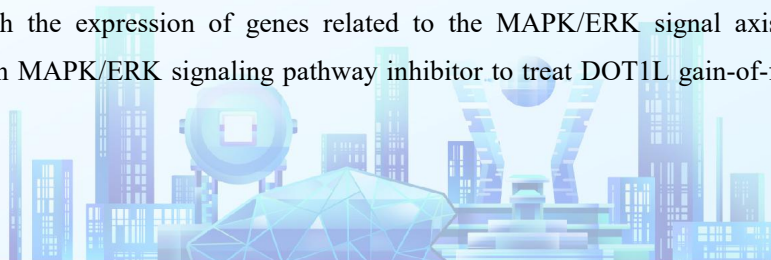
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Shenyang Pharmaceutical University

Background: The tumorigenesis of lung cancer is always accompanied by the inactivation of tumor suppressor genes and the activation of oncogenes. However, loss-of-function mutations such as inactivated tumor suppressor genes are considered as “undruggable”. Therefore, the discovery and identification of lung cancer-related activated oncogenes, such gain-of-function mutations, are of great value for us to understand the pathogenesis of lung cancer and to find precise treatments.

Methods: Immunohistochemical staining was used to detect DOT1L expression in lung cancer specimens. Subsequently, the prognosis of lung cancer patients with DOT1L mutation was proved by bioinformatics. A series of DOT1L mutant plasmids were constructed using molecular biology methods. Structural biology, proliferation, migration and invasion assays were performed in vitro and in vivo to determine the effect of DOT1L gain-of-function mutation on the malignant phenotype and drug resistance of lung cancer. Tet-on system was used for gene manipulation to further determine the role of DOT1L gain-of-function mutation. A gene microarray was used to screen the genes related to malignant phenotype and drug resistance in DOT1L gain-of-function mutant cell lines. RNA sequencing and CHIP assay were used to determine the mechanism by which DOT1L gain-of-function mutation activates the MAPK/ERK signaling pathway. In addition, in vitro and in vivo experiments were conducted through DOT1L small molecule inhibitor combined MAPK/ERK axis inhibitor to clarify the effects of targeting DOT1L and MAPK/ERK pathway on DOT1L gain-of-function mutation.

Results: DOT1L is highly expressed in human lung cancer and the patients with DOT1L missense mutations have poor prognosis. After successfully constructing a series of plasmids carrying different mutation sites, immunoblotting, molecular docking and biological characteristics assays were used to further determine that the DOT1L mutation Q is a gain-of-function mutation. By altering the methylation level of the substrate, remodeling the chromosome structure cause the malignancy and drug resistance of lung cancer. DOT1L mutation Q mediates a variety of malignant phenotypes of lung cancer through the expression of genes related to the MAPK/ERK signal axis. DOT1L inhibitor combined with MAPK/ERK signaling pathway inhibitor to treat DOT1L gain-of-function mutation Q



can significantly inhibit the proliferation, migration and invasion of mutant cells, and reverse drug resistance of lung cancer.

Conclusion: Our results indicate that the DOT1L gain-of-function mutation Q promotes lung cancer tumorigenesis and induces drug resistance via the MAPK/ERK signaling pathway, and the combination of DOT1L inhibitor and MAPK/ERK axis inhibitor can reverse the effect of DOT1L gain-of-function mutation Q.

Key words: Gain-of-function mutation; DOT1L; Lung cancer; MAPK/ERK

532. Plasma D-dimer and IL-6 associated with treatment response and progress free survival in advanced non-small cell lung cancer patients treated with anti-PD-1 therapy

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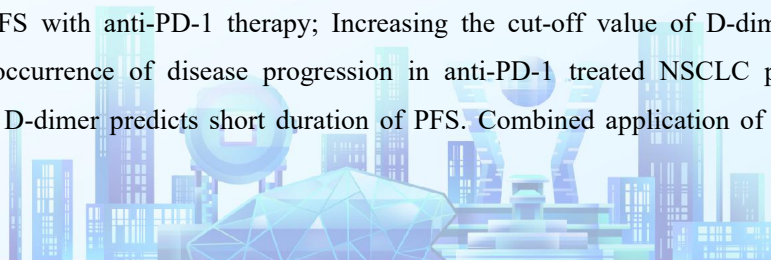
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Background: The treatment response of immune checkpoint inhibitors (ICIs) remains unexpected and there is significant individual variability in the efficacy of different patients with advanced non-small cell lung cancer. This study aims to find peripheral blood biomarkers predicting the efficacy and PFS (progression-free survival) of anti-programmed death-1 (anti-PD-1) treatment in patients with advanced non-small cell lung cancer (NSCLC), which can be used to guide the adjustment of anti-PD-1 treatment regimens to bring greater clinical benefit to NSCLC patients.

Methods: A systematic review of 103 patients with advanced or recurrent NSCLC who received anti-PD-1 therapy (pembrolizumab or carrelizumab) inpatiently at Tianjin Medical University Cancer Hospital between January 2018 and April 2021. The cut-off values for carcinoembryonic antigen (CEA), cytokeratin19 fragment 21-1 (CYFR21-1), squamous cell carcinoma (SCC), tissue polypeptide-specific antigens (TPSA), D-dimer and serum inflammatory markers were determined by receiver operating characteristic curve analysis. Tumor response was assessed by computed tomography according to the Response Evaluation Criteria in Solid Tumors, version 1.1.

Results: Peripheral blood biomarkers IL-6 and D-dimer can predict the clinical value of treatment effect at 6-8 weeks of anti-PD-1 treatment, with AUC areas corresponding to 0.765 and 0.804. Analyses of survival showed that $IL-6 \geq 8.03 \text{ pg/mL}$ and $DD \geq 917.2 \text{ ng/mL}$ were independent predictors of progression-free survival (PFS). A PFS prediction model for anti-PD-1 treatment of NSCLC using the new cut-off values: using " $IL-6 \geq 8.03 \text{ pg/mL}$ " or " $DD \geq 917.20 \text{ ng/mL}$ " as a score of "1". The results showed that the higher the score of combined IL-6 and D-dimer, the shorter the PFS time.

Conclusions: High expression of IL-6 in patients with advanced NSCLC predicts poor efficacy and short duration of PFS with anti-PD-1 therapy; Increasing the cut-off value of D-dimer to 917.20ng/mL predicts the occurrence of disease progression in anti-PD-1 treated NSCLC patients, while high expression of D-dimer predicts short duration of PFS. Combined application of inflammatory index



(IL-6) and fibrinolytic index (D-dimer) scores to predict the efficacy of anti-PD-1-treated NSCLC patients and to establish a predictive model for PFS in anti-PD-1-treated NSCLC.

Key words: D-dimer; IL-6; advanced non-small cell lung cancer; anti-PD-1 therapy

533. Peritoneal resident macrophages in mice with MLL-AF9-induced acute myeloid leukemia show an M2-like phenotype

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Background: Acute myeloid leukemia (AML) is a devastating disease with a poor prognosis. Innate and adaptive immunity is closely related to the progression of leukemia. Macrophages within the leukemic microenvironment have a tendency toward a leukemia-permissive phenotype. However, the characteristics of macrophages in leukemia, including their kinetics, gene expression, and functional roles have not been fully illuminated.

Methods: In the current study, the characteristics of peritoneal resident macrophages, which were large peritoneal macrophages (LPM), from mice with mixed lineage leukemia (MLL)-AF9-induced AML were investigated. AML-associated large macrophages (AML-LPM) were gated as F4/80^{high} MHC-II⁺ by flow cytometry. To further investigate the relationship between the leukemic microenvironment and macrophage characteristics, RNA sequencing was performed. Meanwhile, apoptosis, killing ability, and phagocytic function of peritoneal resident macrophages in MLL-AF9-induced AML were assessed.

Results: The results suggested that AML microenvironment was found to affect the kinetics and morphology of peritoneal resident macrophages. The results of RNA sequencing suggested that the gene expression of AML-LPMs differed significantly from that of normal LPMs. The AML microenvironment also had effects on the apoptosis, killing ability, and phagocytic function of peritoneal resident macrophages.

Conclusions: These data suggest that peritoneal resident macrophages in mice with AML induced by MLL-AF9 show an M2-like phenotype. The reversal of macrophage polarization in the leukemic microenvironment may potentially enhance the immunotherapeutic effect in AML.

Key words: Peritoneal resident macrophages; large peritoneal macrophages (LPM); leukemic microenvironment; MLL-AF9-induced acute myeloid leukemia; M2-like phenotype

534. Clinical haematological nomograms for prediction of lymph node metastasis and prognosis in resectable esophagogastric junction adenocarcinoma

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Background: Esophagogastric junction adenocarcinoma (EJA) lacks blood-based predictive indicators for lymph node status and prognosis. We aimed to build nomograms with the preoperative haematological parameters to predict lymph node metastasis (LNM) and prognosis in resectable EJA.

Methods: The training cohort consisted of resectable EJA patients from December 2003 to December 2010, and patients in the validation cohort were collected from January 2011 to December 2017. 52 candidate indicators for nomogram construction included sociodemographic data and preoperative clinical laboratory haematological baseline data. Lasso regression was used to build LNM prediction nomogram (H-score nomogram). Univariate and multivariate Cox regression analysis was applied to select factors for overall survival prediction nomogram (OS nomogram).

Results: 465 resectable EJA patients were appointed to the training cohort, and the validation cohort was comprised of 289 patients. For predicting LNM, the H-score nomogram containing seven indicators showed good discrimination and calibration ability, with C-indexes of 0.684 and 0.630 in the training and validation cohorts, respectively. Moreover, the OS nomogram for survival prediction composed of 12 factors yielded C-indexes of 0.652 and 0.613 in the training and validation cohorts, respectively. Kaplan-Meier survival analysis showed patients with high OS nomogram scores had worse 5-year OS than those with low scores (training cohort: 59.6% vs. 26.2%; validation cohort: 58.6% vs. 38.6%; all $P < 0.0001$).

Conclusions: Nomograms constructed based on the clinical laboratory haematological indicators are potential prediction models for lymph node status and survival of resectable EJA.

Key words: Esophagogastric junction adenocarcinoma; clinical haematological indicators; nomogram; lymph node metastasis; prognosis

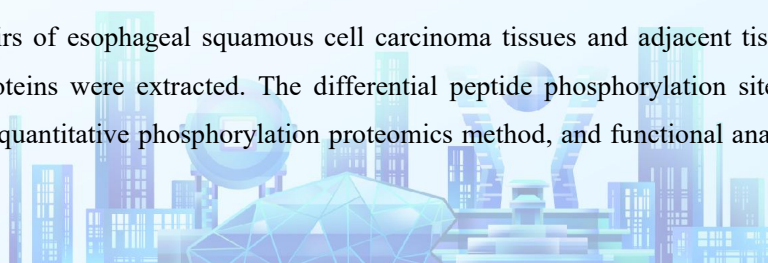
535. DEAD-box helicase 23 restrains proliferation and metastasis of esophageal squamous cell carcinoma.

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Objective: Our previous studies have shown that the expression level of DDX23 in tumor tissues of ESCC patients was higher than that in normal tissues, and its expression level was closely related to the clinical stage of ESCC, suggesting that it is a tumor-promoting protein of ESCC. And in vitro cell function experiments confirmed that ESCC cells overexpressing DDX23 have enhanced proliferation and invasion ability. To explore the possibility of DDX23 as a new target for gene therapy and prognosis index of ESCC.

Methods: Five pairs of esophageal squamous cell carcinoma tissues and adjacent tissues were collected, and tissue proteins were extracted. The differential peptide phosphorylation sites were detected by TMT-labeled quantitative phosphorylation proteomics method, and functional analysis was performed



in combination with MaxQuant database. The UALCAN database was used to detect the expression level of differential peptide DDX23 in esophageal cancer and its prognostic impact. The role of DDX23 in esophageal squamous cell carcinoma was pre-evaluated by binding peptide expression levels and phosphorylation levels. We verified the expression of DDX23 in fresh ESCC tissues by Western blotting. And then the immunohistochemistry was performed to investigate the DDX23 expression in 100 ESCC tissue specimens. Moreover, we combined with clinical data for multivariate model and survival analysis. DDX23 upregulated KYSE410 and Eca109 cells were constructed by Lentivirus overexpression. The function of DDX23 in ESCC proliferation and metastasis were studied by transwell and wound healing in vitro.

Results: We confirmed upregulated of DDX23 in 12 pairs of fresh ESCC tissues by western blotting. According to the clinicopathological features, We performed immunohistochemistry on the expression of DDX23 in cancer and adjacent tissues in 100 patients with ESCC. we found that the expression of DDX23 was remarkably positively correlated with the depth of invasion (T) ($P=0.044$), tumor node metastasis (TNM) stage ($P<0.039$). we found that DDX23 upregulated ESCC cells promote proliferation both in vitro. Increased expression of DDX23 significantly enhanced the proliferation capacity.

The results showed that DDX23 overexpression notably accelerated the proliferation of Eca109 and KYSE410 compared with that of the empty vector controls. On the other hand, DDX23 up-regulated Eca109 and KYSE410 caused a significant increase in their migration capacity ability compared with the blank controls. Collectively, these discoveries support that the increased expression of DDX23 in ESCC cells promoted a proliferation and migratory phenotype

Conclusions: The results indicated that the up-regulation of DDX23 in ESCC is positively related to malignant progression, and DDX23 plays an essential role in promoting proliferation and metastasis in ESCC. Thence, our findings revealed DDX23 can be used as a novel predictive biomarker, thus providing a novel diagnosis and therapeutic target for ESCC patients.

Key words: ESCC; DDX23; proliferation; invasion ability

536. The association between MGRN1 methylation in peripheral blood and breast cancer in the Chinese population

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Aims: Mahogunin ring finger 1 (*MGRN1*), an E3 ubiquitin ligase of the Really Interesting New Gene finger family, plays a pivotal role in many biological and cellular mechanisms. The DNA hypomethylation in *MGRN1* has been reported to be associated with breast cancer (BC) in the Caucasian previously.

However, the association has not been studied in other population. In this case-control study, we attempted to study the relationship between *MGRN1* DNA methylation and BC in the Chinese population.

Materials and Methods: 4 *MGRN1* CpG sites were quantitatively measured through mass spectrometry in the case-control study with 234 sporadic BC cases and 222 controls. The interquartile analysis was performed by calculating the quartiles from the methylation data from the total participants. The logistic regression adjusted for covariants and non-parametric tests were used to investigate the association between *MGRN1* methylation level and the status of BC.

Results: We observed four *MGRN1* CpG sites (*MGRN1*_CpG_1, *MGRN1*_CpG_2, *MGRN1*_CpG_3,4) were associated with BC. A significant tendency was also found for two *MGRN1* CpG sites ($P \leq 0.016$, Table 1). In addition, we found significant associations between BC and altered *MGRN1* methylation at different age groups, mostly in women at postmenopausal (age ≥ 50 years old, odds ratios (ORs) per-10% methylation: 1.58-1.85, $P \leq 0.031$ for three of four CpG loci; age < 50 years old, ORs per-10% methylation = 0.77, $P=0.033$ for one CpG site, Table 2). This age-related *MGRN1* methylation was also modified by the status of human epidermal growth factor receptor 2 (HER2) (HER2 negative, ORs per-10% methylation: 0.86-1.28, $P \leq 0.045$ for all four CpG loci; HER2 positive, ORs per-10% methylation = 0.79, $P = 0.022$ for one CpG site, Table 2).

Conclusion: In the Chinese population, we reported a significant association between BC and the blood-based *MGRN1* methylation modified by age and the status of HER2. Above all, this study provided evidence of potential DNA methylation markers for early BC diagnosis.

Key words: Chinese population; Breast cancer; *MGRN1*; Methylation; Blood.

537. Identification and Validation of *HYAL1* DNA Methylation in Differentiating Malignant from Benign Thyroid Nodules

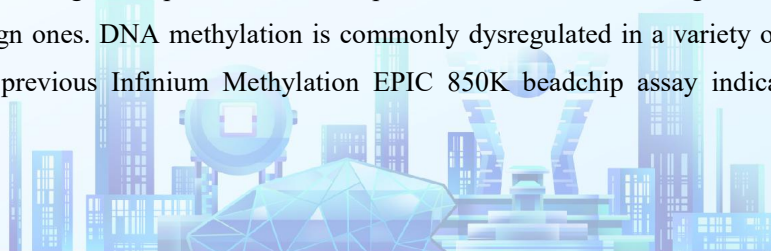
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Background: Thyroid cancer (TC) is the most common endocrine cancer around the world, of which papillary thyroid cancer (PTC) accounts for about 85%. Fine-needle aspiration biopsy (FNAB) is the preferred method for the diagnosis of thyroid nodules in the clinical application. However, about 20-30% of cases are indeterminate nodules according to FNAB, of which approximately 69% are classified as benign by postoperative pathology. Besides, the sensitivities of FNAB are 65-99% across studies. It is thus of great importance to develop novel biomarkers to distinguish the malignant tumors from the benign ones. DNA methylation is commonly dysregulated in a variety of diseases including cancers. Our previous Infinium Methylation EPIC 850K beadchip assay indicated a differentially



methyated CpG site (cg02183083) within hyaluronidase 1 (*HYAL1*) gene. Here, we conducted a validation study to explore the association between *HYAL1* and thyroid cancer.

Materials and methods: We measured the *HYAL1* methylation level in formalin-fixed paraffin-embedded (FFPE) tissues of 195 early-stage PTC (91.05% PTC at stage I) and 195 age- and gender-matched benign tumors collected during 2019-2020. The median (interquartile range, IQR) ages of malignant and benign cases were 51.00 (44.00-57.00) and 53.00 (46.00-60.25) years old, respectively. Females accounted for 78.95% (150/190) in both PTC and benign cases. Protein expression of *HYAL1* was evaluated in another 55 pairs of early-stage PTC (89.09% PTC at stage I) and benign tumors collected during 2013-2016, of which 34 pairs of cases were females. The median age was 43.00 (31.00-51.00) and 47.00 (36.00-52.00) years in PTC and benign tumors. DNA methylation was quantified by matrix-assisted laser desorption ionization time-of-flight mass spectrometry and protein expression was detected by immunohistochemical (IHC) staining. Binary logistic regression and Mann-Whitney U test were used for the data analysis. Two-sided P values < 0.05 were considered as statistically significant.

Results: A 165 bp amplicon located in the second exon of *HYAL1* gene was designed (Figure 1). It contained 4 CpG sites including cg02183083, of which *HYAL1*_CpG_3 and *HYAL1*_CpG_4 were merged as *HYAL1*_CpG_3.4 since they shared the same mass. **The association of *HYAL1* hypermethylation in FFPE tissue and PTC:** To investigate the association between *HYAL1* methylation and PTC, we performed binary logistic regression with the adjustment of age, gender and experimental batches. Compared to individuals with benign nodules, PTC patients presented a higher methylation level of *HYAL1*_CpG_3.4 and the adjusted odds ratio (OR), with 95% confidence interval (95% CI), was 1.52 (1.05-2.19) ($P = 0.025$; Figure 2A). After excluding the 17 PTC cases at stage II from the analysis, the association was still robust between hypermethylation of *HYAL1*_CpG_3.4 and PTC at very early stage (adjusted OR = 1.55, 95% CI: 1.06-2.25, $P = 0.022$; Figure 2B). Further gender-stratified analysis suggested that, in the females, *HYAL1*_CpG_3.4 methylation was obviously higher in PTC patients than that in benign tumors. The hypermethylation of *HYAL1*_CpG_3.4 was correlated with PTC even adjusted for age and experimental batches (OR = 1.55, 95% CI: 1.04-2.33, $P = 0.032$; Figure 2C). ***HYAL1* is highly expressed in human PTC:** We assessed *HYAL1* protein expression level of 55 human PTC and 55 matched benign cases with H score which takes both staining intensity and percentage of the positive cells into consideration. Our results suggested that, compared to benign tumors, PTCs showed a remarkably higher level of staining for *HYAL1* ($P = 1.00E-06$; Figure 3C).

Conclusion: Taken together, our study disclosed that both hypermethylation of the second exon within *HYAL1* gene and increased *HYAL1* protein expression in FFPE tissues were associated with PTC. Also, large-scale studies with comprehensive information are needed to verify our findings.

Key words: Thyroid nodules; *HYAL1*; Identification; DNA methylation; Protein

538. CCL2/CCR2 信号通路在乳腺癌发生发展中的研究进展

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乳腺癌作为一种侵袭性的恶性肿瘤，目前尚缺乏有效的治疗手段。近来研究表明，乳腺癌居女性所患癌症的第一位，研究乳腺癌发生发展的相关机制有望找到有价值的靶向标志物以控制其进展。肿瘤微环境中的炎症反应被证实在癌症进展中至关重要，替代策略是靶向针对乳腺癌肿瘤微环境中的相关免疫细胞（如肿瘤相关巨噬细胞（TAM），肿瘤相关噬中性粒细胞等）。与乳腺癌有关的炎性介质包括细胞因子和趋化因子等，其中 CCL2/CCR2（趋化因子 2 及其受体）的作用是募集单核细胞/巨噬细胞以及促进肿瘤的血管生成并且与乳腺癌诊断及进展密切相关。有研究表明，由肿瘤和基质细胞合成的 CCL2 可以诱导巨噬细胞进入乳腺癌的微环境中并且极化为 M2 型巨噬细胞促进肿瘤的进展；此外，CCL2 阳性的乳腺癌和 CD14 阳性 TAM 相互作用是导致肿瘤快速复发的重要危险因素。除此之外，转化生长因子- β （TGF- β ）以阶段依赖方式调控乳腺癌 CCL2 的表达，进而调节 TAM 分泌吸引 Th2 的趋化因子 CCL22，从而决定了肿瘤微环境内的 Th1-Th2 平衡。对于乳腺癌，CCL2 / CCR2 趋化因子信号可通过 p42/44MAPK 和 SMAD3 依赖性机制调控乳腺癌自身的发生发展。因此，我们希望通过调控乳腺癌 CCL2 的表达或减少促癌作用的 M2 型巨噬细胞，或调节 MAPK-SMAD3 机制轴进一步抑制肿瘤的进展。

关键词: 乳腺癌; CCL2; CCR2

539. 基于免疫相关基因构建乳腺癌免疫预后模型

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目的: 筛选影响乳腺癌患者预后的预测因素, 构建评价乳腺癌患者免疫基因相关的预后模型。

方法: 基因表达芯片数据来源于癌症基因组图谱 TCGA 数据库中乳腺癌 1222 例样本（T: 1109/N:113）的基因表达数据及对应其中 1097 例样本的临床信息。并在 ImmPort Portal 数据库提取免疫基因相关文件，与 TCGA 乳腺癌转录组的差异基因取交集。利用单因素 COX 回归筛选出对预测乳腺癌患者预后有意义的预测因子, 并构建 Cox 比例风险模型。利用校准图评价模型的准确性。利用受试者工作曲线（ROC 曲线）分别在训练集以及验证集中评价模型的鉴别能力, 并与单纯纳入 TNM 预后分期因素（原发肿瘤大小, 区域淋巴结以及远处转移）以预测患者预后的准确性进行对比。

结果: 通过筛选以 PSME2, ULBP2, MMP9, IL18, CCL24, IGHE, SCG2, TSLP, FLT3, SDC1, SSTR1 及 TNFRSF8 十二个基因构建预后模型。以模型的 riskScore 做生存分析得到 $P=1.217e-07<0.05$, 则说明构建的模型和生存极为相关。ROC 曲线的 AUC 值为 0.759, 证明在训练集以及验证集中评价模型的鉴别能力较强。单因素临床性状分析中年龄, 病理分期, TNM 分期及 riskScore 是能够预测患者生存的独立预测因子; 多因素分析中仅年龄及 riskScore 可作为预测患者生存的独立预测因子。

结论：与单纯依靠传统的 TNM 预后因素预测预后相比,该模型能够更准确的量化,评估患者的预后,可为医生,病人以及医疗政策制定者提供直观的信息。

关键词：乳腺癌；免疫基因；预后模型

540. The role of CRKL regulated by bone marrow stromal cells exosome miR-429 in chronic myeloid leukemia

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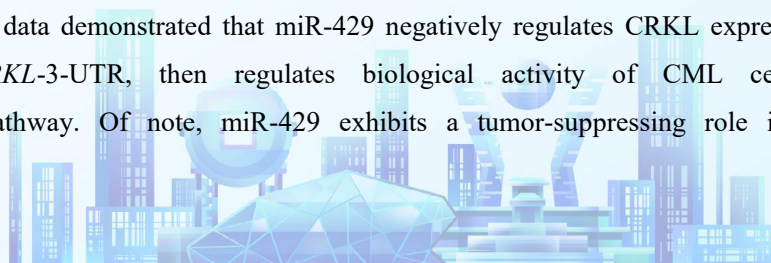
Background: Philadelphia chromosome (Ph1) is the characteristic marker of chronic myeloid leukemia (CML), which leads to the formation of the *BCR-ABL1* fusion gene. It encodes a protein that is a constitutively activated tyrosine kinase. CRKL is an oncogene that encodes the protein CrkL, which is the substrate of BCR-ABL tyrosine kinase and the major tyrosine phosphorylated protein of CML. In a variety of malignant tumors, miR-429 can inhibit the expression of CrkL, therefore suppressing the proliferation, invasion, migration of cancer cells. In addition, bone marrow stromal cells (BMSCs) derived exosome miR-429 can change the function and phenotype of leukemia cells in bone marrow. However, the correlation between miR-429 and CrkL in CML is unclear.

Objective: In the current study, on the premise that BMSCs-exosomes promote the growth of CML cells, we investigated the mechanism of altering the expression of miR-429 and CRKL in CML cells to affect the characteristics of CML cells, so as to regulate the expression of miR-429 and CRKL in CML cells through exosomes, and provide data for the clinical treatment of CML.

Methods: Western blot, quantitative real-time PCR were used to detect the expression levels of miR-429 and CRKL in different myeloid leukemia cell lines, and the dual-luciferase reporter assay was used to verify that *CRKL* is a direct target of miR-429. The expression of *CRKL* and miR-429 in K562 and KU812 cells were down-regulated and up-regulated respectively by lentiviral vector and miR-429 mimics. Subsequently, cell growth activity was measured by MTS, apoptosis and the ROS level were detected by flow cytometry, the content of ATP,lactate acid (LA) were tested by spectrophotometry, BCR-ABL^{P210} and C3G/Rap1 pathway proteins were examined by Western blot.

Results: K562 and KU812 cells with high expression of CRKL and low expression of miR-429 were selected as the experimental cells. *CRKL*-shRNA and miR-429 mimics were successfully constructed. It suppressed cell proliferation and induced cell apoptosis. The content of ATP was increased, the content of LA was decreased, and the level of ROS was decreased. The expression of BCR-ABL^{P210} protein was decreased. Both *CRKL*-shRNA and miR-429 mimics reduced the protein levels of C3G, Rap1 and GLUT1 in K562 and KU812 cells.

Conclusions: Our data demonstrated that miR-429 negatively regulates CRKL expression by selectively targeting *CRKL*-3-UTR, then regulates biological activity of CML cells via inhibiting C3G/Rap1 pathway. Of note, miR-429 exhibits a tumor-suppressing role in CML, which is



different from CrkL. Altering the expression of miR-429 and CRKL in CML cells with the help of BMSCs-exosomes provides new insights into the treatment of CML.

Key words: miR-429; CRKL; CML; C3G/ Rap1; exosomes

541. NTF4 possesses both anti-tumorigenic and pro-metastatic roles in breast cancer progression

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Background: The molecular underpinnings behind malignant progression of breast cancer (BrCa) from a localized lesion to an invasion and ultimately metastatic disease are incompletely understood. Here we report that neurotrophin 4 (NTF4) plays a dual role in mammary tumorigenesis and metastasis.

Materials and Methods: NTF4 functions were analyzed by various cell biology assays in vitro. Subcutaneous tumor model and metastatic lung colonization model were used to explore NTF4 effects in vivo. WB, IHC, IF, qRT-PCR, Co-IP, Mass Spectrum analysis, and iTRAQ were further applied to determine the detailed mechanism.

Results: NTF4 was downregulated in primary breast tumors, but upregulated in normal breast tissues and metastatic lymph nodes. NTF4 inhibited cell proliferation and colony formation in vitro and xenograft tumorigenicity in vivo. Meanwhile, NTF4 promoted cell apoptosis and cell cycle arrest in vitro. Surprisingly, NTF4 promoted epithelial-mesenchymal transition (EMT), cell motility, and invasiveness in vitro and metastatic lung colonization in vivo. Clinical data showed that expression levels of NTF4 were associated with poor clinical outcomes, supporting the notion that metastasis, rather than primary cancer, is the major determinant of the mortality of BrCa patients. Mechanistic investigations further revealed that NTF4 elicits its pro-metastasis effects by targeting DNA-PKcs and ANXA1. Importantly, using DNA-PKcs inhibitor and AKT inhibitor, and knockdown ANXA1 rescued NTF4-mediated promotion of EMT, cell migration, and invasion, respectively. Interestingly, NTF4 exerts its anti-proliferation effects by increasing the phosphoserine level of ANXA1, which was important for ANXA1 to import into the nucleus. Then ANXA1 nuclear translocation induced expression of the pro-apoptotic Bid gene, and activated the caspase-3 apoptotic pathway, which was almost completely reversed by knockdown ANXA1.

Conclusion: Collectively, these findings uncover an unexpected dual role for NTF4 in mammary tumorigenesis and metastatic progression and represent a predictive and therapeutic target for BrCa.

Key words: Breast cancer; invasion and metastasis; epithelial-mesenchymal transition; NTF4

542. Inhibiting ADRB2 signaling suppresses HCC chemoresistance by regulating HIF-1 α expression



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Background: Chemoresistance of hepatocellular carcinoma (HCC) is a major clinical problem.

There has been evidence that adrenergic signaling is closely related to tumor progression as well as chemoresistance. The present study aims to determine the function of β_2 -adrenergic receptor (ADRB2) signaling in chemoresistance of HCC.

Methods: Change in proportion of ADRB2 positive cells in HCC cell lines undergoing chemotherapy was tested. The effects of inhibiting ADRB2 signaling on cisplatin and doxorubicin chemoresistance of HCC cells were then detected via in vitro proliferation and apoptosis assays. Subsequently, the expression of HIF-1 α during this process was observed by western-blot assays. Moreover, the efficacy of inhibiting ADRB2 signaling on cisplatin chemoresistance of HCC cells was examined again after HIF-1 α stabilization.

Results: The proportion of ADRB2 positive cells in HCC cell lines markedly increased in response to chemotherapy. ICI118,551-mediated inhibition of ADRB2 signaling further reduced the viability of HCC cells undergoing chemotherapy. Meanwhile, HIF-1 α was confirmed to be further down-regulated. HIF-1 α stabilization abolished the effect of blocking ADRB2 signaling on viability suppression of HCC cells undergoing chemotherapy.

Conclusion: Our data uncovers that inhibiting ADRB2 signaling plays a critical role in suppressing HCC chemoresistance via decreasing HIF-1 α expression.

Key words: ADRB2; HCC; chemoresistance; HIF-1 α

543. 尿液外泌体长链非编码 RNA MALAT1 和 HIF1A-AS2 对膀胱癌诊断的价值

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目的: 探讨尿液外泌体中 lncRNA MALAT1 和 HIF1A-AS2 水平与膀胱癌发生和发展的关系及对膀胱癌诊断的价值。

方法: 分别测定 40 例膀胱癌患者,膀胱良性疾病患者及健康人尿液外泌体中 MALAT1 和 HIF1A-AS2 的水平。比较 3 组尿液中 MALAT1 和 HIF1A-AS2 水平的差异,并分析膀胱癌患者 MALAT1 和 HIF1A-AS2 水平与肿瘤病理分级,分期及肿瘤大小的关系。应用 ROC 曲线分析 MALAT1 和 HIF1A-AS2 诊断膀胱癌的敏感度和特异度。

结果: 膀胱癌组尿液外泌体中 MALAT1 和 HIF1A-AS2 水平显著高于膀胱良性疾病组和健康对照组,差异具有统计学意义 ($P < 0.01$); 膀胱癌 G1 级组 MALAT1 和 HIF1A-AS2 水平与 G2-G3 级组比较,差异无统计学意义 ($P > 0.05$)。膀胱癌不同分期的比较结果显示, Ta 期, T1-T2 期和 T3-

T4 期 3 组之间 MALAT1 和 HIF1A-AS2 水平差异无统计学意义 ($P>0.05$)；而肿瘤直径 $\geq 3.0\text{cm}$ 组患者 MALAT1 和 HIF1A-AS2 水平明显高于直径 $<3.0\text{cm}$ 组，且差异具有统计学意义 ($P<0.05$)。结果表明，MALAT1 的 ROC 曲线下面积(AUCROC)为 0.777，当 cut-off 值为 398.64 时，其筛查膀胱癌的敏感性为 77.5%，特异性为 70.0%；HIF1A-AS2 的 ROC 曲线下面积(AUCROC)为 0.797，当 cut-off 值为 350.21 时，其筛查膀胱癌的敏感性为 72.5%，特异性为 80.0%；MALAT1 和 HIF1A-AS2 联合检测的 AUCROC 为 0.862，敏感性为 80.0%，特异性为 92.5%，均高于两项指标的单独筛查价值。**结论：**膀胱癌患者尿液外泌体 MALAT1 和 HIF1A-AS2 表达水平明显升高，MALAT1 和 HIF1A-AS2 有望成为膀胱癌诊断的潜在生物学标志物。

关键词：尿液；外泌体；人肺腺癌转移相关转录因子 1(MALAT1)；缺氧诱导因子 1 α 反义 RNA2(HIF1A-AS2)；膀胱癌；诊断

544. Molecular characterization and prognostication of large cell neuroendocrine carcinoma and large cell carcinoma

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Purpose: Large cell neuroendocrine carcinoma (LCNEC) and classic large cell carcinoma (LCC) are two distinct entities with different histological and biological characteristics. However, the mutational profiles and the clinical behavior of the two subtypes of lung cancer remain to be explored.

Patients and methods: We genetically profiled 10 patients with LCNEC and 7 with LCC and performed association analysis of overall survival with genetic features.

Results: Both LCNEC and LCC showed high prevalence in male patients, with no clear association with smoking history. Potential targetable mutations in KRAS and RET were detected in the study cohort. However, LCNEC and LCC showed distinct mutational profiles with an enrichment of RB1/TP53 co-mutations in a subset of LCNEC patients. SMARCA4 and KEAP1 mutations were exclusively found in LCC patients, and RICTOR, BRAF, ROS1 and TET2 mutations were only detected in LCNEC. LCC patients in the cohort had shorter survival compared to LCNEC patients ($P=0.006$). Survival analysis revealed an association between SMARCA4 mutations and poor outcome in the study cohort and in the LCC subset. Mutations in BRAF were associated with a trend of increased survival in the study cohort, as well as in the LCNEC subset. Finally, TET2 mutations were associated with poor outcome in the LCNEC cohort.



Conclusion: LCC and LCNEC were both heterogeneous diseases with limited treatment options. Our study identified potential targetable mutations and prognostic biomarkers that might provide more therapeutic options and improve individualized patient care.

Key words: large cell carcinoma; SMARCA4; KEAP1; BRAF; RB1; TET2

545. 抑癌基因 LRP1B 突变在肺腺癌治疗和预后中的作用

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全球癌症相关死亡病例中, 肺癌相关死亡病例远超其他癌症类型, 位居癌症相关死亡人数第一。近年来, 免疫检查点抑制剂 (ICI) 如纳武单抗, 阿替利珠单抗, 帕博利珠单抗, 在晚期非小细胞肺癌 (NSCLC) 中有显著的临床治疗效果。肿瘤突变负荷 (TMB) 被定义为每百万碱基中被检测出的体细胞基因编码错误、碱基替换、基因插入或缺失错误的总数, 是预测免疫检查点抑制剂治疗效果评估的最新标志物。低密度脂蛋白受体相关蛋白 1B (LRP1B) 属于 LDL 受体家族, 最初是在对肺癌细胞系的研究中发现的。LRP1B 基因组改变在肺癌的发病机制中非常重要, 在近 50% 的非小细胞肺癌细胞系中, 观察到 LRP1B 基因外显子纯合缺失或异常转录致 LRP1B 部分缺失的现象。LRP1B 是一种重要的抑癌基因, LRP1B 的错义突变、剪接区突变、同义突变和内含子突变均与高肿瘤突变负荷相关, 这提示高肿瘤突变负荷与特定的 LRP1B 突变类型无关, 并且 LRP1B 全序列突变可能与全基因组的突变负荷增加有关。现阶段已有研究证明 LRP1B 单基因突变与肺癌高突变负荷相关, 这一研究结果为日后找到更简单, 互补或者是替代肿瘤突变负荷作为免疫检查点抑制剂治疗标志物的方法提供了新证据。但 LRP1B 突变与免疫检查点抑制剂治疗效果和预后的关系需要进一步的研究。

关键词: 肺腺癌; LRP1B; 基因突变; 突变负荷; 治疗和预后

546. The progress in the study of IRF4

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The appearance of checkpoint blockade therapy significantly improved the survival and the prognosis of patients with tumors. But the checkpoint blockade therapy also has its own limitations, for a large number of patients showed resistance to these strategies. So, nowadays, all of these situations clarified that new strategies should be employed to advance the field. In the normal tissue, the role of regulatory CD4⁺ T cells (Tregs) is to protect the body from autoimmunity, allergy and immunopathology through several mechanisms such as expressing cell-surface inhibitors like CTLA-4; or producing inhibitory cytokines like IL-10, TGF- β , IL-35, and so on. As recently reports, there are aberrant increase of Tregs in the tumor site, which results in the obvious decrease of anti-tumor immune response. According to clinical data, depletion or inhibition of Tregs can suppress the inhibitory

function and promotes tumor regression. But indeed, neither depletion nor inhibition of Tregs are safe, they will lead to autoimmunity, allergy and immunopathology.

So there we found the Interferon regulatory factor 4. It is specifically expressed by intratumoral CD4⁺ Tregs with potently suppressive function. Compared with IRF4⁻ Tregs, the IRF4⁺ Tregs can produce a series of inhibitory molecules. And the presence of these molecules may relate to the exhausted T cells. It has been pronounced that IRF4 plays a crucial role in the generation of effector Tregs. The IRF4 depleted Tregs would remain a naive-like phenotype, and the inhibitory molecules (ICOS, CTLA-4, IL-10) would also be low-expressed. In conclusion, IRF4 can control the inhibitory molecules in the tumor microenvironment. IRF4 has a synergistic effect with BATF, a AP-1 family members, in DNA binding. And the detail mechanism about how IRF4 regulate the Tregs' transcription and function is still unknown. The profile of IRF4 expression in breast, bladder and prostate tumors also need to be explore. Whether IRF4 alone or in combination with it's partner BATF will regulate the inhibitory molecules in these tumors or not and if they will have effect on the prognosis of this tumors are the problems that we ought to research.

In a word, IRF4 is a potential target to improve the survival and prognosis of many types of tumors.

Key words: IRF4; Tregs

547. 乳酸在肿瘤微环境中的作用

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Warburg 效应是肿瘤代谢的特征之一，为癌细胞提供能量并产生大量乳酸，在最近的研究中我们发现乳酸在肿瘤生长,免疫耐受,迁移等过程中发挥着重要的作用。乳酸作为癌细胞改造微环境的重要工具，首先乳酸提供的酸性环境可以提供质子梯度，为癌细胞的质子偶运蛋白提供驱动力，抑制其他正常细胞的生长。乳酸通过作为 G 蛋白偶联受体 GPR81 的激动剂发挥信号分子的作用，激活癌症自分泌生长因子，同时激活癌细胞旁分泌促进血管生成,免疫逃避和化学抗性。研究表明乳酸激活肿瘤细胞的旁分泌，抑制 MHCII 的细胞表面呈递，阻止树突状细胞的抗原提呈作用。乳酸介导的免疫细胞重编程有助于建立疾病特异性免疫状态。大量乳酸引发的组蛋白乳酸化对巨噬细胞 M2 型极化通道的基因表达升高有显著的促进作用，进一步削弱免疫杀伤作用加长炎症浸润时间。组蛋白乳酸化还会调节癌细胞的细胞代谢，非小细胞肺癌细胞中糖酵解酶（HK-1,PKM）和 TCA 循环酶（SDHA,IDH3G）的 mRNA 水平分别被组蛋白乳酸化下调和上调，维持线粒体稳态。免疫细胞的快速增殖很大程度上也提高了乳酸水平。研究发现通过抑制 BCAP 可以有效抑制有氧糖酵解和乳酸生成，降低肿瘤耐药性，这转化为组蛋白乳酸化减少和修复性巨噬细胞基因表达减少。基因突变是癌细胞产生的根本原因，然而物质代谢变化同样是癌症发生发展不可忽视的重要因素，癌症患者的营养支持对癌症患者的预后有很大改善，联合治疗会是癌症治疗的新方向。

关键词: 乳酸,物质代谢; GPR81; 组蛋白乳酸化

548. Lung Cancer-associated Blood-based Hypomethylation of HYAL2 in Two Independent Case-control Studies as well as the Two Studies in Combination by Mass Spectrometry

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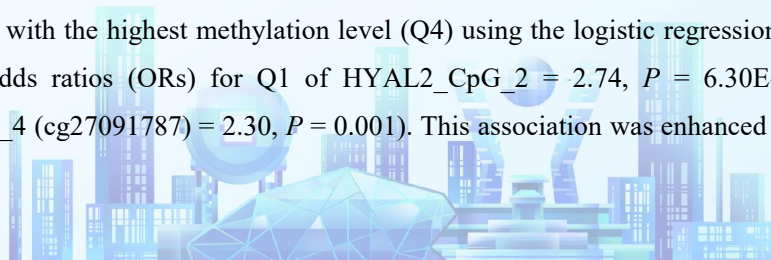
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Background and aim: Lung cancer (LC) is the second commonly diagnosed cancer and the leading cause of cancer-related mortality worldwide, with 2.2 million new cases and 1.8 million deaths in 2020. The median survivals and 5-year survival rates of LC decrease with increasing stage, from 21 months to 12 months and 50-65% to 2-3% at stage I and IV, respectively. Thus, early detection is essential to improve the survival and life quality of LC patients. Changes in DNA methylation in peripheral blood could be associated with malignancy at early stage. Previous works have shown that blood-based hyaluronoglucosaminidase 2 gene (HYAL2) methylation was associated with a variety of cancers, but not with LC. Here, we aim to investigate the association between blood-based methylation of HYAL2 and LC in the Chinese population.

Materials and methods: The methylation levels of two HYAL2 CpG sites were quantified via MALDI-TOF mass spectrometry in two independent case-control studies of the Chinese population with a total of 960 LC cases and 1472 age and gender matched controls. The association between methylation intensities and LC was estimated by interquartile analysis using the logistic regression model adjusted for age, gender, and batch effect in Study I, Study II as well as combining Study I and II. The logistic regression analysis was performed to compare the DNA methylation differences between early-stage LC cases (Stage I LC cases) and intermediate & advanced LC cases (Stage II&III LC cases) adjusted for age, gender, and batch effect.

Results: In Study I, the hypomethylation of HYAL2_CpG_2 and HYAL2_CpG_4 (cg27091787) showed a significant association with LC in most of the lower quartiles of methylation levels (Q1-Q3) compared to the quartile with the highest methylation level (Q4) using the logistic regression model adjusted for covariants (Odds ratios (ORs) for Q1 of HYAL2_CpG_2 = 2.74, $P = 6.30E-05$; OR for Q1 of HYAL2_CpG_4 (cg27091787) = 2.30, $P = 0.001$). This association was enhanced with lower quartiles



(Ptrend for HYAL2_CpG_2 = 1.00E-05, Ptrend for HYAL2_CpG_4 (cg27091787) = 3.50E-04). We proposed a correlation between the hypomethylation of HYAL2 and the increased risk of LC and performed further validation in Study II with another independent subjects, where the hypomethylation of HYAL2 was a risk factor for LC (Ptrend for HYAL2_CpG_2 = 2.04E-04, Ptrend for HYAL2_CpG_4 (cg27091787) = 0.001) as indicated in Study I. When combining the subjects of the two studies, hypomethylation of HAYL2 was a risk factor for both female and male individuals (Female: Ptrend for HYAL2_CpG_2 = 0.002, Ptrend for HYAL2_CpG_4 (cg27091787) = 0.003; male: Ptrend for HYAL2_CpG_2 = 6.00E-06, Ptrend for HYAL2_CpG_4 (cg27091787) = 8.00E-06), especially for male subjects. Similarly, hypomethylation of HAYL2 was correlated with LC among subjects ≤ 55 years old and > 55 years old (Age ≤ 55 years old: Ptrend for HYAL2_CpG_2 = 1.11E-04, Ptrend for HYAL2_CpG_4 (cg27091787) = 3.58E-04; age > 55 years old: Ptrend for HYAL2_CpG_2 = 2.44E-04, Ptrend for HYAL2_CpG_4 (cg27091787) = 7.50E-05). Moreover, these altered DNA methylation patterns in the blood-based HYAL2 could be detected in the early stage of pulmonary function impairment (Stage I LC cases) and became even more aberrant in the patients with intermediate & advanced pulmonary function impairment (Stage II&III LC cases) (Median of methylation levels = 0.19 (Stage I LC cases) and 0.16 (Stage II&III LC cases), 0.51 (Stage I LC cases) and 0.48 (Stage II&III LC cases), OR per -10% methylation = 1.40, 1.31, $P = 0.023$, 0.014, for HYAL2_CpG_2 and HYAL2_CpG_4 (cg27091787), respectively, by logistic regression adjusted for age, gender, and batch effect). This indicated that the aberrant HYAL2 methylation would be strengthened along with the impairment of pulmonary function.

Conclusions: Our study elucidates a gender and age-independent association between LC and blood-based HYAL2 hypomethylation in the Chinese population and suggests the alternations of DNA methylation in blood, or say in the blood leukocytes, may play a role in the occurrence and even the progress of LC.

Key words: Lung cancer; early detection; DNA methylation; HYAL2; peripheral blood

549. HTRA1/CDK1 axis promotes pancreatitis initiated pancreatic ductal adenocarcinoma

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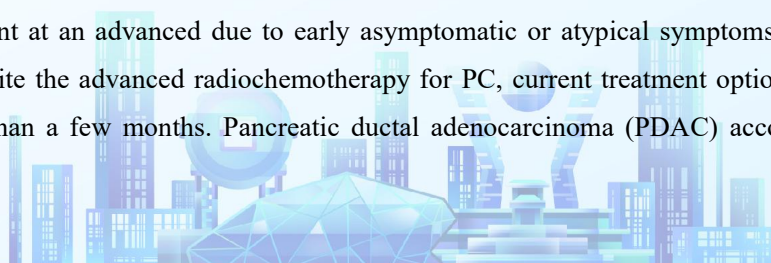
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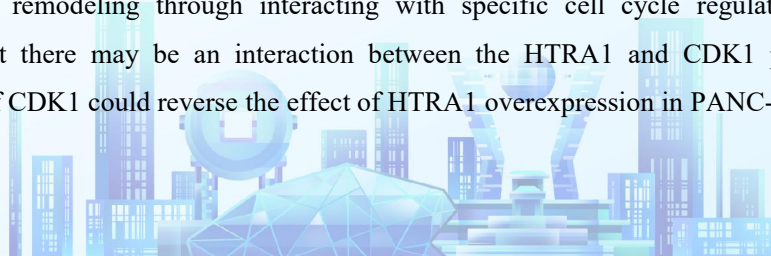
Background: Pancreatic cancer (PC) is one of the most lethal malignancies that occurs in the digestive system, and will become the 2nd most common cause of cancer-related mortality by 2030. Most PC patients present at an advanced due to early asymptomatic or atypical symptoms, not candidates for surgery. Despite the advanced radiochemotherapy for PC, current treatment options enhance survival by no more than a few months. Pancreatic ductal adenocarcinoma (PDAC) accounts for more than



90% of all PC cases, which mainly originates from the pancreatic ductal epithelium and acinar cells. Pancreatitis characterized by damage to acinar cells, is a crucial factor for PDAC development. Adult acinar cells are not very susceptible to transformation by oncogenic Kras alone, however, pancreatitis, as an inhibitor of oncogene-induced senescence, induces a process of acinar cell reprogramming known as acinar-to-ductal metaplasia (ADM). ADM is a precursor of pancreatic intraepithelial neoplasia (PanINs) lesions that can progress to PDAC. High-temperature requirement protein A1 (HTRA1) is a serine protease that serves as a tumor marker and/or prognostic factor, which is connected to tumorigenesis via regulating cancer cell proliferation, migration, apoptosis, and differentiation. HTRA1 has been hypothesized to play a role as a tumor suppressor of PC, but the tumor-promoting or anti-tumor effect of HTRA1 remains controversial. Our previous research found HTRA1 is significantly up-regulated in acute pancreatitis (AP) with ADM. Thus, we speculate that HTRA1 may play an important role in pancreatitis initiated PDAC, but the mechanism is unclear.

Methods: On the basis of TCGA, GSE15471, GSE28735 databases, the expressions of HTRA1 gene in tumor tissue were compared with normal tissue in PC patients. Subsequently, the HTRA1 gene and protein expression levels were verified on two PC cell lines (SW1990 and PANC-1) and normal human pancreatic ductal epithelial cell line (HPDE6-C7), as well as tissue microarrays from PDAC patients. The cell viability, apoptosis, proliferation, adhesion and migration of PANC-1 cells were observed after knockdown or overexpression of HTRA1. Meanwhile, a chronic pancreatitis (CP) mice model was induced by administering six intraperitoneal injections of caerulein at 1 h interval (50 μ g/kg body weight, 3 times/week) for 8 weeks, and ADM and HTRA1 expression in pancreas were detected. To further reveal the action and mechanism of HTRA1 in pancreatitis transforming into PDAC, immunoprecipitation and LC-MS/MS analysis were used to filter the proteins that interact with HTRA1. Subsequently, the interaction between the cyclin-dependent kinase 1 (CDK1) and HTRA1 was verified by co-immunoprecipitation. CDK1 gene in HTRA1-overexpressed PANC-1 cells line was knocked down to further verify the regulatory relationship between CDK1 and HTRA1.

Results: According to TCGA, GSE15471, GSE28735 databases, the HTRA1 mRNA levels were significantly higher in tumor tissues than that in normal samples provided by PC patients. The gene and protein expressions of HTRA1 were also up-regulated in SW1990 and PANC-1 cells, as well as in human tumor tissue compared to the adjacent tissue, whose high expression was associated with a decreased survival rate in PDAC patients. Knockdown of HTRA1 expression disrupted pancreatic cancer cell viability, invasion, and adhesion, and arrested the cell cycle at the G2M phase. However, the above phenotypes were reversed by overexpression of HTRA1. ADM lesion was observed in caerulein-induced CP mice compared to the normal acinar by HE, AB/PAS staining and amylase/CK19 double-positive stains; and increased HTRA1 expression was also observed in CP mice. HTRA1 protein could pull down CDK1 protein, a serine/threonine kinase that regulate the cell cycle and adhesion remodeling through interacting with specific cell cycle regulatory cyclins, which suggested that there may be an interaction between the HTRA1 and CDK1 proteins. Moreover, knockdown of CDK1 could reverse the effect of HTRA1 overexpression in PANC-1 cells.



Conclusion: Our findings underscore the instrumental role of HTRA1 overexpression in development of PDAC from pancreatitis and highlight a potential to impede PDAC progression by inhibiting the HTRA1/CDK1 axis.

Key words: pancreatitis; pancreatic ductal adenocarcinoma; acinar-to-ductal metaplasia; HTRA1; CDK1

550. Clinical Application of Free/Total Prostate Specific Antigen Ratio for Diagnosing Prostate Cancer in Western Chinese Men over 50years with Total PSA Levels of 2.0-25.0 ng/ml

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Objective: To investigate the clinical application of free to total prostate specific antigen (f/t PSA) ratio with a new broad serum Total-PSA (T-PSA) "gray zone" of 2.0-25.0 ng/ml in differentially diagnosing Prostate cancer (PCa) from benign prostate diseases (BPD) in Western Chinese men over 50years.

Methods: We included 1655 patients including 528 PCa and 1127 BPD, and analyzed their T-PSA, Free-PSA (F-PSA) and f/t PSA. Receiver operating characteristic curves according to age, T-PSA level, TNM stage and prognosis stage were used to assess the efficiency of PSA and f/t PSA.

Results: There were 47.4% PCa patients with T-PSA of 2.0-25.0ng/ml. When T-PSA were 2.0-4.0, 4.0-10.0, 10.0-25.0, 25.0-50.0 and 50.0-100.0ng/ml, the AUCs of f/t PSA were 0.749, 0.769, 0.761, 0.590 and 0.603 respectively. And f/t PSA ratio acquired the best AUC of 0.811 in T-PSA 2.0-25.0 ng/ml with specificity of 73.2%, sensitivity of 78.8% and an optimal cut-off value of 15.501. The AUCs of f/t PSA ratio in four age groups (50-59yr, 60-69yr, 70-79yr and ≥ 80 yr) were 0.767, 0.806, 0.815 and 0.833, respectively, the best sensitivity (85.7%) and specificity (80.2%) was appeared in age over 80yr. The trend of T-PSA was in accordance with Gleason score, TNM stage, and AJCC prognosis group with spearman correlation coefficient of 0.243, 0.273, 0.363 ($P < 0.05$).

Conclusion: The f/t PSA ratio can significantly improve accuracy of differential diagnosis between PCa and BPD in a new broad T-PSA "gray zone" of 2.0-25.0 ng/ml in Western Chinese Men. And T-PSA can also be used as Gleason score and prognosis prediction indicators.

Key words: Total prostate specific antigen; free/total PSA ratio; gray zone; prostate cancer

551. Research on the Role of Contralateral Prophylactic Mastectomy Among Women Undergoing Breast Reconstruction following Mastectomy Based on SEER Database



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Purpose: We aimed to explore and identify the curative effectiveness of CPM in female breast cancer (FBC) patients undergoing breast reconstruction.

Methods: Kaplan-Meier analysis, Cox proportional hazards model, competing risk model analysis, and competing risk regression mode analysis were applied to evaluate the prognostic effects of CPM on overall survival (OS), breast cancer-specific survival (BCSS), and breast cancer-specific death (BCSD).

Results: A total of 5952 patients died in this cohort study, and 4104 (69.0%) of them were BCSD, while 1848 (31.0%) were other cause-specific death (OCSD). Breast reconstruction patients in CPM group had both improved OS (HR = 0.73, 95% CI: 0.69–0.77, $P < 0.0001$) and BCSS (HR = 0.77, 95% CI: 0.72–0.82, $P < 0.0001$) in comparison with those in the non-CPM group, with the risk of death from all causes and breast decreased by 27% and 23%. Subjects in CPM subgroup tended to have both lower cumulative incidences of BCSD ($P < 0.0001$) and OCSD ($P < 0.0001$) than those in the non-CPM subgroup. Fine and Gray multivariable regression analysis indicated that patients in CPM subgroup had better BCSD (HR = 0.864, 95% CI: 0.806–0.927, $P < 0.0001$) and OCSD (HR = 0.764, 95% CI: 0.684–0.852, $P < 0.0001$).

Conclusion: Our study demonstrated that the administration of CPM tended to decrease the risk of death from all causes, BCSD and OCSD, which provided a valid therapeutic strategy for FBC patients undergoing breast reconstruction.

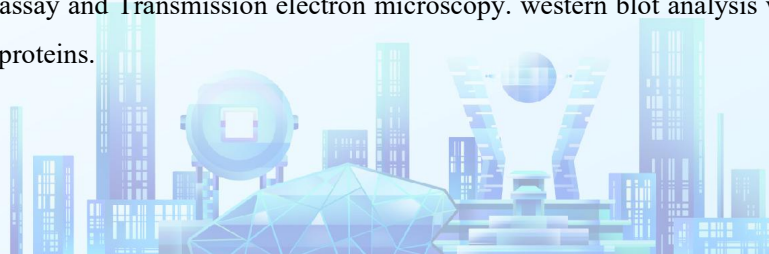
Key words: Female breast carcinoma; contralateral prophylactic mastectomy; competing risk model; SEER; breast reconstruction

552. 2,5-dimethyl celecoxib induces apoptosis and autophagy via activation of ROS/JNK axis in nasopharyngeal carcinoma cells

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Purpose: To investigate the potential mechanism of apoptosis and autophagy induced in nasopharyngeal carcinoma by 2,5-dimethyl celecoxib (DMC).

Methods: The cells viability assay and Colony formation assay were used to determine relative cell viability in vitro at 24 and 48 hours. The effects of DMC on apoptosis and autophagy were determined by Apoptosis assay and Transmission electron microscopy. western blot analysis was used to evaluate expression of proteins.



Results: Mechanismly, we found DMC induced apoptosis and autophagy for anticancer therapy against nasopharyngeal carcinoma. Furthermore, DMC-induced autophagy could remarkably attenuate after the treatment of reactive oxygen species (ROS) scavenger N-acetyl cysteine (NAC) and c-Jun N-terminal kinase (JNK) inhibitor SP600125 (SP).

Conclusion: Taken together, these results suggested DMC induced apoptosis and autophagic death via activation of ROS/JNK axis in NPC cells, which providing us new insights into developing potential therapeutic agents for nasopharyngeal carcinoma patients.

Key words: 2,5-dimethyl celecoxib; autophagy; apoptosis; nasopharyngeal carcinoma

553. 糖基化通过 YAP/TFRC 通路增加肝癌细胞对铁死亡的敏感

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目的: 铁死亡是近年来新发现的一种铁依赖的非凋亡形式的细胞死亡方式, 索拉非尼对肝癌细胞的毒性作用也部分依赖于铁死亡的发生, 诱导铁死亡或可成为治疗肿瘤的新策略。有研究表明 YAP 高表达的肿瘤细胞更容易发生铁死亡。癌基因 YAP 本应促进肿瘤发生发展, 却因为铁死亡这一独特的细胞死亡方式而成为治疗的靶点。而 O-糖基化对于 YAP 的功能起重要的调控作用。深入探究糖基化是否通过 YAP 增加肝癌细胞对铁死亡的敏感性, 能为临床治疗提供新的方向, 具有重大意义。

方法: 肝癌细胞 SMMC-7721 和 Bel-7402 细胞系为研究对象, MTT 实验, Lipid ROS 以及 MDA 检测作为铁死亡检测表型。构建干扰 YAP1 表达的细胞株, 转录组高通量测序检测 YAP1 对下游基因的调控作用。免疫荧光和 Western Blot 实验检测蛋白定位和表达。LUC 和 ChIP 实验检测 YAP 和下游基因启动子区域结合。小鼠荷瘤实验检测细胞处理后成瘤活性。

结果: 糖基化诱导剂处理细胞后, RSL3 更易诱导细胞发生铁死亡。在干扰 YAP 后, 这种糖基化促进铁死亡敏感性的现象消失, 并且这一现象依赖于 YAP 的 Thr241 糖基化位点。干扰 YAP 后转录组学结果提示, YAP 调控铁死亡相关基因 TFRC 的表达。进一步实验发现, YAP 糖基化后入核明显增加, 促进 TFRC mRNA 水平上升, 增加细胞内铁离子含量。根据 LUC 实验和 ChIP 实验结果显示, YAP 直接和 TFRC 基因启动子结合, 调控 TFRC 转录。

结论: 糖基化通过增加 YAP 转录活性, 促进 TFRC 表达, 增加细胞内铁离子水平, 增加了肝癌细胞对铁死亡的敏感性。该机制或可让诱导铁死亡成为治疗肝癌的新方向。

关键词: 糖基化; YAP; 铁死亡; 肝癌

554. 先天性巨结肠粘膜活检的特殊染色方法及诊断分析

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目的: 通过粘膜活检技术剂特殊染色技术, 术前明确先天性巨结肠的诊断。

方法: 粘膜冰冻制片后, 通过乙酰胆碱酯酶染色法后观察切片情况。

结果: 先天性巨结肠患儿乙酰胆碱酯酶染色明确阳性; 先天性巨结肠同源病患儿, 乙酰胆碱酯酶染色弱阳性; 结直肠冗长症等患儿乙酰胆碱酯酶染色阴性。

结论: 具有先天性巨结肠临床表现的患儿, 通过取粘膜活检, 并冰冻制片乙酰胆碱酯酶染色后便可明确诊断。

关键词: 先天性巨结肠; 粘膜活检; 乙酰胆碱酯酶

555. Immune-associated molecule CTNNB1 for predicting the survival and tumor immunotherapy in hepatocellular carcinoma

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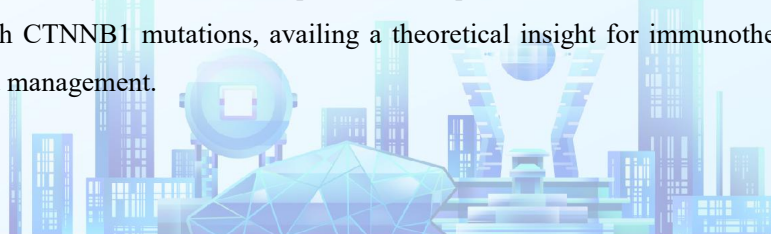
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Objective: Emerging study has inferred that immune checkpoint genes and the gene CTNNB1 encoding β -catenin act as the vital role in the pathogenesis and growth of liver cancer. Nevertheless, the differentially expression and its value to evaluate the prognosis of immune checkpoint genes in hepatocellular carcinoma (HCC) with or without different CTNNB1 status are still in blank.

Methods: We comprehensively collected and analyzed gene expression data from HCC tissues and normal tissues in The Cancer Genome Atlas (TCGA) database. Differentially expressed genes analysis was applied to investigate the potential immune checkpoint genes that affecting the process of HCC, including the patient survival. Moreover, correlation analysis, gene-gene co-expression and survival analysis helped identify key immune checkpoint biomarkers associated with CTNNB1 mutations.

Results: It was shown that five immune checkpoint genes (CD274, PDCD1, CTLA4, LAG3, and HAVCR2) were lowly expression in HCC tumors, and some of them might be highly related to the pathogenesis of HCC. The comparisons of CTNNB1 wild-type and mutant patients revealed that elevated expressions of PDCD1, CD274, CTLA4, and HAVCR2 were found in CTNNB1 wild-type group. Infiltration and survival analysis confirmed that CTNNB1-wildtype expression level was raised significantly than CTNNB1-mutation in CD8⁺ T cell, CD4⁺ T cell, macrophage, neutrophil cell and dendritic cell (besides B cell). Also, HCC patients in CTNNB1 mutation group with high expression of CD274 ($P < 0.001$), PDCD1 ($P = 0.012$) had a better survival.

Conclusions: Totally, our research screened potential differentially expression of immune checkpoint genes in different stages of HCC, and provided comprehensive and new immune checkpoint genes connected with CTNNB1 mutations, availing a theoretical insight for immunotherapy, especially the individualized management.



Key words: Hepatocellular carcinoma (HCC); immune checkpoint genes; CTNNB1 mutations; Bioinformatic analysis, TCGA

556. LINC00973 在 NSCLC 中的作用及机制研究

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研究目的: 通过高通量测序筛选出 NSCLC 中差异表达的长链非编码 RNA(long noncoding RNA, lncRNA), 检测 LINC00973 在非小细胞肺癌(non-small cell lung cancer, NSCLC)中的表达情况, 研究 LINC00973 在 NSCLC 中的生物学功能, 初步探讨其分子作用机制, 为 NSCLC 诊疗提供新的靶点。

材料与方法: 对 NSCLC 组织进行全转录组测序筛选候选 LncRNA, 采用实时荧光定量 PCR(quantitative real-time PCR, qRT-PCR)验证其在 NSCLC 细胞中的表达。采用 qRT-PCR 检测 NSCLC 组织中 LINC00973 的表达情况, 通过受试者工作特征曲线(receiver operating characteristic curve, ROC curve)分析其临床价值。采用小干扰 RNA(small interfering RNA, siRNA)和过表达质粒分别敲减和过表达 NSCLC 细胞中的 LINC00973, 通过细胞生长曲线和平板克隆形成检测细胞的增殖能力, 通过 Transwell 迁移实验与基质胶侵袭实验检测细胞的转移能力, 用流式细胞术检测细胞周期变化和凋亡情况。采用 Western blot 检测相关蛋白表达情况。采用转录组测序分析敲减 LINC00973 后影响的靶基因和信号通路, 用 qRT-PCR 和 Western blot 进行验证。采用标记 RNA 亲和纯化实验(tagged RNA affinity purification, TRAP)收集与 LINC00973 结合的蛋白质并通过液相色谱-质谱分析进行鉴定, 用 RNA 结合蛋白免疫沉淀实验(RNA Binding Protein Immunoprecipitation, RIP)验证该蛋白与 LINC00973 的结合情况, 通过 Western blot 检测敲减或过表达 LINC00973 后对该蛋白表达的影响。采用小干扰 RNA 敲减 NSCLC 细胞中的 DTX3L, 用细胞生长曲线和平板克隆形成实验检测细胞的增殖能力, 用 Transwell 迁移实验与基质胶侵袭实验检测细胞的转移能力, 用流式细胞术检测细胞凋亡情况。

结果: 全转录组测序共筛选出 173 个差异表达的 LncRNA, 其中 84 个在 NSCLC 组织中表达上调, 89 个表达下调。LINC00973 在 NSCLC 细胞和组织中呈高表达模式。敲减 LINC00973 削弱了 NSCLC 细胞的增殖和转移能力, 诱导细胞发生 G1 期阻滞并促进凋亡, LINC00973 基因沉默下调上皮间质转化(epithelial-mesenchymal transition, EMT)相关蛋白和增殖相关蛋白的表达, 敲减 LINC00973 导致促肿瘤相关基因如 MMP9 和 VCAM1 表达下调, Akt-mTOR 信号通路受到抑制。过表达 LINC00973 则与之相反。机制研究发现 LINC00973 能与 DTX3L/PARP9 蛋白复合物结



合, 且正向调控 DTX3L 蛋白表达。敲减 DTX3L 具有抑制 NSCLC 细胞增殖, 转移并促进其凋亡的生物学功能。

结论: LINC00973 在 NSCLC 中表达上调, 发挥促癌作用, 具有作为诊断标志物的潜力。

LINC00973 可能通过与 DTX3L/PARP9 蛋白复合物结合发挥作用。

关键词: LncRNA; LINC00973; NSCLC; DTX3L/PARP9; 分子标志物

557. 循环血清外泌体长链非编码 RNA POC1B 作为结直肠癌诊断标志物的研究

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背景: 长链非编码 RNA (lncRNAs) 具有调节肿瘤生长和转移的能力, 被认为是肿瘤诊断和预后的生物标志物。本研究的目的是鉴定循环血清外泌体中一种或多种 lncRNAs 对结直肠癌 (CRC) 的诊断价值。

材料与方法: 采用超高速离心法从所有受试者血清中分离出外泌体, 并用透射电镜 (TEM), qNano 和免疫印迹法进行外泌体鉴定。对 4 例结直肠癌患者和 2 例健康者的血清外泌体进行 RNA 提取和 lncRNA 测序。应用荧光定量 PCR 技术对 203 例初治的结直肠癌患者和 201 例健康者血清外泌体 lncRNAs 的表达进行了筛选和评价。采用受试者操作特征曲线 (ROC) 评价血清外泌体 lncRNAs 的诊断效能。

结果: 根据 lncRNA 测序和基因表达结果筛选出 20 个候选的 lncRNA。只有外泌体 POC1B 在结直肠癌患者和健康人之间存在显著差异。203 例大肠癌患者的血清外泌体 POC1B 水平显著高于 201 例健康者和 20 例良性疾病患者。此外, 外泌体中 POC1B 的诊断效率最高, AUC 高达 0.599。与 201 名健康献血者和 20 名良性疾病患者相比, 80 名早期结直肠癌患者的外泌体中 POC1B 表达水平显著升高。此外, 与术前测定的基线水平相比, 术后结直肠癌患者外泌体中 POC1B 的表达水平显著降低。

结论: 外泌体 lncRNA POC1B 可作为诊断结直肠癌和早期结直肠癌的一种无创、敏感、特异的生物标志物。

关键词: 外泌体; 长链非编码 RNA; 结直肠癌; 诊断; 生物标志物

558. Development and validation of a proteomic derived-biomarker signature to predict distant metastasis in stage II-



III colorectal cancer: a retrospective, multicenter, cohort study

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Background: Distant metastasis is the major cause of death in stage II-III colorectal cancer. There is an urgent need to identify improved biomarkers to predict distant metastasis and stratify patients to refine the selection of adjuvant treatment. We aimed to develop and validate a proteomic derived biomarker signature for distant metastasis in stage II-III colorectal cancer.

Methods: In this retrospective, multicenter study, 702 patients with stage II-III colorectal cancer were included from three centers. Using mass spectrometry (MS)-based high-throughput proteomic, we analyzed 60 pairs of matched tumor and normal tissue from stage II-III colorectal cancer patients with or without distant metastasis after curative treatment. We used LASSO and SVM algorithms to select four significant proteins. Four significant proteins were further examined by multiplex immunohistochemistry (IHC) in a tissue microarray (TMA) to build a classifier using a Cox regression model in a training cohort (n=193). The prognostic accuracy of the classifier was validated in an internal validation cohort of 193 patients and an external validation cohort of 316 patients. The primary outcome was distant metastasis-free survival, and the secondary endpoint was disease-free survival.

Findings: A proteomic-derived biomarker signature to predict distant metastasis in stage II-III colorectal cancer (DMPS) that consisted of 4 proteins was developed to classify patients into high-risk and low-risk groups. Patients with high-risk scores had shorter metastasis-free survival than patients with low-risk scores in the training cohort (hazard ratio [HR] 4.16, 95% CI 2.14-8.09; $P<0.001$), internal validation cohort (HR 3.28, 1.63–6.60; $P<0.0001$), and external validation cohort (HR 3.20, 2.0–5.13; $P<0.001$). A similar trend was observed regarding disease-free survival in all cohorts (all $P<0.05$). Multivariate analyses in every cohort showed that the DMPS was independently associated with distant metastasis-free survival after adjusting for clinicopathological risk factors, including the TNM classification system. Furthermore, we developed a nomogram that integrated the DMPS and other risk factors to predict the individualized risk of distant metastasis.

Interpretation: Our DMPS provides a reliable estimate of the risk of metastasis and was generated using proteomic analysis and multiplex IHC assays combined with AI-assisted methods. The DMPS was validated in large, independent patient populations, and outperformed established risk factors; thus, it might facilitate patient counseling and guide individualized treatment.

Key words: stage II-III colorectal cancer; proteomic; distant metastasis; multiplex immunohistochemistry; AI-assisted method



559. Association of peripheral blood biomarkers with response to anti-PD-1 immunotherapy for patients with dMMR metastatic colorectal cancer: a multicenter cohort study

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Background: Mismatch repair deficient (dMMR) is an established biomarker for response to anti-PD-1 immunotherapy in metastatic colorectal carcinoma (mCRC). Although patients with dMMR mCRC could achieve a high incidence of disease control and favorable progression-free survival (PFS), reported response rates to PD-1 inhibitors are variable with 28%–52%, indicating that additional predictive biomarkers are warranted.

Methods: This multicenter cohort study enrolled patients with dMMR mCRC receiving anti-PD-1 immunotherapy at Sun Yat-sen University, the Sixth Affiliated Hospital and Sun Yat-sen University Cancer Center between December, 2016 to December, 2019. A total of 20 peripheral blood biomarkers, including T cells (frequency of CD4⁺ T cell, frequency of CD8⁺ T cell, ratio of CD4⁺/CD8⁺), carcinoembryonic antigen (CEA), inflammatory markers and lipid metabolism markers. The association between response or survival and peripheral blood parameters was analyzed.

Results: Among tested parameters, ratio of CD4⁺/CD8⁺, frequency of CD4⁺ T cell was significantly associated with PFS ($P=0.023$, $P=0.012$) and OS ($P=0.027$, $P=0.019$) in univariate analysis. Lower level of CD4⁺/CD8⁺ ratio or frequency of CD4⁺ T cell showed significant association with better overall response rates (ORR; $P=0.03$, $P=0.01$). Ratio of CD4⁺/CD8⁺, and frequency of CD4⁺ T cell maintained significance in multivariate Cox model for PFS (HR=9.23, $P=0.004$; HR=4.83, $P=0.02$) and OS (HR=15.22, $P=0.009$; HR=16.21, $P=0.025$).

Conclusions: Ratio of CD4⁺/CD8⁺ and frequency of CD4⁺ T cell might be crucial independent biomarkers within dMMR mCRC to better identify patients for response to PD-1 inhibitors. If validated in prospective clinical trials, ratio of CD4⁺/CD8⁺ and frequency of CD4⁺ T cell might provide aid in guiding the treatment of PD-1 inhibitors in dMMR mCRC.

Key words: ratio of CD4⁺/CD8⁺; frequency of CD4⁺ T cell; mismatch repair deficient (dMMR); colorectal cancer (CRC); anti-PD-1 immunotherapy

560. CircHMGCS1 Promotes Hepatoblastoma Cell Proliferation by Regulating the IGF Signaling Pathway and Glutaminolysis

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Circular RNAs (circRNAs), a novel class of endogenous RNAs, have been recently shown to participate in cellular development and several pathophysiological processes. The identification of dysregulated circRNAs and their function in cancer have attracted considerable attention. Nevertheless, the expression profile and role of circRNAs in human hepatoblastoma (HB) remain to be studied. In this report, we analyzed the expression profile of circRNAs in HB tissues and identified circHMGCS1 (3-hydroxy-3-methylglutaryl-CoA synthase 1; hsa_circ_0072391) as a remarkably upregulated circRNA. Methods: The expression profile of circRNAs in HB tissues were investigated through circRNA sequencing analyses. ISH and qRT-PCR assays were performed to measure the expression level of circHMGCS1. The effect of knocking down circHMGCS1 in HB cells in vitro and in vivo were evaluated by colony formation assay, flow cytometry, xenograft tumors assay and untargeted metabolomics assay. MRE analysis and dual luciferase assay were performed to explore the underlying molecular mechanisms. Results: HB patients with high circHMGCS1 expression have shortened overall survival. Knockdown of circHMGCS1 inhibits HB cells proliferation and induces apoptosis. CircHMGCS1 regulates IGF2 and IGF1R expression via sponging miR-503-5p, and affects the downstream PI3K-Akt signaling pathway to regulate HB cell proliferation and glutaminolysis. Conclusions: The circHMGCS1/miR-503-5p/IGF-PI3K-Akt axis regulates the proliferation, apoptosis and glutaminolysis of HB cells, implying that circHMGCS1 is a promising therapeutic target and prognostic marker for HB patients.

Key words: hepatoblastoma; circRNA; IGF2; PI3K; glutaminolysis

561. The dangerous minority in the ovarian cancer cells: polyploid giant cancer cells

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Background: Mismatch repair deficient (dMMR) is an established biomarker for response to anti-PD-1. With low early detection rate and high recurrence rate, ovarian cancer is the most lethal cause among female urogenital neoplasms. Heterogeneity of the histological types and genetic features made it hard to be targeted and monitored during tumor progression.

Methods: Polyploid giant cancer cells (PGCC), a subpopulation of polyploid cancer cells and cancer stem cells, have been increasingly reported to appear in ovarian cancer tissues and tumor cells. With blastomere-like structure, this subtype shares morphological and molecular characteristics with both senescent cells and embryonic stem cells (ESC). Possessing these unique features, PGCC can survive and renew through asymmetric cell division including bursting and budding when confronted with pressure from cytotoxic drugs and hypoxic microenvironment. Besides, PGCC can generate erythroid cells to maintain the oxygen supply through forming vasculogenic mimicry under hypoxia. With the passages increasing, PGCC with their progeny can improve the abilities of migration, invasion, and proliferation of ovarian cancer cells. Mounting evidence has suggested that this minority was related to

higher pathological grade and metastasis of ovarian cancer. However, it is still unclear that if PGCC might be the cancer initial cells during tumor progression and repopulation of ovarian cancer.

Conclusions: To date, the mysteries of the mononucleated or multinucleated giant cancer cells have appealed lots of oncologists. For further study of the potentially “dangerous” subpopulation of ovarian cancer cells, we provide an overview of present papers on PGCC in tumorigenesis, progression and drug resistance. In this review, we also concluded cell cycle regulation, embryonic program activation and senescence regulation to give potential therapeutic targets of PGCC and their progeny in ovarian cancer.

Key words Ovarian cancer; Polyploid giant cancer cells; Senescence; Embryonic stem cells; Tumor heterogeneity; Drug resistance

562. miR-133b targets NCAPH to promote β -catenin degradation and reduce cancer stem cell maintenance in non-small cell lung cancer

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Non-small cell lung cancer (NSCLC), one of the most common lung cancers, is well known to have diverse pathological features. Although many signaling pathways and therapeutic targets have been defined to play important roles in NSCLC, limiting efficacies have been achieved. Here, we identified that non-SMC condensin I complex subunit H (NCAPH), which is highly expressed in NSCLC, correlates with worse clinical outcome. We found that NCAPH is increased in cancerous cell lines (H1299, A549, H1975, SPC-A1, H838 and GLC-82) than that in normal human bronchial epithelium cell line (BEAS-2B), and NCAPH knockdown inhibits cell proliferation and migration. Furthermore, we validated that miR-133b directly targets NCAPH, and that miR-133b is downregulated in both cancerous cell lines and peripheral blood serum isolated from NSCLC patients. Forced expression of miR-133b inhibits the proliferation, migration and xenograft tumor formation abilities of tumor cells. In addition, mechanistic study showed that NCAPH promotes cancer stem cells (CSCs) maintenance in NSCLC through inhibiting Akt1-mediated phosphorylation and degradation of β -catenin proteins, which in turn leads to suppressed Wnt signaling activity and tumorigenesis. In summary, our findings reveal the critical role of miR-133b/NCAPH axis during NSCLC progression, indicating that miR-133b or NCAPH can be used as novel therapeutic targets in the future.

Key words: non-SMC condensin I complex subunit H (NCAPH); miR-133b; non-small cell lung cancer; cancer stem cells (CSCs)



563. 慢性肾脏病患者肺癌相关血清肿瘤标志物水平的改变及临床价值分析

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目的: 探讨肺癌相关血清肿瘤标志物在慢性肾脏病 (chronic kidney disease, CKD) 患者中的表达变化及临床诊断价值, 并初步估计参考范围。

方法: 选取 2020 年 3 月-2020 年 9 月四川大学华西医院 729 例 CKD 患者为病例组, 94 例健康体检者为对照组; 检测血清中糖类抗原 125 (CA125), 细胞角蛋白 19 片段 (CYFRA21-1), 鳞状细胞癌抗原 (SCC), 神经元特异性烯醇化酶 (NSE), 胃泌素释放肽前体 (ProGRP) 的水平, 比较各指标在两组间差异及不同 CKD 分期中水平的变化, 对 CKD 各期患者肺癌相关肿瘤标志物阳性率进行比较分析并应用 ROC 曲线对其临床诊断价值进行评价; 采用非参数法初步估计 CKD3~5 期肺癌相关指标的 95%参考范围。

结果: CKD 患者肺癌相关肿瘤标志物水平除 NSE 外均明显高于健康对照组 ($P<0.05$), 其中 CYFRA21-1, ProGRP 水平在 CKD2~5 期患者中均明显高于对照组 ($P<0.01$), SCC 在 CKD3~5 期, CA125 在 CKD4~5 期患者中明显升高 ($P<0.01$)。CYFRA21-1, ProGRP 在 CKD3~5 期患者中阳性率均大于 60%明显高于对照组 ($P<0.001$)。在 ROC 曲线分析中, ProGRP, CYFRA21-1, SCC 对 CKD 诊断的灵敏度分别为 83.3%, 90.9%, 75.9%, 曲线下的面积分别为 0.933, 0.928, 0.789。ProGRP 在 CKD3, 4, 5 期患者中的 95%参考范围上限分别为 148.5 pg/ml, 225.9 pg/ml, 375.5 pg/ml; CYFRA21-1, SCC 在 CKD3 和 CKD4~5 期患者中的 95%参考范围上限分别为 7.56 ng/ml, 11.27 ng/ml 和 4.52 ng/ml, 8.92 ng/ml。

结论: 血清 ProGRP, CYFRA21-1, SCC, CA125 的水平随着 CKD 分期的递增而显著增高, NSE 水平不受影响, ProGRP, CYFRA21-1 对于 CKD 的诊断及分期具有较高的诊断价值。建议 CKD 患者联合检测肺癌相关血清肿瘤标志物并采用恰当的参考限值进行结果解释。

关键词: 慢性肾脏病; 血清肿瘤标志物; 肺癌; 诊断价值; 参考范围

564. 血清鳞状上皮细胞癌抗原在银屑病患者皮损及疗效评估中的临床价值

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背景及目的：血清鳞状上皮细胞癌抗原(Squamous cell carcinoma antigen, SCCA)常作为各类鳞癌患者的肿瘤标志物进行检测，近年来发现，皮肤损伤疾病患者也存在 SCCA 异常增高。银屑病是临床常见的皮损相关疾病，本研究旨在探讨 SCCA 在银屑病患者辅助诊断及疗效评估的临床应用价值。**方法：**纳入 2020 年 6 月至 2021 年 1 月我院临床确诊 401 例皮肤疾病患者，包括银屑病 187 例，天疱疮 147 例，湿疹 28 例，特发性皮炎 27 例，红皮病 12 例，另外选取同期 660 例健康体检正常人群作为对照组，检测血清 SCCA 水平，采用 SPSS 统计软件分析数据。

结果：SCCA 测定结果显示，SCCA 在银屑病、天疱疮、湿疹、特应性皮炎、红皮病、对照组中的阳性率分别为 66.84%、17.00%、28.57%、62.96%、91.67%、2.42%，中位数分别为 4.49 (2.05-11.30) ng/ml、0.89 (0.62-1.53) ng/ml、1.96 (0.90-2.80) ng/ml、5.31 (1.54-13.90) ng/ml、22.05 (9.26-37.70) ng/ml、1.16 (0.91-1.47) ng/ml。各组间 SCCA 定量比较有统计学差异，红皮病患者最高，其次为特应性皮炎和银屑病患者，天疱疮和湿疹患者与健康对照相似。进一步针对银屑病亚类分析，未分类银屑病阳性率 73.68%，寻常型银屑病（含点滴型和斑块状银屑病）阳性率 63.16%，其他单独型别组（含脓疱型、红皮病型及关节病型）阳性率 65.38%，两种以上复合型银屑病组阳性率 64.29%，各银屑病亚类间血清 SCCA 水平无显著性差异（ $P>0.05$ ）。银屑病患者治疗前皮损面积和严重程度指数(Psoriasis area and severity index, PASI)及体表受累面积(body surface area, BSA)与 SCCA 水平呈指数相关（PASI $R=0.675$ ，BSA $R=0.609$ ），治疗后皮损好转者 SCCA 显著降低（ $P<0.001$ ）。

结论：血清 SCCA 水平可因皮损等原因在银屑病、红皮病及特异性皮炎中明显增加；血清 SCCA 检测可有效评估银屑病患者皮损受累程度和治疗效果。

关键词：鳞状上皮细胞癌抗原；银屑病；皮损程度；疗效评估

565. 骨肿瘤免疫标记与分子检测

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研究目的：骨肿瘤发病率较低，种类繁多，骨质沉积程度有限，相互间存在形态叠加等特点，尚缺乏有效辅助诊断方式，病理诊断存在巨大挑战，随着现代分子生物学技术的发展，骨肿瘤相关分子标记物被发现，我们的研究就新近我中心骨肿瘤病例检测与诊断情况做出分析与评价，旨在为骨肿瘤的诊断与鉴别诊断提供可靠依据，为临床骨肿瘤个体化治疗与靶点药物的开发提供思路，使得骨肿瘤早期预警及保肢成为可能。

研究方法：收集中国人民解放军总医院第四医学中心病理科骨肿瘤病例资料 50 例，切片均经三级病理医生复诊，石蜡包埋法制片，切片厚度约 3-3.5 微米/张，并进行 HE 染色、SP 法免疫组织化学染色、PCR 法分子检测以及荧光原位杂交的 FISH 测，结果采用 Graphpad8.0.1 进行数据统计与制图，OLYMPUS 显微成像系统进行图像采集。



研究结果：1.软骨性肿瘤：8例软骨母细胞瘤中，H3K36M 阳性率 100%，H3F3BK36M 位于 17 号染色体，研究报道其在软骨母细胞瘤中突变率高达 95%，可作为鉴别软骨母细胞瘤的特异指标。11 例软骨肉瘤中，S-100 阳性率 90.90%，S-100 可反应软骨细胞分化程度。同时我们也进行 Vim,EMA,CEA,CK,SATB2,Brachyury,F8,Ki67 等指标鉴别与辅助检测。此外，IDH1/2 分子检测发现 IDH1/2 在内生性软骨瘤及去分化软骨肉瘤存在突变，除外软骨母细胞瘤。**2.成骨性肿瘤：**SATB2 位于 2 号染色体，10 例骨肉瘤中发现 SATB2 阳性率达 90.00%，骨旁骨肉瘤与中央型低级别骨肉瘤中除 SATB2 阳性外常伴有 MDM2 和 CDK4 的扩增，应用二者可与普通型成骨肉瘤区分，同样利用 MDM2 FISH 检测可明显看到基因扩增，敏感性达 95.00%以上。**3.脊索瘤：**Brachyury 和 INI1 是脊索瘤的可依赖性指标，在 4 例脊索瘤病例中，Brachyury 阳性 100%，INI1 阳性率 100%，**4.尤文肉瘤及原始神经外胚层瘤：**该类典型特点是形成融合基因，基因重排检测发现 EWSR1-FLI-1 和 EWSR1-ERG 融合，（以 EWSR1-FLI-1 融合为主达 85.00%以上）。免疫组织化学采用 NKX2.2/PAX7 标记，7 例病例中呈特异性染色阳性率达 85.71%。**5.富于破骨巨细胞肿瘤：**骨巨细胞瘤中 H3.3 G34W 突变抗体是诊断 GCTB 高度灵敏和特异的标志物，10 例骨巨细胞瘤病例中，我们检测到 H3.3 G34W 阳性率达 87.50%，与 Amary 等报道基本一致。

研究结论：我们的研究阐明了当前骨肿瘤病理诊断最新的辅助检测手段，旨在为骨肿瘤抗体试剂临床应用以及骨肿瘤鉴别诊断提供证据，为骨肿瘤精准医疗做出贡献，由于病例有限，部分数据值过低，日后工作中将逐渐补充更新。

关键词：骨肿瘤；免疫标记；分子检测；个体化治疗

566. CXCL13 and its receptor CXCR5 in cancer: a review and perspectives

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Purpose: During the occurrence and development of tumors, tumor cells interact with stromal cells and immune cells, and a variety of growth factors, cytokines and chemokines are involved. Current evidences showed that C-X-C motif chemokine ligand 13 (CXCL13) and its receptor C-X-C motif chemokine receptor 5 (CXCR5) could affect the functional phenotype of tumor cells and played an important role in tumor progression. Exploring how CXCL13/CXCR5 regulates the interaction between tumor cells and tumor microenvironment can provide new strategies for tumor treatment.

Materials and methods: In this review, we first summarized the clinical significance of the abnormal expression of CXCL13/CXCR5 in different solid tumors, and then summarized its mechanisms for regulating tumor cell proliferation, migration and invasion characteristics. In addition, we also discussed the influence of the CXCL13/CXCR5 signal axis on the tumor immune microenvironment.



Results: The biological effects of the CXCL13/CXCR5 signal axis in tumors are complex and organ-specific. The prognostic effects of this pathway in different solid tumors are not the same, and there may be different mechanisms of action in different tumors to promote or inhibit the occurrence and development of tumors; in addition, there are also two-way effects on the tumor immune microenvironment, and there is still a lack of in-depth research to explain the mechanism of this phenomenon.

Conclusions: To clarify how CXCL13/CXCR5 regulates the interaction between tumor cells and tumor microenvironment, and to study its value as an anti-tumor target is expected to provide new therapeutic strategies for tumor therapies.

Key words: CXCL13; CXCR5; Chemokine; Tumor

567. 甲状腺乳头状瘤中挖掘潜在生物学标志物及生物信息学分析

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目的: 通过生物信息学技术筛选甲状腺乳头状瘤 (Papillary thyroid carcinoma, PTC) 中表达差异的基因, 为甲状腺乳头状瘤的治疗提供新的思路和靶点。

方法: 从 GEO 数据库下载甲状腺乳头状瘤的芯片数据集 GSE58545, GSE35570, GSE33630, GSE27155, 使用在线分析工具 GEO2R 筛选甲状腺乳头状瘤及其癌旁正常甲状腺组织间的差异表达基因, 使用网络分析工具 Metascape 进行差异基因的 GO 分析及 KEGG 通路富集, 通过 STRING 在线软件进行差异表达基因的蛋白-蛋白相互作用分析, 并应用 Cytoscape 对蛋白-蛋白相互作用网络进行模块分析, 提取核心基因。基于 TCGA-THCA 数据集提取核心基因表达数据, 分析其表达水平。基于 ProteinAtlas 数据库比较正常甲状腺组织及甲状腺乳头状瘤组织中核心基因表达差异。

结果: 本研究共提取 159 例甲状腺乳头状瘤组织及 116 例正常甲状腺组织间共筛选出 28 个差异表达基因 (DEGs) ($|\log FC| > 1$, $\text{adj.} P < 0.05$), 其中上调的 DEGs 共 18 个, 下调的 DEGs 共 10 个。GO 分析和 KEGG 通路富集显示, 这些差异表达的基因主要富集在多个代谢、免疫调节及 PPAR 信号通路等。通过蛋白-蛋白相互作用网络的构建及核心基因提取, 我们筛选出 JUN, CTNNB1, KIT, CCR7, CCL21, NMU 六个枢纽差异表达基因。TCGA-THCA 数据集和 ProteinAtlas 数据库免疫组化分析结果均显示, 与正常甲状腺组织相比, JUN, KIT, CCR7, CCL21 在肿瘤组织中表达下调, CTNNB1, NMU 在肿瘤组织中表达上调。

结论: 本研究为进一步深入理解甲状腺乳头状瘤的生物学机制, 探索其治疗的有效方案提供了新思路。



关键词：甲状腺乳头状瘤；GEO 数据库；差异表达基因；生物信息学分析

568. LncRNA-MEG3 在胃癌的临床病理意义及对铂类化疗敏感性的研究

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目的：研究 LncRNA-MEG3 在胃癌中的表达并探讨其与临床病理因素及对患者术后铂类化疗敏感性的影响，进而通过体内体外实验深入分析其作用机制。

方法：(1)采用 PV8000 二步法检测有完整随访资料的 346 例胃癌及 80 例癌旁组织中 MEG3 的表达情况。(2)以人正常胃黏膜上皮细胞 GES1 作为对照细胞，将 BGC823 细胞分为 pcDNA3.1 组,pcDNA3.1-MEG3 组,顺铂组及 pcDNA3.1-MEG3+顺铂组，转染 48 h 后，qRT-PCR 和 Western blot 检测细胞中 LncRNA-MEG3,P53 和 MMR 蛋白的表达；细胞计数法及流式细胞仪检测细胞活力及凋亡率。

结果：(1)胃癌中 MEG3 的表达低于癌旁组织中的表达($P<0.05$)；MEG3 的表达与肿瘤淋巴结转移数目及远处转移相关($P<0.05$)。(2) pcDNA3.1-MEG3 组和顺铂组 P53 的蛋白表达低于 pcDNA3.1 组($P<0.05$)；细胞凋亡率高于 pcDNA3.1 组($P<0.05$)。

结论：胃癌细胞及组织中 LncRNA-MEG3 表达降低，细胞中过表达 LncRNA-MEG3 可降低胃癌细胞活力并诱导细胞凋亡，增加顺铂的化疗敏感性，其机制与下调 P53 信号通路，同时影响 MMR 蛋白表达有关，LncRNA-MEG3 可考虑作为胃癌临床评价肿瘤生物学行为及评估化疗敏感性的有用指标。

关键词：胃肿瘤；免疫组化；LncRNA-MEG3；P53；顺铂

569. 构建多形性胶质母细胞瘤患者铁死亡相关 lncRNA 预后模型

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目的：多形性胶质母细胞瘤（glioblastoma multiforme, GBM）约占神经胶质瘤的 60~70%，是最高级别的胶质瘤，具有高致死率,高复发率的特点，即使采取积极的临床治疗，患者的生存率依然较低。铁死亡是一种新型的细胞程序性死亡，其在二价铁或酯氧合酶的作用下，催化细胞膜上高表达的不饱和脂肪酸，发生脂质过氧化，从而诱导细胞死亡。大量研究表明，铁死亡与 GBM 的恶性进展与治疗密切相关，靶向铁死亡有望成为治疗该类肿瘤的新手段，而长链非编码 RNA（lncRNA）作为调控基因表达的关键因素，其与铁死亡过程密切相关。由于目前缺乏

基于铁死亡相关基因的 GBM 患者生物标志物，本研究试图通过寻找与 GBM 预后相关的铁死亡相关 lncRNA，构建生存预后风险评估模型，为其个性化诊疗和靶向研究提供依据。

方法：通过 TCGA 数据库下载 GBM 的 mRNA 与 lncRNA 转录组测序数据与临床信息，通过 FerrDb 数据库下载 382 个与铁死亡有关的基因信息。首先，将 mRNA 表达矩阵中的基因与铁死亡相关基因取交集，之后对 lncRNA 表达矩阵与铁死亡相关基因的表达矩阵进行相关性检验（设置相关性系数 $\text{cor} > 0.6$, $P < 0.001$ ），从而找到与铁死亡相关基因具有共表达关系的铁死亡相关 lncRNA。对 lncRNA 进行差异分析（设置： $|\log_2\text{FC}| > 2$, $P_{\text{adj}} < 0.05$ ），将差异表达的 lncRNA 同临床数据合并，通过单因素 Cox 回归及 Lasso 回归分析构建预后模型，并将模型在 CGGA 数据库中进行验证。计算每个患者的风险值，以中位数为界将样本分为高低风险两组，利用生存曲线、单因素独立预后分析、ROC 曲线以及 DCA 决策曲线等，评估预后模型的准确与可靠性。利用 GSEA 富集分析探究高低风险组间差异基因所参与的主要通路，利用 TIMER，CIBERSORT 等算法评估高低风险组之间免疫细胞的浸润程度差异，利用 ssGSEA 富集评估高低风险组之间免疫反应的激活差异。

结果：共得到 123 个差异表达的铁死亡相关 lncRNA，单因素 Cox 回归分析得到 18 个与患者生存预后相关的 lncRNA，多因素 Cox 与 Lasso 回归分析构建的预后模型计算公式为：风险值（risk score）= $\text{AC126407.1 表达量} * (-0.157) + \text{AC010655.2 表达量} * 0.216 + \text{PTPRN2-AS1 表达量} * 0.255 + \text{AC023043.3 表达量} * 0.887 + \text{LINC01574 表达量} * 1.079$ 。生存曲线显示，高风险组的生存率远低于低风险组（ $P < 0.001$ ）；独立预后分析显示 risk score 相较传统临床指标是 GBM 患者更好的一个预后因素；1，2，3 年的 ROC 曲线下面积（AUC 值）分别为 0.763，0.678，0.821，提示构建的预后模型具有较好的预测能力。免疫分析显示，M1 巨噬细胞与 NK 细胞在高风险组被显著抑制，而高风险组的抗原提呈细胞与 T 细胞共刺激反应水平更高。

结论：本研究首次在 GBM 患者中构建基于铁死亡相关 lncRNA 的预后模型，为临床预后评估提供理论依据，并为基于铁死亡的相关靶向治疗提供重要参考。

关键词：多形性胶质母细胞瘤；铁死亡；lncRNA；预后模型

570. Circ0028129 调控 PGC-1 β 表达影响结直肠肿瘤增殖迁移的分子机制研究

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目的：通过结直肠癌临床组织标本验证 Circ0028129 低表达的普遍性及与临床的分期的相关性，测过表达 Circ0028129 对 miR-150, APC 基因及 Axin 和 β -catenin 蛋白的表达。揭示 Circ0028129-



miR-150- APC-Wnt 轴作用在结直肠癌中的功能, 为结直肠癌早期筛查, 靶向治疗和预后提供新的思路。

方法: 选择结直肠癌及癌旁组织标本进行高通量芯片检测, 经生物信息学分析筛选, 结合 qRT-PCR 初步验证获得与结直肠癌中低表达的 circRNA 分子: Circ0028129; 收集 50 对结直肠癌及癌旁组织标本, 利用 qRT-PCR 法进一步验证该 Circ0028129 分子在结直肠癌中低表达的普遍性以便作为候选的分子标志物; 选择结直肠癌细胞系 SW620, HT29, HCT116, LOVO 和正常结肠细胞系 NCM460 做 Circ0028129 表达差异检测, 选择合适的细胞做功能研究。

结果: 我们成功收集结直肠癌组织和癌旁对照标本采用人类环状 RNA 芯片 v2 表达谱芯片检测筛查或得在结直肠癌中表达上调和下调的 circRNA 分子, 分析了与 Circ0028129 关系紧密的 miRNA: miR-181b-3p, miR-135b-3p, miR-150-3p 和 miR-18a-5p。经过靶基因预测及验证实验初步推测 Circ0028129 可能结合 miR-150-3p 调控其靶基因 APC 作用于结直肠癌, 影响其凋亡程序。

结论: 我们推测 Circ0028129 通过调控 PGC-1 β 表达对结直肠癌的增殖, 侵袭, 迁移和凋亡发挥作用。

以上研究基础为我们后续实验做出了良好的铺垫。

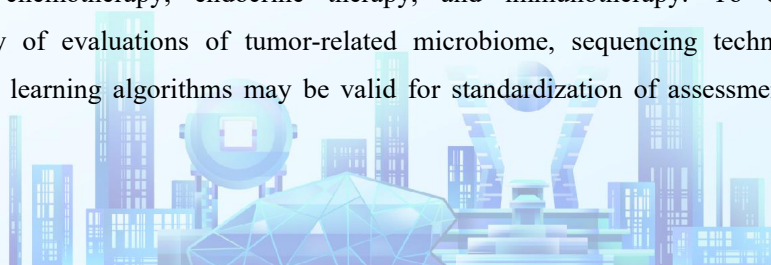
关键词: CircRNA; 结直肠肿瘤; 过表达

571. Tumor-related Microbiome In The Breast Microenvironment And Breast Cancer

Junnan Xu*, Na Wang

Liaoning Cancer Hospital & Institute

Despite the significant progress in diagnosis and treatment over the past years in the understanding of breast cancer pathophysiology, it remains one of the leading causes of mortality worldwide among females. Novel technologies are needed to improve better diagnostic and therapeutic approaches, and to better understand the role of tumor-environment microbiome players involved in the progression of this disease. The gut environment is enriched with over 100 trillion microorganisms, which participate in metabolic diseases, obesity, and inflammation, and influence the response to therapy. In addition to the direct metabolic effects of the gut microbiome, accumulating evidence has revealed that a microbiome also exists in the breast and in breast cancer tissue. This microbiome enriched in the breast environment and the tumor microenvironment may modulate effects potentially associated with carcinogenesis and therapeutic interventions in breast tissue, which to date have not been properly acknowledged. Herein, we review the most recent works associated with the population dynamics of breast microbes and explore the significance of the microbiome on diagnosis, tumor development, response to chemotherapy, endocrine therapy, and immunotherapy. To overcome the low reproducibility of evaluations of tumor-related microbiome, sequencing technical escalation and machine deep learning algorithms may be valid for standardization of assessment for breast-related



microbiome and their applications as powerful biomarkers for prognosis and predictive response in the future.

Key words: microbiome; breast cancer; gut microbiota; diversity

572. The Diversity of Microbiome: Diagnosis and Therapy in Lung Neoplasms

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Recently, with the research progressing, the human microbiome is connected with the occurrence and development of tumors. Emerging evidence has suggested that it is not sterile in lung, and the environment can induce the lung neoplasms and influence the prognosis. In general, alpha diversity is significantly lower in lung tumor tissues than in non-malignant lung tissues, while the abundance of Proteobacteria is higher. Increased Capnocytophaga and Veillonella that are detected in saliva of lung-cancer patients could be used as candidate biomarkers. Differences of microbiome scale are shown in diverse type and stage of lung neoplasms, with increased Thermus in advanced lung tumor tissues. At the same time, increasing of pathogens and decreasing of probiotics are observed in gut, and the gut microbiome may interfere the physiological state of lung by gut-lung axis. The variation of human microbiome would change the effect of chemotherapy, immunotherapy, radiotherapy, gene therapy, and targeted therapy. It is more effective in patients whose are abundant with Bacteroides ovatus and Bacteroides xylanisolvens in gut. The pharmacological effects of cisplatin could be reduced by ABX (an antibiotic cocktail of vancomycin, ampicillin, and neomycin). In this review, we will summarize the possibility of diagnosis and relevance of treatment by microbiome in lung neoplasms. In addition, the area that includes prediction of occurrence, analysis of presents, and evaluation of treatment will be discussed during the interplay between microbiome and lung neoplasms, which may promote more strategies for personalized prevention and treatment.

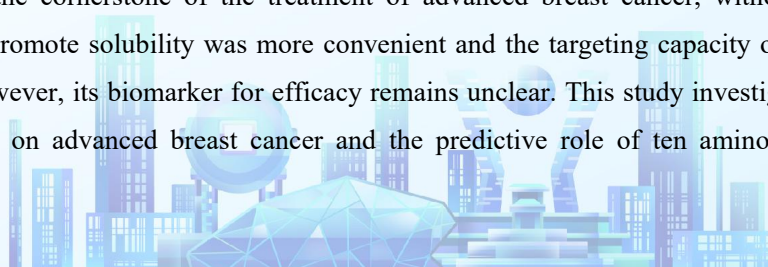
Key words: Lung Cancer; microbiome; immunotherapy

573. Efficacy of nab-paclitaxel on advanced breast cancer and plasma biomarker as predictor for nab-paclitaxel response

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Nab-paclitaxel is the cornerstone of the treatment of advanced breast cancer, without polyoxyethylene castor oil to promote solubility was more convenient and the targeting capacity of tumour tissue was enhanced, however, its biomarker for efficacy remains unclear. This study investigated the efficacy of nab-paclitaxel on advanced breast cancer and the predictive role of ten amino acid metabolomics



including L-Tryptophan for evaluating chemotherapy sensitivity of nab-paclitaxel. Method: In total fifty-five cases with advanced breast cancer were collected and received nab-paclitaxel as 1st line chemotherapy in Liaoning Cancer Hospital & Institute between Mar 1st 2016 and Nov 30th 2018. All patients were evaluated with RECIST 1.1 criteria for the efficacy of chemotherapy for solid tumors, which were divided into PR, SD and PD per 2 cycles. Plasma amino acids was quantified and standard by utilizing liquid chromatography-tandem mass spectrometry (LC-MS/MS) with 2 mL peripheral blood prior to nab-paclitaxel chemotherapy. Correlation between baseline amino acid and efficacy were analyzed by Non-parametric Kruskal-Wallis. Result: Among 55 evaluable patients, the Objective response rate (ORR) was 20.0% (11/55) and the Disease Control rate was 78.2% (43/55), including 43 individual in Disease-control group (11 cases in PR; 32 cases in SD) and 12 cases in Disease-progression group according to efficacy of nab-P. Baseline tryptophan in PD cohort (Mean $\pm$ SEM, 9.32 ± 1.72) was significantly higher than that in PR group (4.67 ± 1.31 , $P=0.091$). And L-Serine and L-citrulline were greater in PD group (L-Serine: PR 0.55 ± 0.18 , PD 1.39 ± 0.18 , $P=0.003$; L-citrulline: PR 0.22 ± 0.05 , PD 0.52 ± 0.11 , $P=0.099$) was indicated the similar predictive role with L-Tryptophan. Sarcosine was non-significantly lower in PD group than that in PR. group (0.22 ± 0.09 vs. 0.38 ± 0.09 , $P=0.326$) and the trend of difference was exact opposite to tryptophan, L-serine and L-citrulline. The predictive value of tryptophan for nab-paclitaxel was superior in the subgroups of young, premenopausal, ER-positive and Ki-67-positive patients based on $P < 0.10$ and high relative content. Conclusion: Nab-paclitaxel is an effective treatment in patients with MBC, and plasma L-Tryptophan, L-serine and L-citrulline have proven to be an effective predictor for nab-paclitaxel response and may improve precision strategies in advanced breast cancer.

Key words: advanced breast cancer; Nab-Paclitaxel; L-Tryptophan; LC-MS/MS; sarcosine

574. The Inhibitory Effect and Mechanism of Natural Green Tea Extract EGCG in 5-FU-induced Inflammation of Colorectal Cancer Cells

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3. 华南理工大学

Background: Colorectal cancer (CRC) is the third most common cancer in the world, 5-FU is the most commonly used chemotherapeutic drug for colorectal cancer, simultaneously the side effects of 5-FU, such as inflammation, the extent of the damage could not have been foreseen. we studied the inhibitory effect of epigallocatechin-3-gallate (EGCG) on 5-Fluorouracil(5-FU)-induced inflammation and its underlying mechanism in colorectal cancer (CRC) cells.



Methods: HCT116 and RKO cells were stimulated with 5-FU and EGCG for 72h. The changes in cell viability were determined by the CCK-8 assay. It was found that 5-FU indeed significantly attenuated cell viability in a dose-dependent manner in CRC cell lines, while low-dose EGCG had no significant effect on cell viability. CRC cells were cultured with 25 μ M, 50 μ M 5-FU and/or 20 μ M EGCG for 24h. Levels of inflammatory factors were determined by quantitative Real-Time PCR (qPCR). 5-FU promotes the inflammatory response by inducing a significant increase in the expression of chemokines, such as C-X-C motif chemokine ligand 1 protein (CXCL1) and chemokine (C-C motif) ligand 5 (CCL5). Low-dose EGCG significantly reduced 5-FU-induced inflammatory response. Western blotting was used to determine inflammation-inhibiting effect was mediated by NF- κ B and STAT3 signaling pathways. Immunofluorescence also confirmed that in protein localization.

Results: Low-dose EGCG can attenuate the 5-FU-induced inflammatory response in CRC cells by inhibiting NF- κ B and STAT3 signaling pathways.

Conclusions: The study indicated that inhibition of NF- κ B and STAT3 pathways by low-dose EGCG treatment is essential for inhibition of 5-FU-induced inflammation in human CRC cells.

Key words: Inflammation; 5-FU; Low-dose EGCG; Colorectal cancer cells

575. PTEN 与食管鳞状细胞癌血管生成的关系及潜在机制

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研究目的: 食管鳞状细胞癌 (esophageal squamous cell carcinoma, ESCC) 是发病率和死亡率最高的上消化道肿瘤之一, 具有较强的浸润转移能力, 在肿瘤早期就能够形成微血管以促进癌细胞转移。因此探究 ESCC 的血管生成机制对于食管癌治疗模式的创新和改善患者预后具有重要意义。

材料方法: 收集郑州大学第一附属医院病理科 49 例 ESCC 组织和癌旁正常食管黏膜组织, 通过免疫组织化学染色法, 探究 PTEN 表达与 M1/M2 型巨噬细胞的相关性, 以及与血管生成的关系。在食管鳞癌-EC9706 细胞系中过表达和沉默 PTEN, 收集上清液作为条件培养基培养 M1 型巨噬细胞, 然后再收集巨噬细胞的培养基作为条件培养基培养食管癌相关血管内皮细胞 (tumor endothelial cell, TEC), 比较不同组 TEC 的恶性生物学行为。

结果: 首先与癌旁正常食管黏膜组织相比, ESCC 中 M1 型巨噬细胞浸润数量低, M2 型巨噬细胞浸润数量高, 微血管密度 (MVD) 值大, PTEN 表达下调, PI3K/Akt 通路被激活。ESCC 组织中的巨噬细胞浸润数量, MVD 值, PTEN/PI3K/p-Akt 蛋白表达均与肿瘤浸润深度, 淋巴结转移和 TNM 分期相关。其次进行相关性分析发现 M1 型巨噬细胞浸润数量与 M2 型巨噬细胞浸润数量, MVD 值呈负相关, 而 M2 型巨噬细胞浸润数量与 MVD 值呈正相关。PTEN 蛋白表达与 MVD 值, M2 型巨噬细胞浸润数量呈负相关, 与 M1 型巨噬细胞浸润数量呈正相关。然后在体外

沉默 (siRNA 组) 或过表达 (pEX1 组) EC9706 细胞中 PTEN 表达, 条件培养基培养 M1 型巨噬细胞后, 发现 pEX1 组巨噬细胞仍为 M1 型, siRNA 组巨噬细胞表型完全极化为 M2 型, 而且 siRNA 组 VEGF 含量显著升高。siRNA 组巨噬细胞内 PI3K/Akt 基因高表达, 存在活化的 PI3K/Akt 信号途径, 而 pEX1 组情况相反。然后利用条件培养基诱导获得 TEC 并进行功能鉴定, 发现 TEC 比静脉内皮细胞具有更强的迁移、侵袭、增殖和分泌 VEGF 的能力, 并且 TEC 高表达肿瘤相关内皮细胞标志物 TEM5 和 TEM7。最后探究调节 PTEN 表达后诱导 M1 型巨噬细胞极化对 TEC 功能的影响, 发现 siRNA 组的 TEC 细胞增殖、迁移、侵袭、成管、分泌 VEGF 能力均高于 NC 组和 pEX1 组, pEX1 组能力还弱于 NC 组。

结论: 食管鳞癌组织中 PTEN 表达下调能够激活巨噬细胞内 PI3K/Akt 信号通路, 诱导 M1 型巨噬细胞向 M2 型极化, 进而促进 ESCC 血管形成。沉默 PTEN 表达, 可体外促进 M2 型巨噬细胞的极化, 增强 TEC 细胞的增殖、迁移、侵袭和成管能力, 上调肿瘤微环境中 VEGF 含量, 从而促进肿瘤的血管生成。

关键词: 食管鳞状细胞癌; 肿瘤相关巨噬细胞; PTEN; PI3K/Akt 信号

576. 中药外用联合综合消肿疗法治疗妇科恶性肿瘤术后淋巴水肿的临床疗效研究

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中国人民解放军北部战区总医院

目的: 研究中药外用联合综合消肿疗法治疗妇科恶性肿瘤术后下肢淋巴水肿的临床疗效。

方法: 选取 2017 年 5 月至 2021 年 5 月收治的妇科恶性肿瘤术后下肢淋巴水肿患者共计 60 例, 随机分为观察组和对照组, 每组各 30 例。对照组应用淋巴水肿综合消肿治疗, 观察组在综合消肿治疗基础上, 联合中药外治。两疗程后, 比较两组缓解率、患侧肢体周径、LEFS 及 WHOQOL-BREF 量表评分, 肢体组织水分情况及肢体功能障碍改善情况。

结果: 观察组总有效率为 83.3%。对照组总有效率为 75.0%。观察组疗效优于对照组, 但差异无统计学意义 ($P > 0.05$)。治疗后, 与对照组相比, 观察组患侧肢体周径缩小明显, 两组差异显著 ($P < 0.05$)。两组患者淋巴水肿相关症状评估较治疗前有明显改善 ($P > 0.05$)。组间比较, 观察组的发热疼痛、肿胀麻木、紧绷沉重感改善情况优于对照组 ($P > 0.05$)。治疗后两组患者关节活动度均明显改善, 且观察组优于对照组 ($P < 0.05$)。与治疗前相比, 治疗后两组患者的 LEFS 评分及 WHOQOL-BREF 评分改善明显 ($P < 0.05$), 且治疗后的组间差异显著 ($P < 0.05$)。两组患者治疗后, 组织水分比率均较治疗前明显改善 ($P < 0.05$), 治疗后组间差异不显著 ($P > 0.05$)。

结论: 中药外用联合综合消肿疗法治疗妇科恶性肿瘤术后淋巴水肿临床疗效可靠。



关键词：淋巴水肿；恶性肿瘤；外治法

577. Ablation of TNFAIP3-Interacting Protein 1 induces the growth arrest and apoptosis of breast cancer cells

Zhaozhe Liu*, Xiaodong Xie

General Hospital of Northern Theater Command

Breast cancer is one of the leading causes for mortality of women around the world. TNIP1 is a widely expressed ubiquitin-binding protein. The function of TNIP1 in breast cancer cells remains unknown. The aim of this study was to illustrate the molecular mechanism of TNIP1 regulation in proliferation and apoptosis of breast cancer cells. Ablation of TNIP1 induced breast cancer cells growth arrest. TNIP1 directly interacted with CCNG1, and TNIP1 knockdown increased the ubiquitination of CCNG1. CCNG1 knockdown induced MCF-7 cells growth arrest. TNIP1 knockdown activated the NF- κ B pathway and induced the apoptosis of MCF-7 cells. Our findings indicated that TNIP1 could control the proliferation and apoptosis of breast cancer cells, suggesting that TNIP1 might act as a potential marker for breast cancer.

Key words: Breast cancer cells; TNIP1; CCNG1; Proliferation; Apoptosis

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Key words: Breast cancer cells; TNIP1; CCNG1; Proliferation; Apoptosis



579. The prognostic potential and immunological analysis of PTEN in pan-cancer

Lin Wang*, Xiaoxiao He, Xue Long, Xinyue Song, Minjie Wei, Lin Zhao

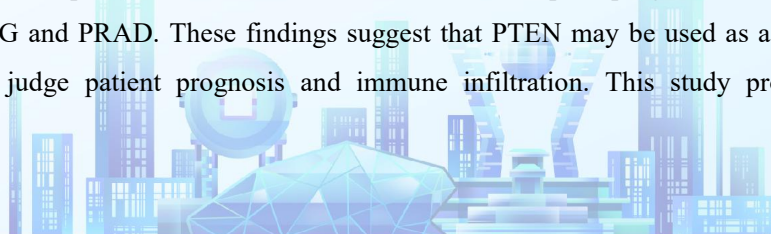
China Medical University

Background: Phosphatase and tensin homologue (PTEN) controls crucial signaling events and processes including cell growth, proliferation, survival, and migration. However, the expression level and the prognostic potential of PTEN have not been studied from the perspective of pan-cancer. Therefore, we aimed to analyze the expression and prognostic value of PTEN in pan-cancer and to gain insights into the association between PTEN and immune infiltration.

Methods: The differential expression of PTEN in 27 human cancers was analyzed by Genotype-Tissue Expression (GTEx) and The Cancer Genome Atlas (TCGA) database. The effect of PTEN on the prognosis of pan-cancer was evaluated by univariate Cox analysis. In addition, the correlation between PTEN and tumor infiltrating-immune cells was analyzed via Tumor Immune Evaluation Resource (TIMER) database. In order to study the immunological and prognostic role of PTEN in cancers, the relationship between PTEN and different immune checkpoints, RNAss, DNAss, neoantigen, tumor mutational burden and microsatellite instability in pan-cancer were comprehensively analyzed. Somatic mutations in PTEN and DNA methylation in pan-cancer were also evaluated.

Results: PTEN was significantly different in 24 of 27 cancers, which is up-regulated in 7 cancers and down-regulated in 17 cancers. Univariate COX survival analysis showed that PTEN was significantly correlated with overall survival (OS) of two cancers, disease-free interval (DFI) of four cancers, disease-specific survival (DSS) of two cancers and progression free interval (PFI) of three cancers. It is worth noting that although the expression of PTEN in various cancers had significant prognostic value, PTEN played a protective or harmful role in different cancers. In brain lower grade glioma (LGG), PTEN was significantly over-expressed in LGG patients, and whether it was OS ($P=0.0290$, hazard ratio (HR)=0.96), DFI ($P=0.0036$, HR=0.87), PFI ($P=0.0110$, HR=0.97) or DSS ($P=0.0110$, HR=0.95), PTEN over-expression group was closely related to better prognosis. However, PTEN is low expressed in prostate adenocarcinoma (PRAD) patients, and for PFI ($P=0.0320$, HR=0.98) and DFI ($P=0.0006$, HR=0.93), PTEN-high expression group was associated with poor prognosis. Furthermore, in colon adenocarcinoma, renal clear cell carcinoma and head and neck squamous cell carcinoma (HNSC), PTEN was positively correlated with immune infiltrating cells (including B cells, neutrophils, CD4⁺ T cells, macrophages, CD8⁺ T cells and dendritic cells). In addition, PTEN is closely related to immune checkpoint genes in pan-cancer. PTEN was closely related to the neoantigens in breast carcinoma, HNSC and thyroid cancer, and had the highest somatic mutation rate (57.36%) in uterine corpus endometrial carcinoma.

Conclusion: The low expression of PTEN is associated with the poor prognosis in a variety of cancers, especially LGG and PRAD. These findings suggest that PTEN may be used as a potential molecular biomarker to judge patient prognosis and immune infiltration. This study provides a promising



prognostic signature and reveals that survival-related immune cells represent novel potential targets for immunotherapy and individualized therapies in cancers.

Key words: pan-cancer; PTEN; prognostic biomarker; immune infiltration; mutation

580. 新辅助化疗联合胃癌根治术治疗进展期胃癌疗效和安全性的 meta 分析

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2. 延安大学医学院

目的: 使用 meta 分析进行评价新辅助化疗联合胃癌根治术治疗进展期胃癌的疗效以及安全性。

方法: 应用计算机检索中国知网 (CNKI) 及万方医学网, PubMed 等相关医学数据库, 查找建库到 2021 年 7 月份的新辅助化疗联合胃癌根治术治疗进展期胃癌疗效和安全性的文献。对照组为单纯胃癌根治术, 观察组为新辅助化疗联合胃癌根治术治疗。整理检索到的文献并提取相关数据, 使用病例对照研究质量评价表 (Oxford CASP, 2004) 进行文章质量评价, 进而采用 Stata/SE 15.0 软件进行 meta 分析。

结果: 本文章共纳入 28 篇文献, 共 2157 例患者。对比单纯胃癌根治术治疗进展期胃癌, 新辅助化疗联合胃癌根治术治疗具有更高的疾病控制率 (DCR) ($OR=2.585$, $95\%CI: 1.790\sim3.734$, $P=0.000$); 更高的 R0 切除率 ($OR=3.653$, $95\%CI: 2.403\sim5.555$, $P=0.000$), 差异具有统计学意义; 白细胞减少 ($OR=1.007$, $95\%CI: 0.690\sim1.470$, $P=0.971$), 切口感染 ($OR=0.725$, $95\%CI: 0.439\sim1.197$, $P=0.208$), 肺部感染 ($OR=0.685$, $95\%CI: 0.359\sim1.308$, $P=0.251$), 吻合口瘘 ($OR=0.491$, $95\%CI: 0.127\sim1.908$, $P=0.305$) 等不良反应的发生率差异无统计学意义; 手术时间 ($WMD=-0.843$, $95\%CI: -6.134\sim4.448$, $P=0.755$), 淋巴结清扫数量 ($WMD=-1.800$, $95\%CI: -4.283\sim0.682$, $P=0.155$), 术中出血量 ($WMD=-1.925$, $95\%CI: -18.298\sim14.448$, $P=0.818$) 二者差异无统计学意义。

结论: 新辅助化疗联合胃癌根治术治疗进展期胃癌可在不影响手术及术后恢复的情况下显著提高疾病的控制率 (DCR) 和根治性切除率, 改善生活质量, 不增加术后并发症。

关键词: 新辅助化疗; 胃切除术; meta 分析

581. 肺癌合并慢性阻塞性肺疾病与单纯肺癌的临床特征的 Meta 分析

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2. 西安市中心医院

目的：通过 Meta 分析了解肺癌合并慢性阻塞性肺疾病与单纯肺癌临床特征的差异，准确掌握肺癌合并慢性阻塞性肺疾病的临床表现及特征，从而可以给予患者更准确的对症治疗。

方法：利用万方数据库（WanFang Data）、PubMed 数据库,和中国知网（CNKI），检索有关肺癌合并慢性阻塞性肺疾病与单纯肺癌的临床特征的随机对照试验（RCT）。对符合纳入标准的研究进行质量评价，使用 Review Manager 5.4 软件进行荟萃分析。

结果：最终有 16 项 RCT 符合纳入标准，总计 3131 例患者。研究结果显示：肺癌合并慢性阻塞性肺疾病观察组与单纯肺癌对照组相比，观察组男性患者比例高于对照组[RR=2.40，95%CI（1.94，2.98）， $P<0.00001$]，观察组具有吸烟史患者的患病率高于对照组[RR=2.28，95%CI（1.83, 2.84）， $P<0.00001$]，以上对比结果差异均有统计学意义。两组患者肺癌病理分型比较，观察组以鳞癌为主，高于对照组[RR=2.35，95%CI（1.90, 2.90）， $P<0.00001$]；对照组以腺癌为主，高于观察组 [RR=0.57，95%CI（0.45, 0.70）， $P<0.00001$]，以上对比结果差异均有统计学意义。两组患者肺癌临床分期对比，观察组 I 期[RR=1.51，95%CI（1.14, 2.01）， $P=0.004$]，II 期[RR=1.84，95%CI（1.43, 2.45）， $P<0.00001$]，III 期[RR=2.22，95%CI（1.78, 2.78）， $P<0.00001$]肺癌患者均高于对照组，差异有统计学意义；而两组的 IV 期肺癌患者比例无明显差异。对比两组患者的临床症状，观察组咯血[RR=3.77，95%CI（2.89, 4.94）， $P<0.00001$]，呼吸困难[RR=4.67，95%CI（3.54, 6.15）， $P<0.00001$]，胸痛[RR=2.81，95%CI（2.16, 3.66）， $P<0.00001$]，骨转移痛[RR=1.62，95%CI（1.06, 2.49）， $P=0.03$]，发热[RR=3.14，95%CI（1.75, 5.62）， $P=0.0001$]发生率均高于对照组，差异具有统计学意义；而两组的咳嗽、声音嘶哑症状无明显统计学差异。对比两组患者影像学表现，观察组胸腔积液[RR=2.34，95%CI（1.67, 3.28）， $P<0.00001$]，肺不张[RR=3.03，95%CI（2.04, 4.51）， $P<0.00001$]发生率高于对照组，差异具有统计学意义。两组患者肺功能对比，观察组 FEV1/FVC 低于对照组[RR=-6.95，95%CI（-11.00, -2.89）， $P=0.0008$]，差异具有统计学意义。观察组 DLCO 低于对照组[RR=-3.35，95%CI（-4.55, -2.15）， $P<0.00001$]，差异具有统计学意义。

结论：近些年来，肺癌合并慢性阻塞性肺疾病患者越来越多，若疾病特征了解不详细，很容易漏诊，导致延误病情，增加患者的痛苦，可能会因为诊断不及时，影响患者预后，甚至缩短患者生存期。因此掌握肺癌合并慢性阻塞性肺疾病与单纯肺癌的临床特征差异，有助于我们早发现、早诊断、早治疗，从而提高患者生存率。

关键词：肺癌；慢性阻塞性肺疾病；临床特征；Meta 分析

582. Risk prediction models based on nutrition factors for chemotherapy-induced adverse effects in Chinese colorectal cancer patients



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Purpose: The high incidence of chemotherapy-induced adverse effects (CIAEs) remains a tricky problem that influenced the treatment in Chinese colorectal (CRC) patients. We aimed to identify risk factors and develop novel prediction models using food/nutrition data in CRC patients receiving capecitabine-based chemotherapy.

Methods: We collected data from 130 Chinese CRC patients receiving post-operative capecitabine-based chemotherapy who had complete food/nutritional data. Univariate and multivariate logistic regression analyses were used to identify CIAE-related food/nutritional factors. Prediction models were constructed based on the combination of these factors. The area under the receiver operating characteristic curve (AUROC) was used to evaluate the discrimination ability of models.

Results: A total of 19 food/nutrition factors associated with CIAEs were identified in the univariate analysis after adjustments for total energy and potential confounding factors. Based on multivariate analysis, we found that, among these factors, dessert, eggs, poultry, and milk etc. were associated with several CIAEs. Most importantly, poultry was an overall protective factor; milk and egg were risk factors for hand-foot syndrome and bone marrow suppression, respectively. Developed multivariate models in predicting grade 1-3 CIAEs and grade 2/3 CIAEs both had good discrimination accuracy (AUROC values from 0.671 to 0.778, 0.736 to 0.982 respectively).

Conclusions: Food consumption and nutrition factors were the susceptible factors for CIAEs. The models incorporating these CIAE-related factors had potential clinical application value in the early prediction of CIAEs, especially for more severe CIAEs. Our findings advanced the post-chemotherapy treatment of CRC with better safety.

Key words: colorectal cancer; capecitabine; chemotherapy-induced adverse effects; food/nutrition factor; bone marrow suppression; anemia; chemotherapy-induced nausea and vomiting

583. The clinical of oral microbiota as a screening tool for oral squamous cell carcinomas

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Research purpose: Oral squamous cell carcinoma seriously endangers the physical and mental health of patients. In a large population, the prognosis of OSCC depends on the early diagnosis of OSCC. Therefore, this study aimed to establish an early screening model based on the relationship between oral squamous cell carcinoma and oral microbiota.

Materials and Methods: 164 samples were collected from 47 patients with oral squamous cell carcinoma and 48 healthy people as controls, including saliva, subgingival plaque, tumor surface, healthy mucosa, and tumor tissue. Based on 16S rRNA gene sequences, data from all five sites, and saliva samples, two machine learning models were developed to screening OSCC.

Results: The average accuracy of five sites and saliva was 98.95% and 95.70%, respectively. The cross-validation results showed that the estimated external prediction accuracy was 96.67% and 93.58% respectively. The false-negative rate was 0%. In addition, studies have shown that OSCC can be diagnosed in any of the five sites. In this model, Actinobacteria, Fusobacterium, Moraxella, Bacillus, and Veillonella were closely associated with oral squamous cell carcinoma.

Conclusion: This study provided a non-radiation, non-invasive and cheaper method for the diagnosis of oral malignant tumors based on oral microbiota. The application of the machine learning method in microbiome data OSCC diagnosis was an example of other microbial-assisted malignant tumor diagnosis models.

Key words: oral microbiota; OSCC; machine-learning methods; screening tool; sequencing

584. N4-Acetylcytidine of FOXP1 promotes cervical cancer progression via driving metabolic reprogramming

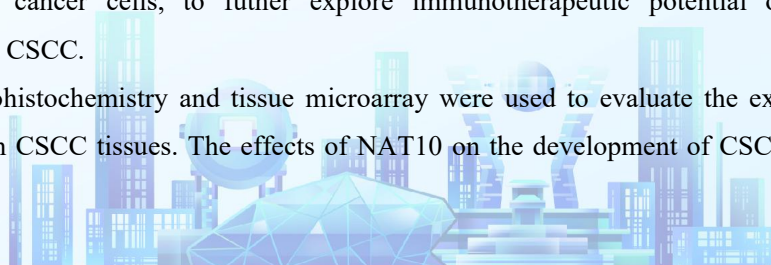
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Objective: Mounting evidences showed that metabolic reprogramming and immune evasion, known as the hallmarks of cancer, are the main causes of the progression and prognosis in cervical squamous cell carcinoma (CSCC). However, little is known about the interaction between the tumor metabolism remodeling and tumor microenvironment (TME) in CSCC. Furthermore, N4-acetylcytidine (ac4C), which has been considered as an epitranscriptomic RNA modification on human mRNA, involved in mRNA transcriptional translation process, plays a vital role in the development, progression, and prognosis of cancer. In this study, we identified that N4-Acetylcytidine (ac4C) RNA acetylation of FOXP1 catalyzed by acetyltransferase NAT10 is closely related to the progression of cervical squamous cell carcinoma, which instigates immunosuppression by utilizing the increased glycolysis of cancer cells, to further explore immunotherapeutic potential of targeting cancer metabolism in CSCC.

Methods: Immunohistochemistry and tissue microarray were used to evaluate the expression of NAT10 and FOXP1 in CSCC tissues. The effects of NAT10 on the development of CSCC were investigated



through in vitro and in vivo assays. Moreover, the ac4C of FOXP1 catalyzed by NAT10 in CSCC cells was quantified through acRIP-sequencing as well as ac4C acetylated RNA immunoprecipitation quantitative reverse transcription polymerase chain reaction (acRIP qRTPCR) assay. Further, glycolytic activity was identified by the extracellular acidification rate kinetic profiles using Seahorse XF96. To investigate the mechanism of immune evasion caused by tumor microenvironment, we examined the tumor-infiltrating immune cells in murine models through Flow cytometry.

Results: Here, we interrogated that the level of ac4C RNA was significantly increased in CSCC, and NAT10 expression, a regulator involved in the abundant ac4C RNA modification, was significantly elevated in CSCC tissues with development of tumor and associated with tumor metastasis through tissue microarray analysis, which revealed that NAT10 expression was also positively correlated with Ki-67 expression. Functionally, knockdown of NAT10 suppressed CSCC proliferation in vitro and in vivo, while NAT10 was required for tumor metastasis, tube formation, and colony formation in vitro. Mechanistically, we revealed the NAT10-mediated ac4C modification profile in CSCC cells and identified the transcription factor FOXP1 as a target of NAT10. In addition, activation mediated by HOXC8 in the promoter of NAT10 facilitated NAT10 transcription, which further stimulated ac4C modification of FOXP1 mRNA, and strongly enhanced the FOXP1 transcripts stability in an ac4C-dependent manner in CSCC. Subsequently, tumor metabolism remodeling induced by FOXP1-ac4C-LDHA axis significantly promoted increased lactate released from glycolytic tumor cells, which contributed to reshape the composition of the TME, as a candidate target for therapeutic intervention in CSCC.

Conclusion: Collectively, our finding uncovers that ac4C modification induced by NAT10 plays a critical role in the interaction between cancer cells and TME via promoting cancer glycolysis, laying the foundation for the FOXP1-ac4C-LDHA axis as a potential therapeutic target for human CSCC.

Key words: Cervical squamous cell carcinoma; ac4C modification; NAT10-ac4C-FOXP1 axis; metabolic reprogramming; immune evasion

585. Prognostic relevance of estrogen receptor status in circulating tumor cells in breast cancer patients treated with endocrine therapy

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Background: The treatment decision of endocrine therapy with unsatisfactory prognosis might attribute to the discordances in ER expression between primary tumors and their metastases, the existing hysteresis at point-in-time between treatment and biopsy, and the impossibility to acquire patients' biopsy samples repeatedly. The purpose of this study was to evaluate the prognostic and predictive value of ER status in circulating tumor cells (CTCs) in BC patients.

Methods: We used the Pep@MNPs method to isolate and analyze CTCs in 2.0 ml of blood samples from 70 patients with BC and 67 healthy females. The concordance and discordance in the expression of ER among CTCs, primary tumor biopsies, and metastases biopsies were compared and analyzed. The predictive and prognostic value of ER expression in CTCs for progression-free survival (PFS) and overall survival (OS) of patients in response to therapies were assessed.

Results: CTCs were detected in 95.71% (67/70) of the patients, with a median of 8 CTCs within 2 ml of peripheral venous blood (PVB). Compared to the healthy controls, the area under the curve (AUC) was 0.958 (67). The concordance in the expression of ER between CTC and primary tumor and metastases was 69.23% and 76.56% (AUC=0.757) respectively. The PFS of patients with ER⁺ expression CTCs (CTC^{ER+}) was significantly improved compared with that of patients without ER⁺ expression CTCs (CTC^{ER-}) ($P<0.05$), whereas there was no significant difference between PFS of patients with ER⁺ biopsies and that of patients with ER⁻ biopsies. The OS of CTC^{ER+} patients was significantly improved compared with CTC^{ER-} patients ($P<0.01$). Otherwise, there was no significant difference of OS curve between patients of ER⁺ biopsies and of ER⁻ biopsies.

Conclusions: Compared with diagnosis based on biopsies, ER expression on CTCs of BC patients might provide more valuable predictive and prognostic insights into endocrine therapies.

Key words: Circulating tumor cells; Estrogen receptor; Companion diagnosis; Liquid biopsy

586. Pilot study for risk stratification of papillary thyroid cancer by TumorFisher® circulating tumor cells technique

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Background: In recent years, thyroid cancer has become the fastest-growing malignant tumor at home and abroad, in which papillary thyroid cancer (PTC) accounts for more than 90%. There are many patients who depend on different pathological treatment guidelines, but there are still many risks for patients with thyroid cancer. The purpose of this study is to achieve accurate risk stratification for papillary thyroid cancer patients before treatment, so as to avoid over treatment and insufficient treatment.

Methods: We used the TumorFisher® technology to isolate and analyze CTCs in 2.0 ml of blood samples from 83 patients with PTC before surgery. To compare and analyze the correlation between the number of CTCs and the risk assessment of PTC. The sensitivity and specificity of different CTCs numbers as cut-off values were compared and analyzed to distinguish high-risk and non-high-risk patients. The correlation between the number of CTCs and lymph node metastasis was compared and analyzed.

Results: The detection rate of CTCs was 73.91% (17/23) in high-risk patients, 20% (4/20) in middle-risk patients and 17.5% (7/40) in low-risk patients. The CTCs number cut-off value=2 significantly distinguished between high-risk and non-high-risk patients with sensitivity=60.9% and specificity=93.3% (AUC=0.82). Setting the cut-off value of CTCs=2, the accuracy can reach 84.3% in predicting high-risk PTC, which means patients have more than 5 lymph nodes metastasis according to clinical judgment criteria.

Conclusion: Utilization TumorFisher® technology to detect the CTCs in the blood of patients with PTC, which can be used for noninvasive early risk stratification. If a large number of clinical studies are carried out in the future, it may provide a basis for the treatment guidelines of thyroid cancer.

Key words: Circulating tumor cells; Papillary thyroid cancer; Liquid biopsy; Companion diagnosis

587. SZC010 induced apoptosis and G2/M phase arrest by inhibition of NF- κ B activation via PI3K/Akt/mTOR pathway in human breast cancer cells

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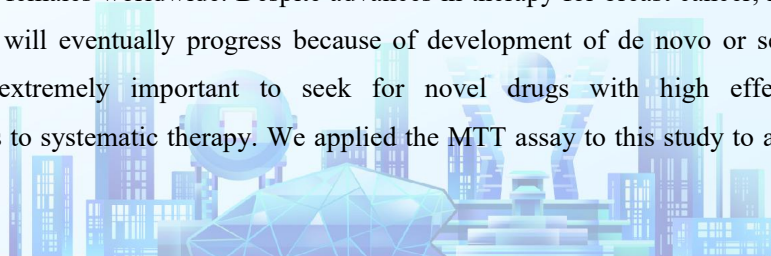
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Breast cancer has become one of the leading causes of cancer deaths and the most frequently diagnosed cancer among females worldwide. Despite advances in therapy for breast cancer, metastatic disease in most patients will eventually progress because of development of de novo or secondary resistance. Thus, it is extremely important to seek for novel drugs with high effectiveness and low poisonousness to systematic therapy. We applied the MTT assay to this study to analyze and evaluate



the cytotoxic activity of Oleanolic acid and OA derivatives in three types of breast cancer cell lines (MDA-MB-231, MCF-7 and MDA-MB-453). Flow cytometry assay was done to access the mechanisms of apoptosis and cell cycle analysis of SZC010 in MDA-MB-453 cells. Apoptosis-related proteins and cyclin-related proteins were evaluated by Western Blot. The key proteins of NF- κ B and PI3K-Akt-mTOR signaling pathway were also evaluated by Western Blot. Our results revealed all of OA derivatives were more effective than OA in three types of breast cancer cell lines (MCF-7, MDA-MB-231 and MDA-MB-453). Among these seven OA derivatives, SZC010 exhibited the most potent cytotoxicity in MDA-MB-453 cells. Additionally, we observed that SZC010 treatment caused a dose- and time-dependent inhibition of growth in MDA-MB-453 cells. Furthermore, we demonstrated that SZC010 induced growth arrest in G2/M phase and apoptosis by inhibition of NF- κ B activation via PI3K/Akt/mTOR signaling pathway. Our data indicates that novel OA derivative SZC010 possesses great potential in breast cancer therapy.

Key words: Oleanolic acid derivatives; SZC010; Apoptosis; NF- κ B; PI3K/Akt/mTOR signaling pathway; Breast cancer

588. The Oleanolic Acid Derivative ZQL-3d Exerts Anticancer Effects via miR-221-3p/ASPP2 and Modulates Trastuzumab Resistance in HER2-positive Breast Cancer

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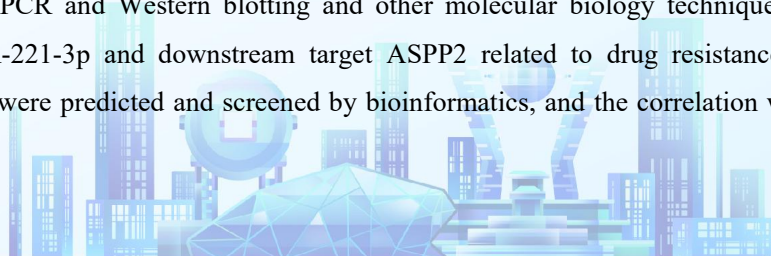
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BackgroundA: With the application of targeted drugs, survival and prognosis of HER2-positive breast cancer patients have improved significantly, but single-target small-molecule kinase inhibitors have developed resistance during clinical application due to mutations in residues at the target protein binding site. Therefore, the development of novel multi-target inhibitors that can overcome tumor resistance is an urgent problem in the current antitumor drug research. In recent years, oleanolic acid (OA) and its derivatives have attracted much attention because of their anti-tumor, anti-inflammatory, antiviral, anti-infective, immunomodulatory and other biological activities. In this study, we investigated the role of an OA derivative ZQL-3d in breast cancer and its relationship with trastuzumab resistance and its molecular mechanism.

Methods: The anticancer effect of ZQL-3d was detected by CCK8, cell cloning assay, flow cytometry, transwell, and scratch assay, and the expression levels of cell function-related pathway indicators were detected by qPCR and Western blotting and other molecular biology techniques. The micro RNA indicator miR-221-3p and downstream target ASPP2 related to drug resistance in HER2-positive breast cancer were predicted and screened by bioinformatics, and the correlation was verified by dual



luciferase reporter gene assay. To investigate the overcoming effect of ZQL-3d on trastuzumab resistance in JIMT-1 and the changes of related pathway indicators when transfected with overexpression and silencing of miR-221-3p and ASPP2.

Results: ZQL-3d was able to exert anticancer effects in breast cancer cells of different molecular fractions, especially in JIMT-1, where ZQL-3d combined with trastuzumab showed significantly superior antitumor effects than trastuzumab alone. The miR-221-3p level was down-regulated after incubation of ZQL-3d in JIMT-1. JIMT-1 resistance to trastuzumab was alleviated after constructing a silent miR-221-3p model, and knockdown of ASPP2 restored resistance. In the overexpression miR-221-3p model, SK-BR-3 appeared resistant to trastuzumab. Meanwhile, overexpression of ASPP2 could overcome the resistance.

Conclusions: The OA derivative (ZQL-3d) affects the apoptotic process through miR-221-3p regulation of ASPP2 to exert oncogenic effects and modulates the resistance to trastuzumab in HER2-positive breast cancer.

Key words: Oleanolic acid; HER2; Breast cancer; Micro RNA; Drug resistance

589. High SYT7 expression is associated with poor prognosis in human non-small cell lung carcinoma

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Synaptotagmin 7 (SYT7) can encode a single-pass 46-kDa transmembrane protein which located on human chromosome 11q12.2. It has been reported to be dysregulated in several cancers; however, there are few reports on the role of SYT7 in non-small cell lung carcinoma (NSCLC). The purpose of our study was to investigate the expression of SYT7 in NSCLC and its relationship with the prognosis of NSCLC. Differences in SYT7 expression were explored by using a public database and tissue samples. The prognostic value of SYT7 and its expression correlation with clinical parameters were evaluated by statistical analysis. Our current study found that elevated mRNA and protein levels of SYT7 in NSCLC tissues compared to adjacent normal tissues. The high expression of SYT7 in NSCLC patients was positively correlated with tumour differentiation ($P = 0.031$) and pT ($P = 0.041$). The higher SYT7 expression had a shorter survival time than those with lower SYT7 expression in NSCLC patients. Furthermore, multivariate analysis demonstrated that the expression of SYT7 was an unfavourable independent prognostic factor for NSCLC ($P = 0.044$). In conclusion, SYT7 was upregulated in NSCLC tissues and maybe a prognostic and diagnostic factor of NSCLC.

Key words: Immunohistochemistry; Non-small cell lung carcinoma; Prognosis; SYT7

590. 替吉奥维持干预在转移性鼻咽癌治疗中的时机优势研究



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背景与目的: 远处转移是鼻咽癌治疗失败的主要原因。尽管多数转移性鼻咽癌经过一线治疗可以获得疾病的控制或缓解,但无疾病进展时间仍不理想,大部分患者在短期内再次进展,需要接受二线治疗,而二线治疗效果往往更不理想。标准治疗获益的患者给与维持干预治疗的模式在多种转移性实体瘤中获得成功,并且转移性鼻咽癌解救化疗后替吉奥维持治疗的前期研究已观察到临床获益,但这种及时维持干预治疗的模式与病情进展后再进行二线治疗的延迟干预模式比较,哪种模式更具有生存获益一直存在争议,通过与转移性鼻咽癌进展后二线治疗模式的生存预后比较,明确转移性鼻咽癌一线治疗后替吉奥(S-1)维持干预治疗的时机优势。

方法: 一线化疗临床获益的转移性鼻咽癌患者,1:2 分层随机为研究组(维持干预组,S-1 维持至疾病进展或不能耐受)和对照组(延迟干预组),评价 S-1 及时维持干预在改善转移性鼻咽癌整体预后中的时机优势。

结果: 至 2019 年 5 月入组 157 例患者,中位随访 20.2 月(8.0~53.1 月)。可评价病例 143 例:维持干预组 51 例,延迟干预组 92 例。与延迟干预组比较,S-1 维持干预提高转移性鼻咽癌一线化疗后的中位首次无疾病进展生存期(mfPFS)(8.4 月 vs 16.0 月, $P<0.001$)及全程无疾病进展生存期(mtPFS)(14.8 月 vs 16.0 月, $P=0.006$);并显著改善患者中位总生存(mOS)(21.1 月 vs 27.5 月, $P=0.003$);亚组分析,转移性鼻咽癌一线化疗后及时的 S-1 维持干预与延迟干预比较,S-1 维持干预显著延长 mtPFS(16.0 月 vs 14.8 月,13.3 月, $P=0.004$)及 mOS(27.5 月 vs 23.4 月,19.6 月, $P<0.001$)。维持干预组耐受性良好,不良反应均主要表现为 1 级的皮肤色素沉着,口腔粘膜炎,手足综合征,恶心等,经过方案调整或短期治疗延迟(<2 周)均可耐受。

结论: 转移性鼻咽癌一线化疗后及时进行替吉奥维持干预比延迟干预明显改善转移性鼻咽癌患者生存预后,患者耐受性良好。

关键词: 转移性鼻咽癌;维持干预;时机优势;预后

591. 基于 TCGA 数据库构建肝细胞癌免疫相关基因的预后风险评分模型

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目的: 免疫相关基因(IRGs)在肿瘤免疫微环境中起着重要作用,本研究基于 IRGs 构建肝细胞癌(HCC)患者的生存预测模型,评估 HCC 患者预后,并探讨其对免疫微环境的影响。

方法: 从癌症基因组图谱(TCGA)和免疫学数据库和分析门户(ImmPort)获取 HCC 样本的免疫相关基因 mRNA 表达数据。使用 limma R 包鉴定差异表达的免疫相关基因(DEIRGs)。对

DEIRGs 进行单变量 cox 回归分析以确定与总生存(OS)相关的 IRGs, 采用 LASSO 回归分析筛选与预后相关的关键基因, 通过多因素 Cox 回归分析构建预测模型。此外, 运用 ICGC 数据库的 LIRI-JP 肝癌数据集进行预测模型的验证。进行 Kaplan-Meier 生存分析以评估 IRGs 的独立预测价值。为了探索 IRGs 的生物学功能, 对 DEIRGs 进行富集分析和通路注释, 以及免疫相关分析。

结果: 在 TCGA 数据集中共获得 401 个差异表达的 IRGs, 其中上调基因 237 个, 下调基因 164 个。

对 237 个上调 IRGs 进行单因素 COX 回归分析, 发现 63 个 IRGs 与 OS 显著相关, 通过 LASSO 回归筛选出 8 个特征基因, 应用多变量 COX 回归分析构建预后特征, 最终共 5 个特征基因被纳入预测模型, 其中包括 SPP1, BIRC5, STC2, GLP1R 和 RAET1E。在 LIRI-JP 肝癌数据集中的验证结果显示, 基于 5 个特征免疫基因的预后模型具有良好的预测价值。独立预后分析显示, 调整其他临床因素后, 基于预后模型的风险评分可能是一个独立的预后指标。进一步分析表明, 这 5 个特征基因高表达与 HCC 患者的预后不良有关。免疫相关分析表明, 高风险组 HCC 患者具有更高的免疫浸润水平, 这提示 5 个特征 IRGs 可能在 HCC 的肿瘤免疫微环境 (TIME) 中中介导免疫逃逸, 免疫耐药而发挥重要作用。

结论: 我们的研究基于 HCC 的 IRGs 建立了预后特征并验证了该模型的性能, 并将其用于预测 HCC 预后和分析免疫细胞浸润, 这可能为探索 HCC 的 TIME 中潜在的 IRGs 提供新的见解。

关键词: 肝细胞癌; 免疫相关基因 (IRGs); Cox 预测模型; 免疫浸润

592. Identification and Validation of an Immune-Related lncRNA Signature to Facilitate Survival Prediction in Gastric Cancer

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It is well-known that lncRNAs play critical roles in regulating cancer development, including cancer immunity. Immune-related lncRNA signatures predicting prognosis have been reported in multiple cancers, but relevant studies in gastric cancer are still lacking. Here, we performed a comprehensive analysis using TCGA and Immport databases and identified an immune-related lncRNA signature to stratify gastric cancer patients into high- and low-risk subgroups. Then, we validated the reliability of the lncRNA signature in an independent 75 gastric cancer samples and demonstrated that high-risk cases frequently suffered from shorter overall survival time. Functional exploration indicated the lncRNA signature might modulate cell adhesion and migration, cytokine-receptor interaction and immune evasion. Additionally, we observed that high-risk samples tended to form an immunosuppressive microenvironment, which had more M2-polarized macrophages and Tregs, but

fewer CD8 effector T cells within tumors. Moreover, we found that PD-1 and PD-L1 were dramatically upregulated in a subset of high-risk gastric cancer patients with abundant M2 and Treg infiltration, implying these patients may benefit from anti-PD-1 and PD-L1 immunotherapy. These results showed that the immune-related lncRNA signature had a prominent capacity to predict overall survival and the immune status of microenvironment, which may be useful for the risk-stratification management and provide a valuable clue to identify proper patients potentially benefit from immune checkpoint therapy in gastric cancer.

Key words: lncRNA signature; gastric cancer; cancer immunity; overall survival; immunosuppressive microenvironment

593. 一种新型外泌体检测方法的研究

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研究目的: 外泌体是由细胞分泌的,大小介于 30-150 nm 之间的膜性囊泡。它们含有大量的生物分子,如蛋白质,核酸等,提供了丰富的供体细胞相关信息。近年研究表明,外泌体可实现细胞间的信息交流和物质传递,与疾病的发生和发展过程有关,被认为是许多疾病(尤其是肿瘤疾病)的重要生物标志物。因此,对外泌体的检测尤为重要。我们报道一种新型,方便,快速的荧光适配体生物传感器,用于外泌体的分析检测。不同于传统静态荧光“开-关”的检测模式,本传感器基于动力学进行分析,有望减少背景荧光的干扰,实现方便,快捷的外泌体传感检测,克服传统检测方法的一些局限。

材料与方法: 基于“点击化学”原理,用 Stilbene-ITC 化合物和 NH₂-CD63 适配体高效合成一种新型的荧光适配体传感器,并通过质谱,荧光发射光谱,紫外发射光谱,高效液相色谱等多种方法对传感器进行表征。此外,用经典的差速离心法分离细胞培养液中的外泌体。简而言之,首先在完全培养基中培养细胞,后换成不含外泌体血清培养基继续培养后收集细胞悬浮液,并通过经典的差速离心法制备得到外泌体(300 × g, 10 min; 2000 × g, 10 min; 10000 × g, 30 min; 100000 × g, 70 min)。随后通过透射电子显微镜,纳米颗粒跟踪分析,蛋白免疫印迹法等对外泌体进行表征。在生物传感测定中,将样品-生物传感器混合均匀,置于荧光分光光度计中,在恒定的波长激发下,观察荧光在一段时间内的变化曲线,并计算曲线的 K_{app} 值,以量化传感器对目标检测物的反应程度。在此基础上,进一步进行传感性能的考察。

结果: 表征结果表明已经成功制备了生物传感器和外泌体。已知 CD63 为常见的外泌体标志物。基于此,我们分别测定了传感器对 CD63 蛋白高表达外泌体和 CD63 蛋白低表达外泌体的响应。传感分析实验结果显示,荧光衰减曲线对 CD63 蛋白高表达外泌体具有较强的响应,而对



CD63 蛋白低表达外泌体相对较弱。通过进一步对其荧光衰减变化动力学参数 K_{app} 进行分析, 可实现对外泌体的量化分析, 从而为疾病检测提供重要证据。

结论: 本研究制备了一种新型的荧光适配体传感器, 用于外泌体的检测。本生物传感器能在加入含有 CD63 蛋白的外泌体时产生荧光衰减动力学的变化。该传感检测有望避免传统静态荧光检测中背景荧光的干扰等问题。鉴于适配体的易置换性, 该新型外泌体检测传感器有望进一步拓展成一种快速、灵敏的外泌体检测平台, 用于疾病的诊断和愈后监测。

关键词: 外泌体; 生物传感器; 肿瘤生物标志物

594. A Novel Fatty Acid Profile Index-the Lipophilic Index-and Risk of Oral Cancer

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Aims/hypothesis: The lipophilic index(LI), which can be derived from the fatty acids(FAs) profile of blood or tissues, has recently been proposed as a novel measure of cell membrane FA fluidity. Abnormalities of cell-membrane profile has been associated directly with chronic disease even cancer in many studies. Furthermore, quite a few research have studied the effect of membrane FA levels alternation in the development of cancer disease with red blood cell membrane as a potential biomarker in various forms of the illness, such as breast, prostate, liver, lung and colorectal. Hence, we conducted a study to evaluate the lipophilic index in relation to the incidence of oral cancer

Method: In a large case-control study from southeast China, fatty acid (FA) in erythrocytes were measured in 396 oral cancer cases and 407 community controls. The lipophilic index was calculated as the sum of the products of the FA proportions with the respective FA melting points. Information on sociodemographic characteristics, lifestyle history, and medical history was gathered by means of a general questionnaire with closed-ended questions. We used Spearman's correlation coefficients to examine the correlations between the specific fatty acids and the LI. The violin plot was used to compare the LI between patients and controls among different population. Restricted cubic spline was used to reveal the potential non-linear relationship between erythrocyte LI and risk of oral cancer. We used unconditional logistic regression to examine the association between LI and risk of oral cancer. We estimated odds ratios (ORs) and 95% confidence interval (95%CI) for quartiles of the LI compared with the respective lowest tertile. Using the same logistic regression models, stratified analysis on the association between the LI and oral cancer after adjusting for potential risk factors.



Results: The highest proportion in erythrocyte membrane were observed for 16:0(24%), 18:0(13%), 18:1(11%), 18:2(11%) and 20:4(12%). Generally, SFA showed positive correlation with the lipophilic index (exception: 22:0), whereas monounsaturated fatty acids (MUFAs) and polyunsaturated fatty acids (PUFAs) were inversely correlated with the LI (exception: 18:1 and 20:5). No statistically significant difference were observed between two groups on gender, residence, marital status, occupational activity (all $P > 0.05$). Compared with controls, cases were older and more likely to have a high proportion of tobacco and alcohol consumption. Then, the potential non-linear association between LI and the risk of oral cancer were explored using the restricted cubic spline. There is a positive but non-linear correlation between the LI and oral cancer (P for non-linearity=0.012). The adjusted OR was 1.65 (95% CI:1.13, 2.41) when comparing top with bottom tertile of the LI. Strong associations were observed between LI and oral cancer among non-smokers ($OR_{\text{tertile3v.1}}=1.47$, 95% CI:1.15,1.88) and non-diabetes ($OR_{\text{tertile3v.1}}=1.28$, 95% CI:1.03,1.59).

Conclusions: A high lipophilic index reflecting a lower fluidity of erythrocyte membranes is associated with a higher risk of oral cancer. In addition, the association was apparently steady in non-smokers and non-diabetic patients.

Key words: fatty acids; membrane fluidity; oral cancer; case-control study

595. 基于 DETX 构建的肿瘤浸润免疫细胞图谱作为分子标志物预测肿瘤治疗结局

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背景: 近年来, 越来越多的研究发现, 抗肿瘤免疫和肿瘤免疫逃逸是肿瘤进展、转移及复发的关键因素。有研究表明, 根据肿瘤免疫逃逸和免疫协调之间的平衡关系将肿瘤分为冷肿瘤、可变肿瘤、热肿瘤后, 三种肿瘤类型的复发风险依次降低, 提示肿瘤免疫微环境中免疫细胞的浸润模式可能与肿瘤的预后相关。本研究开发了基于机器学习模型的反卷积算法 DETX (Deconvolution for Transcriptomic Data), 然后利用此算法分析乳腺癌、结肠癌和接受辅助化疗的全癌种患者的转录组数据, 评价免疫细胞浸润模式作为肿瘤分子标志物预测肿瘤治疗后生存结局的价值。

方法: 开发基于支持向量机模型 CIBERSORT 的反卷积算法 DETX, 并在癌症基因组图谱计划全癌种转录组数据中, 与其它反卷积算法进行交叉验证。运用估算乳腺癌、结肠癌及全癌种接受术后辅助化疗后患者免疫微环境中 22 种免疫细胞的浸润丰度。使用 maximum selected rank statistics 寻找与肿瘤生存结局显著相关的浸润免疫细胞比例阈值, 然后将浸润的各类免疫细胞比例分为高、低浸润两组, 采用 Kaplan-Meier 法和 COX 比例风险回归模型评估各类浸润免疫



细胞对生存结局的预测价值，构建可用于准确预测乳腺癌和结肠癌患者预后及全癌种患者辅助化疗结局的肿瘤浸润免疫细胞图谱。

结果：本研究共纳入乳腺癌 1025 例,结肠癌 235 例和接受辅助化疗的全癌种患者 116 例。乳腺癌,结肠癌和接受辅助化疗的全癌种患者的中位生存时间分别为 10.357 年，6.163 年和 6.909 年。Kaplan-Meier 分析和 COX 比例风险回归模型显示，乳腺癌组织中高浸润的 CD8⁺T 细胞，滤泡辅助 T 细胞和 M1 型巨噬细胞以及低浸润的静息态 CD4⁺记忆 T 细胞和 M2 型巨噬细胞与良好预后显著相关，风险比分别为 1.968(1.196-3.239, $P<0.01$),1.961(1.259-3.055, $P<0.01$), 1.696(1.173-2.453, $P<0.01$)，0.6812(0.4748-0.9775, $P<0.05$)和 0.1863(0.0969-0.3581, $P<0.001$)。结肠癌组织中高浸润的 CD8⁺T 细胞以及低浸润的静息态 CD4⁺记忆 T 细胞，调节性 T 细胞，活化的 NK 细胞和 M2 型巨噬细胞与良好预后显著相关，风险比分别为 3.093(1.126-8.494, $P<0.05$),0.2828(0.1005-0.7955, $P<0.05$)，0.4412(0.2006-0.9702, $P<0.05$)，0.1930(0.0639-0.5829, $P<0.01$)和 0.2780(0.8238-0.9384, $P<0.05$)。在接受辅助化疗的全癌种患者中，肿瘤组织中高浸润的 CD8⁺T 细胞，滤泡辅助 T 细胞以及低浸润的静息态 NK 细胞与良好预后显著相关，风险比分别为 2.173(1.043-4.524, $P<0.05$), 2.171(1.129-4.178, $P<0.05$)和 0.420(0.223-0.791, $P<0.01$)。

结论：本研究利用了多种肿瘤的基因表达谱数据，揭示了与肿瘤生存结局相关的肿瘤浸润免疫细胞图谱。肿瘤组织中，高浸润的 CD8⁺T 细胞,滤泡辅助 T 细胞或 M1 型巨噬细胞与治疗后的良好生存结局相关，而高浸润的静息态 CD4⁺记忆 T 细胞,调节性 T 细胞，M2 型巨噬细胞或低浸润的静息态 NK 细胞则提示生存结局不良。本研究提供了一种可指导临床肿瘤诊疗实践的新型分子标志物，并为后续基础研究的开展提供新的方向。

关键词：乳腺癌；结肠癌；肿瘤微环境；肿瘤浸润免疫细胞；化疗；分子标志物

596. N4-Acetylcytidine of FOXP1 promotes cervical squamous cell carcinoma progression via driving metabolic reprogramming

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Objective: Mounting evidences showed that metabolic reprogramming and immune evasion, known as the hallmarks of cancer, are the main causes of the progression and prognosis in cervical squamous cell carcinoma (CSCC). However, little is known about the interaction between the tumor metabolism remodeling and tumor microenvironment (TME) in CSCC. Furthermore, N4-acetylcytidine (ac4C), which has been considered as an epitranscriptomic RNA modification on human mRNA, involved in mRNA transcriptional translation process, plays a vital role in the development, progression, and prognosis of cancer. In this study, we identified that N4-Acetylcytidine (ac4C) RNA acetylation of FOXP1 catalyzed by acetyltransferase NAT10 is closely related to the progression of cervical

squamous cell carcinoma, which instigates immunosuppression by utilizing the increased glycolysis of cancer cells, to further explore immunotherapeutic potential of targeting cancer metabolism in CSCC.

Methods: Immunohistochemistry and tissue microarray were used to evaluate the expression of NAT10 and FOXP1 in CSCC tissues. The effects of NAT10 on the development of CSCC were investigated through in vitro and in vivo assays. Moreover, the ac4C of FOXP1 catalyzed by NAT10 in CSCC cells was quantified through acRIP-sequencing as well as ac4C acetylated RNA immunoprecipitation quantitative reverse transcription polymerase chain reaction (acRIP qRT-PCR) assay. Further, glycolytic activity was identified by the extracellular acidification rate kinetic profiles using seahorse XF96. To investigate the mechanism of immune evasion caused by tumor microenvironment, we examined the tumor-infiltrating immune cells in murine models through Flow cytometry.

Results: Here, we interrogated that the level of ac4C RNA was significantly increased in CSCC, and NAT10 expression, a regulator involved in the abundant ac4C RNA modification, was significantly elevated in CSCC tissues with development of tumor and associated with tumor metastasis through tissue microarray analysis, which revealed that NAT10 expression was also positively correlated with Ki-67 expression. Functionally, knockdown of NAT10 suppressed CSCC proliferation in vitro and in vivo, while NAT10 was required for tumor metastasis, tube formation, and clony formation in vitro. Mechanistically, we revealed the NAT10-mediated ac4C modification profile in CSCC cells and identified the transcription factor FOXP1 as a target of NAT10. In addition, activation mediated by HOXC8 in the promoter of NAT10 facilitated NAT10 transcription, which further stimulated ac4C modification of FOXP1 mRNA, and strongly enhanced the FOXP1 transcripts stability as well as translation efficiency in an ac4C-dependent manner in CSCC. Subsequently, tumor metabolism remodeling induced by FOXP1-ac4C-LDHA axis significantly promoted increased lactate released from glycolytic tumour cells, which contributed to reshape the composition of the TME, as a candidate target for therapeutic intervention in CSCC.

Conclusion: Collectively, our finding uncovers that ac4C modification induced by NAT10 plays a critical role in the interaction between cancer cells and TME via promoting cancer glycolysis, laying the foundation for the FOXP1-ac4C-LDHA axis as a potential therapeutic target for human CSCC.

Key words: Cervical squamous cell carcinoma; ac4c modification; NAT10-ac4c-FOXP1 axis; metabolic reprogramming; immune evasion

597. CTC 异质性关键分子及免疫特征在胆道癌分期诊断与预后预测中的应用研究

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研究目的：选用多种抗体构建用于分选胆道癌 CTC 的纳米免疫脂质磁珠，建立一套胆道癌 CTC 的多分型分选体系；联合 NGS 测序，结合 PD-L1 免疫特征、组织病理、临床影像特征，进行胆道癌突变基因与 PD-L1 表达，疗效评价的关联性分析；同时，探讨 CTC 特征与胆道癌 TNM 分期，淋巴转移，远处转移的关系。

材料与方法：收集各分期胆道癌患者外周血及匹配组织样本，通过 HSPG 总抗，SDC1/SDC2/GPC1/GPC3 亚型，HSPG 硫酸化类型，以及 EpCAM 与 Vimentin 抗体，构建胆道癌 CTC 分子分型的免疫活性脂质磁球（图 1），并作可视化免疫荧光鉴定（CK+/DAPI+/CD45-），建立评估胆道癌不同分子分型的 CTC 数量评分体系。使用胆道癌 CTC-DNA，进行下游基因突变分析，对照组织样本基因突变谱，可视化变异基因热图，差异表达 mRNA 谱。结合胆道癌 CTC 分子信息（表面标志蛋白，基因组，转录组）及临床影像，病理特征，统计治疗前 CTC 计数基线和分类指标，对预后的评价与预测，包括：随访无瘤生存时间，复发类型，无进展生存时间，进展类型及总生存期等，主要研究终点按亚组设定为 PFS、DFS，次要终点为 OS。

结果：前期进行了胆道肿瘤患者的 CTC 检测，CTC 检出总数如图 2 所示，此外，选用免疫脂质磁珠依次分选及分别分选的检测方法，用以筛选最适宜的检测方法（表 1，表 2）。最终确定采用 HSPG 总抗，HSPG 硫酸化及 4 种亚型（SDC1、SDC2、GPC1、GPC3）构建磁球，对胆道癌 CTC 进行分选。随后，我们选用 5 组磁珠法（HSPG 总抗及其 4 种亚型：SDC1，SDC2，GPC1 和 GPC3）和 6 组磁珠法（HSPG 总抗及其 4 种亚型：SDC1，SDC2，GPC1 和 GPC3，以及 HSPG 硫酸化）进行治疗前胆道癌 CTC 的分离鉴定（图 3-4），结果显示 EpCAM 和 Vimentin 对 CTC 分选呈现较稳定的结果，而特异性分选因子 HSPG 及其 4 种亚型，以及硫酸化的 HSPG 同样展现出在不同的个体之间呈现相异的计数结果。此外，通过对 18 例胆管癌及 11 例胆囊癌患者术前术后外周血 CTC 进行动态监测，结果显示：特异性的几种抗体免疫脂质磁球对于胆道癌 CTC 的捕获能力明显优于 EpCAM 和 Vimentin 活性磁球捕获的，分选出的 CTC 个数均有不同差异（图 5-6）。最后，在对胆道癌患者的 CTC/组织进行的 NGS 测序结果进行分析，发现 19 个突变基因是 CTC 来源与组织来源共同检测到的（图 7-图 9）。

结论：构建的基于胆道癌特异分选因子 HSPG 及多个亚型的免疫脂质磁珠对胆道癌 CTC 分选特异性强，灵敏度更高，CTC-NGS 测定的突变基因也呈现出与组织-NGS 高度的一致性。这为胆道癌诊治提供新的策略与依据。

关键词：胆道癌；CTC；纳米免疫脂质磁珠；NGS

598. Antitumor effect of overexpressed alpha-1-antichymotrypsin on lung cancer

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Background: The glycoprotein alpha-1-antichymotrypsin (AACT), a serine protease inhibitor serpin, is mainly synthesized in the liver then secreted into the blood, and is involved in acute phase response, inflammation, and proteolysis. The dysregulation of AACT is associated with tumor progression and recurrence, and could be used as diagnostic and prognostic biomarkers in tumors. We found the expression levels of AACT were decreased in early non-small cell lung cancer, but its biological functions are unknown.

Methods: The expression changes of AACT in lung cancer tissues were analyzed by GEPIA database. The survival analysis was performed by Kaplan-Meier plotter database. The stable lung cancer cell lines that overexpressed AACT have been constructed. Then, CCK8 assays were used for detection the cell proliferation, the colony formation assays were used for cell growth, the cell apoptosis was analyzed by flow cytometry, the cell invasion and migration were detected by wound healing assays and Transwell assays.

Results: We found the expression levels of AACT was decreased in lung cancer tissues, and it was shown that the down-regulated AACT expression was associated with shorter survival of early lung cancer patients. The cell proliferation of A549 cells, H157 cells and H1437 cells were significantly inhibited when cultured for 24 h and 48 h after AACT overexpressed. The colony formation assays indicated the cell growth of three lung cancer cell lines that overexpressed AACT was slowed. It promoted the cell apoptosis of lung cancer cells when overexpressed AACT that detected by flow cytometry. Finally, the cell invasion and migration were inhibited significantly after overexpressed AACT in three stable lung cancer cell lines.

Conclusion: The data confirmed the antitumor effect of overexpressed AACT in lung cancer, thereby suggesting the AACT may serve as a potential therapeutic target for lung cancer.

Key words: alpha-1-antichymotrypsin; lung cancer; overexpression; antitumor

599. 肿瘤相关纤维细胞通过促进糖酵解在体内外水平介导非小细胞肺癌产生放疗抵抗性的研究

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目的: 肺癌是我国发病率,死亡率均居于首位的恶性肿瘤,其中非小细胞肺癌(Non-small cell lung cancer, NSCLC)约占全部肺癌的85%。放疗作为一种积极有效的局部治疗手段,既可用于早期和局部晚期肺癌的根治性治疗,也可用于晚期肺癌的姑息性治疗。然而,放疗抵抗性的存在严重影响了患者的治疗效果。以往对肺癌放疗抵抗性的研究多着眼于癌细胞自身,而忽略了肿瘤微环境的重要影响。肿瘤相关纤维细胞(Cancer-associated fibroblasts, CAFs)是肿瘤微环境



的主要成员，与肿瘤的发生发展密切相关，本研究拟明确 CAFs 对于 NSCLC 细胞株放疗敏感性的影响及其分子机制。

材料和方法：采用原代培养的方法成功地从初诊的 NSCLC 患者手术切除的癌组织及正常组织中分离培养了 CAFs 及配对的正常纤维细胞（Normal fibroblasts, NFs）。通过 qRT-PCR, Western blotting, 细胞转染, 免疫荧光, 细胞因子/趋化因子芯片高通量筛选, 乳酸排放, 氧消耗检测, 克隆形成实验和裸鼠移植瘤模型构建等在体内外水平检测 CAFs 对 NSCLC 细胞株放疗敏感性的影响及其分子机制。

结果：经鉴定，CAFs 及 NFs 均阴性表达上皮细胞标志物 E-cadherin，阳性表达 Vimentin。此外，癌纤维细胞的活化标志物如 FSP1, α -SMA 和 FAP 在 CAFs 中的表达量显著高于配对的 NFs，提示课题组已成功地分离培养了 CAFs 及其配对的 NFs。当 NSCLC 细胞株 A549, PC-9 与 CAFs 共培养 72 h 后，检测发现细胞内的糖酵解相关的多个基因如葡萄糖转运体（Glucose transporter, GLUT），己糖激酶 2（Hexokinase 2, HK2），磷酸果糖激酶（Phosphofructokinase, PFK），丙酮酸激酶 M2（Pyruvate kinase M2, PKM2），乳酸盐脱氢酶（Lactate dehydrogenase, LDH），乳酸转运体（Monocarboxylate transporter 4, MCT4）等的表达显著提高。且 NSCLC 细胞株与 CAFs 共培养后，细胞的乳酸排放量及氧消耗量显著增加，提示 CAFs 可显著地促进 NSCLC 细胞株的糖酵解作用。课题组的进一步研究显示 CAFs 通过促进糖酵解调节 NSCLC 细胞株放疗后的 DNA 损伤修复响应。抑制 CAFs 介导的糖酵解作用可有效地增加 NSCLC 细胞株放疗后的 DNA 损伤，抑制细胞修复。裸鼠体内的移植瘤模型实验显示抑制 CAFs 介导的糖酵解作用可显著地增加 NSCLC 细胞株的放疗敏感性。采用细胞因子/趋化因子芯片高通量筛选发现 CAFs 通过分泌细胞因子 Midkine 激活 Wnt/ β -catenin 信号通路，引起 c-myc 高表达，同时降低 c-myc 泛素化降解，从而促进 NSCLC 细胞株糖酵解作用并介导产生放化疗抵抗性。

结论：抑制 CAFs 促进的 NSCLC 细胞株糖酵解作用可在体内外水平显著地增加肿瘤组织的放疗敏感性。

关键词：非小细胞肺癌；肿瘤相关纤维细胞；糖酵解；放疗抵抗性；DNA 损伤修复响应；Midkine

600. 金纳米棒@MIL-100 复合材料构建以及用于核磁共振成像引导的光热治疗

贺景超

东南大学医学院

背景/目标：恶性肿瘤缺乏有效的治疗手段和预后差，严重危害人类健康。光热治疗（PTT）是一种非常具有前途的肿瘤治疗方式。目前，临床 PTT 缺乏有效的多功能光热剂。在本项研究中，多功能的金纳米棒@MIL-100 被成功构建，并用于核磁共振成像（MRI）引导的 PTT，从而为临床 PTT 提供潜在的多功能光热剂。



方法：AuNR@MIL-100 首次利用层层自组装技术被制备。采用 FTIR、XPS、XRD、TEM 和 UV-vis 等测试方法对 AuNR@MIL-100 进行了结构和性质表征。体内和体外实验评估 AuNR@MIL-100 的生物相容性和光热效果。H&E 和 TUNEL 实验评估 PTT 导致肿瘤组织的损伤情况。AuNR@MIL-100 的 MRI 性能利用体内实验进行评估。

结果：多功能的 AuNR@MIL-100 首次被成功制备。体内和体外实验显示 AuNR@MIL-100 具有良好的生物相容性。AuNR@MIL-100 在 808nm 激光照射下能消灭癌细胞和抑制体内肿瘤组织生长。H&E 和 TUNEL 实验表明 AuNR@MIL-100 在 808nm 激光照射下可以引起肿瘤组织明显坏死和凋亡。AuNR@MIL-100 在体内表现出优异的 T2 MRI 性能。

结论：本研究工作不仅提供了高效的多功能平台用于 MRI 引导的肿瘤 PTT 而且为构建多功能光热剂提供了新颖的研究思路。

关键词：肿瘤；光热疗法；金纳米棒@MIL-100



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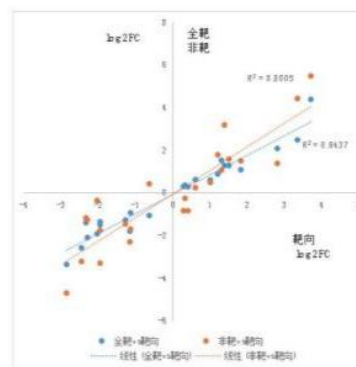
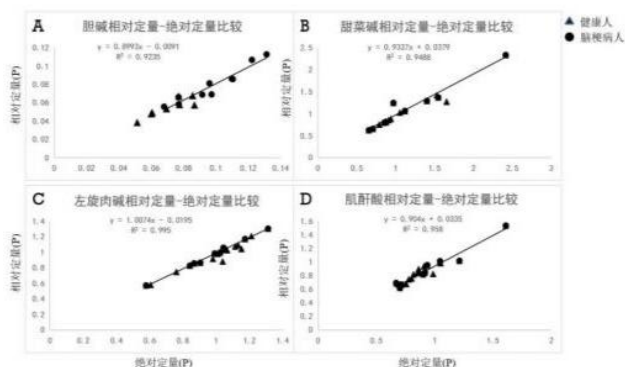


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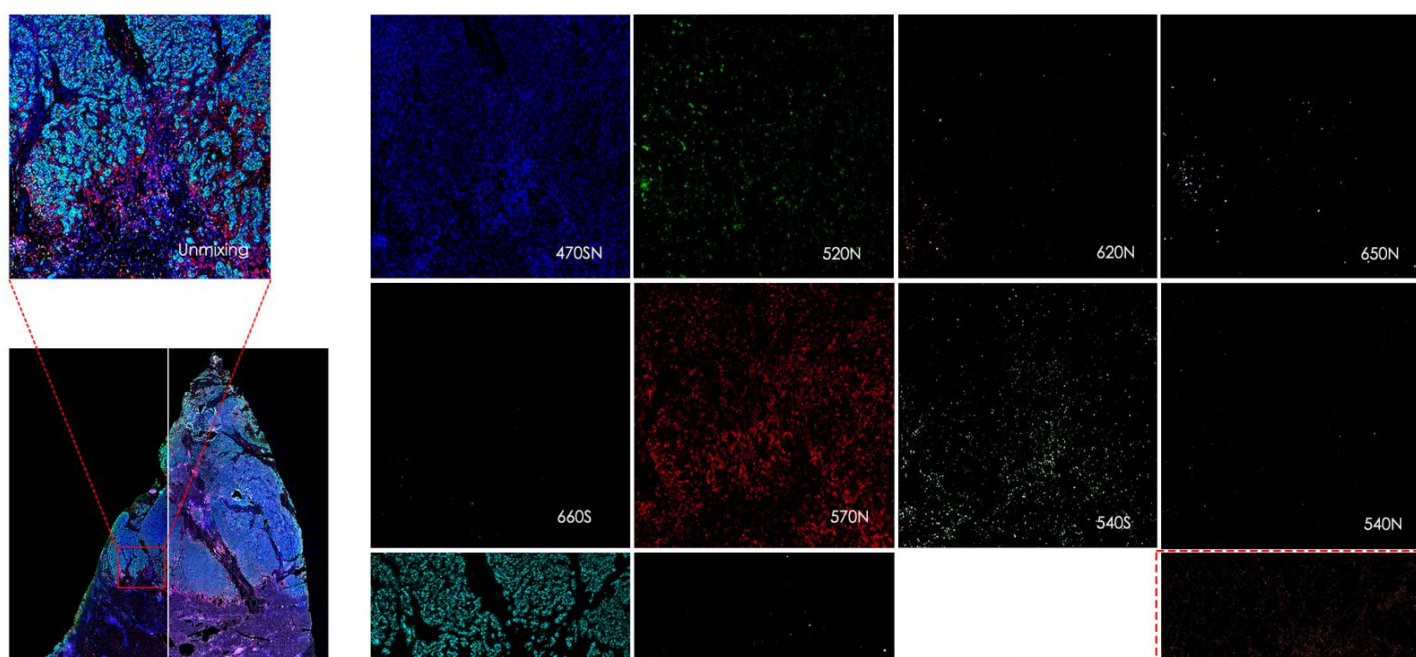
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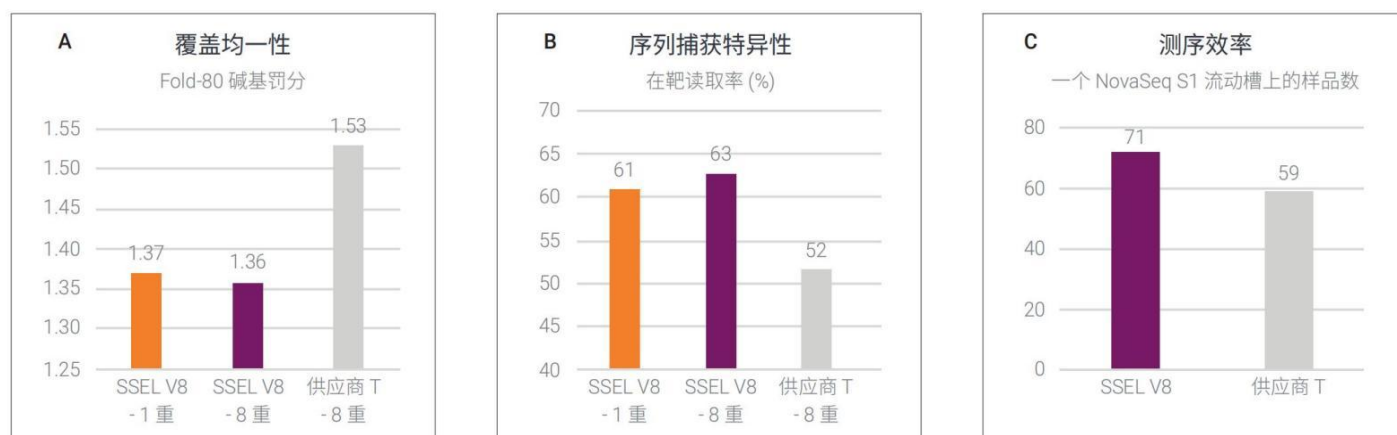
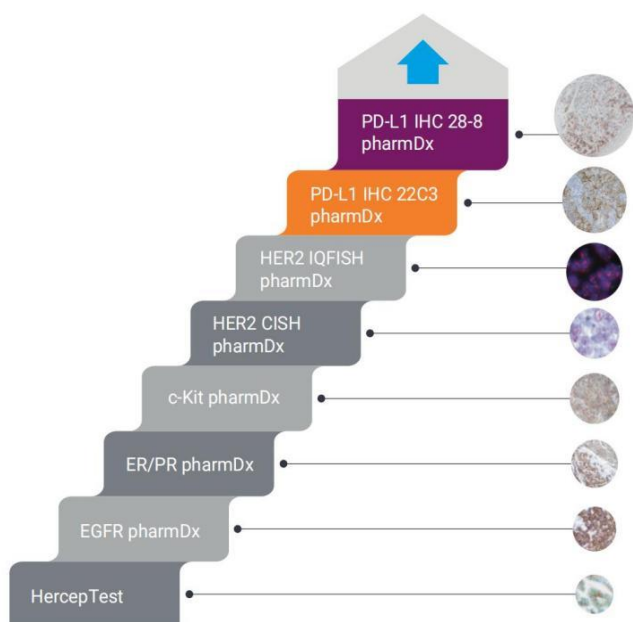


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