第二届免疫代谢前沿论坛

—免疫代谢与稳态和疾病

2024年8月3-4日 苏州

会议主办：中国免疫学会

免疫与炎症全国重点实验室

会议承办：免疫与炎症全国重点实验室

中国医学科学院系统医学研究院

会议日程

2024 年 8 月 3 日下午

14:00-14:15	开幕式	
Session 1　主持人　王　迪		
报告时间	**题目**	**报告人**
14:15~14:55	Journey of CD8+ T cells from naïveto memory	**黄　波** 中国医学科学院 北京协和医学院
14:55~15:35	风湿免疫病创新研究和新型干预技术	**张　烜** 北京医院 / 国家老年医学中心
15:35~15:50	合影　茶歇	
Session 2　主持人　周　洁		
15:50~16:20	New insights into the equilibrium between nutrient absorption and host defense in the small intestine	**王　迪** 浙江大学医学院
16:20~16:50	灵长类动物妊娠的多组织代谢组图谱	**黄仕强** 中国科学院动物研究所
16:50~17:20	Iron withholding maintained by FPN1 facilitates antiviral innate immunity	**赵　伟** 山东大学
17:20~17:50	树突状细胞迁移的代谢调控及自身免疫	**刘　娟** 海军军医大学免疫学研究所
17:50~18:20	ATP 合成酶的结构功能与药物发现	**贡红日** 南开大学生命科学学院
18:30~20:00	招待晚宴	

2024 年 8 月 4 日上午

Session 1　主持人　马瑜婷		
报告时间	**题目**	**报告人**
08:00~08:30	髓系细胞免疫代谢与新生儿炎症	**周　洁** 天津医科大学
08:30~09:00	内质网脂层平衡的代谢及免疫功能初探	**陈晓伟** 北京大学
09:00~09:30	脂滴与 2 型炎症反应	**徐和平** 西湖大学
09:30~09:45	茶歇	
Session 2　主持人　徐和平		
09:45~10:15	肠道菌源酶：免疫相关代谢性疾病的干预新靶标	**姜长涛** 北京大学
10:15~10:45	低密度脂蛋白吸收与胞内运输	**罗　婕** 武汉大学
10:45~11:15	帕金森病神经炎症中 RAGE 和 synuclein 纤维聚集体的相互作用	**李　丹** 上海交通大学 Bio-X 研究院
11:15~11:45	单细胞时空重构与人体免疫图谱的绘制	**任仙文** 昌平国家实验室

2024 年 8 月 4 日下午

Session 1　主持人　刘　娟		
报告时间	**题目**	**报告人**
14:00~14:40	氨基酸代谢与肿瘤微环境重塑	**王　平** 同济大学
14:40~15:10	应激重塑神经内分泌 - 免疫多维对话	**马瑜婷** 中国医学科学院系统医学研究院
15:10~15:40	糖代谢与肿瘤免疫	**邹　强** 上海交通大学医学院
15:40~15:55	茶歇	
Session 2　主持人　邹　强		
15:55~16:25	肿瘤微环境 NK 细胞失能的代谢机制	**郑小虎** 中国科学技术大学
16:25~16:55	肿瘤微环境 T 细胞代谢调控机制	**李贵登** 中国医学科学院系统医学研究院
16:55~17:25	T 细胞分化中的代谢调控	**黄宏龄** 厦门大学生命科学学院
17:25~17:55	记忆性 CD8+ T 细胞通过尿素和瓜氨酸循环解氨促进其发育的机制研究	**唐　科** 华中科技大学基础医学院

Session 3　海选口头报告　主持人　王　迪		
报告时间	题目	报告人
17:55~18:05	Cellular spermine targets JAK signaling to restrain cytokine-mediated autoimmunity	**徐贺楠** 中国医学科学院　北京协和医学院
18:05-18:15	琥珀酸维持 CD8+ T 细胞干性并增强其抗肿瘤免疫反应	**马凯丽** 免疫与炎症全国重点实验室
18:15-18:25	Zika Virus NS5 Protein Inhibits Type I Interferon Signaling via CRL3 E3 ubiquitin Ligase-Mediated Degradation of STAT2	**丁　强** 清华大学
18:25~18:30	最佳海选口头报告、优秀壁报颁奖	
18:30~18:40	闭幕总结	

黄波

■ 中国医学科学院 北京协和医学院

中国医学科学院北京协和医学院特聘教授。实验室围绕肿瘤免疫、免疫细胞的代谢、生物机械力信号、肿瘤休眠、肿瘤囊泡等前沿方向实施交叉研究，试图回答肿瘤、人体代谢变化、以及衰老的核心问题。作为通信作者在 Science、Sci Transl Med、Sci Immunol、Cancer Cell、Mol Cell、Nat Mater、Nat Immunol（4 篇）、Nat Cell Biol（3 篇）、Nat Biomed Eng（2 篇）等杂志上发表论文 90 多篇。完全自主研发的载药肿瘤囊泡 - 新型肿瘤免疫治疗技术已在临床应用，治疗癌性胸腹水及梗阻性胆管癌。

Journey of $CD8^+$ T cells from naïve to memory

T 细胞受抗原刺激而增殖，并活化为效应性 T 细胞，后者将抗原清除后，大部分死亡，仅一小部分存活为记忆性 T 细胞，当再次遇到相同抗原时，能够快速活化并产生更强的应答反应，此即为记忆反应。这一过程涉及记忆的形成与维持这一免疫学的核心问题。记忆的本质在于 T 细胞能够长期存活，而细胞只要生成能量，就能够一直存活。但是，伴随能量产生，两类有害的分子必然会出现，一类是活性氧 ROS（超氧阴离子、过氧化氢和羟自由基），另一类是氨气 NH3，它们的累积终将破坏 ATP 分子的产生，最终引发细胞死亡。因此，记忆性 T 细胞必须进化出特定代谢模式将这两种有害分子清除。我们的研究揭示记忆性 CD8+ T 细胞利用两条核心代谢通路分别对 ROS 和 NH3 进行解毒：（1）酮体代谢来源的 beta 羟基丁酸表观遗传激活 PCK1 的表达，PCK1 则驱动糖异生途径生成 6- 磷酸葡萄糖 G6P，G6P 流向糖原合成和分解再生成 G6P，而此时的 G6P

则可以流向磷酸戊糖途径产生 NADPH 将 ROS 清除；（2）记忆性 T 细胞以谷氨酰胺代谢产生 NH3，同时利用上述的 beta 羟基丁酰化的表观遗传诱导 CPS1 的表达，从而催化 NH3 和 CO2 产生氨基甲酰磷酸，启动鸟氨酸 - 尿素循环，同时还启动了瓜氨酸循环，以便最大限度地对 NH3 及时清除。我们的这些研究对 T 细胞记忆形成和维持提供了基本的理论认识。

张烜

■ 北京医院 / 国家老年医学中心

北京医院 / 国家老年医学中心副院长，中国医学科学院长聘教授兼临床免疫中心主任。长江学者特聘教授，国家杰出青年基金获得者，国家首批万人计划领军人才，国家卫生健康突出贡献中青年专家。兼任《Aging Med》《中国医学前沿杂志》主编，《Clin Immunol》、《SCLS》等副主编。国家临床重点专科学科带头人，从事临床 30 年，成功救治逾十万来自全国疑难危重风湿病患者。第 1 完成人获得中华医学科技奖 1、2 等奖和北京市科技进步奖 1 等奖。在《Nat Med》《Nat BE》《Nat Immunol》、《ARD》等国际 SCI 期刊发表论文近 300 篇，聚焦风湿免疫病机制和诊治。

风湿免疫病创新研究和新型干预技术

风湿免疫病（rheumatic & autoimmune diseases, RAD）中国有超 1 亿患者，致残和致死率高，给社会和家庭带来沉重负担。RAD 临床异质性高，发病机制复杂多样，目前临床常规治疗方法毒副作用大，且部分患者治疗反应性差，亟需寻找新型药物靶点和开发新型诊疗策略，并建立中国特色诊疗方案。目前我国 RAD 领域的研究方向主要围绕遗传易感、环境微生态、免疫耐受失衡新机制、新型生物标志物以及新型治疗手段 / 技术展开。

以解决国家重大健康问题为目的，从 RAD 关键新型机制研究入手，在疾病的发病机制、诊断以及新型治疗和早期干预策略方面能够有重大突破，重点解决如下重要科学

问题：

1. 解析遗传易感和环境微生态与宿主免疫互作在 RAD 中作用。阐明“宿主基因 - 微生态 - 免疫”在细胞死亡 / 免疫代谢 / 炎症风暴发生发展的关键性机制；

2. 挖掘和明确新型分子分型标志物，构建疾病异质性精准分层评价体系和诊疗标志物图谱；

3. 针对免疫代谢新靶点研发新型免疫干预手段 / 药物。将抗体药物修饰、CAR-T 等技术应用于 RAD 的治疗，并在 RAD 领域寻找廉价但有效的中西医结合中国治疗方案，推动研究者发起的高水平临床研究 (IIT), 减轻国家乃至全球在 RAD 诊治健康负担。

王迪

■ 浙江大学医学院

浙江大学求是特聘教授。浙江大学医学院副院长，感染与免疫研究中心主任。作为唯一和最后通讯作者在 Immunity，Science Immunology，Cell Metabolism，Molecular Cell，Developmental Cell 等学术杂志上发表论文多篇。获得国家杰出青年基金、优秀青年基金，教育部“青年长江学者”，浙江省“万人计划”科技创新领军人才，浙江省有突出贡献青年科技人才，药明康德生命化学研究学者奖，树兰医学青年奖等。中国生物化学与分子生物学会理事，中国细胞生物学学会免疫学分会、细胞代谢分会、细胞死亡研究分会委员。

New insights into the equilibrium between nutrient absorption and host defense in the small intestine

饮食营养和进食规律深刻地影响肠道和机体的稳态，进食紊乱往往导致肠道免疫失衡和炎症疾病发生。小肠极为复杂的“饮食 - 微生态 - 宿主”交互环境塑造了 " 营养代谢 - 区域免疫 - 屏障维持 " 协同调节机制。如何将进食营养整合到小肠的区域免疫调节，实现营养吸收和免疫防御功能的互调互稳和此消彼长（trade-off），是亟待解决的小肠生理核心问题。

黄仕强

■ 中国科学院动物研究所

中国科学院动物研究所研究员，博士生导师，国家自然科学基金重大研究计划重点支持项目负责人，科技部国家重点研发计划项目负责人。曾获中源协和生命医学创新突破奖，中国科学院年度创新人物，中国科学院杰出科技成就奖，HHMI International Scholar 霍华德休斯医学院国际学者等。在 Science、Nature、Cell、Cell Stem Cell、Cell Metabolism、Cell Reports 等期刊发表研究论文及综述 60 余篇，总引用次数过万。担任 Cell Prolif 期刊副编辑。

灵长类动物妊娠的多组织代谢组图谱

妊娠引起女性代谢的剧烈变化。然而，人们对这种复杂的代谢重编程仍然知之甚少，尤其是在灵长类动物中的胸腺萎缩及胎盘介导的免疫耐受。我们利用食蟹猴构建了一个全面的多组织代谢组图谱，分析了 23 个妊娠期母体组织的 273 个样本。我们发现，随着妊娠的进展，组织之间的代谢耦合会下降。在灵长类动物怀孕期间，核心代谢通路会重新连接，包括类固醇生成、脂肪酸代谢、以及花生四烯酸代谢。我们的图谱显示 23 种组织的 91 种妊娠适应性代谢产物持续变化，我们在人体细胞模型和患者样本中验证了其作用。皮质酮和棕榈酰肉碱分别调节胎盘成熟和母体组织祖细胞，与母体先兆子痫、糖尿病、心肌肥大以及肌肉和肝脏再生有关。此外，我们发现皮质酮缺乏会导致先兆子痫等疾病，因此图谱具有一定的临床价值。综上所述，我们的多组织代谢组图谱可以帮助阐明代谢调节在女性孕期健康中作用。

赵伟

■ 山东大学

山东大学特聘教授；国家杰出青年科学基金获得者；牛顿高级学者。从事病毒感染与固有免疫研究；相关成果以通讯作者发表于 Nat. Immunol.、Immunity、J.Exp.Med、J Clin Invest. 等杂志。现兼任中国微生物学会理事，山东微生物学会副理事长，山东免疫学会常务理事等。

Iron withholding maintained by FPN1 facilitates antiviral innate immunity

限铁机制通过阻止病原微生物铁的获取，在机体抗感染中发挥重要作用。然而，病毒如何破坏免疫细胞内铁稳态从而实现免疫逃逸、以及破坏限铁机制多固有免疫活化有何影响，尚不清楚。我们发现病毒感染通过上调巨噬细胞 E3 泛素连接酶 DTX3L 表达，促进铁外排受体 FPN1 的泛素化降解，破坏限铁机制，导致细胞内铁过度积累。铁离子促进 STING 豉基化和 TBK1 羟基化修饰，抑制 I 型干扰素表达和自噬，促进病毒免疫逃逸。Fpn1 缺陷抑制了 TBK1 和 STING 依赖的抗病毒固有免疫，促进病毒复制；而 Dtx3l 则相反。该研究揭示了病毒感染通过破坏宿主限铁机制实现免疫逃逸的机制，阐释了 FPN1 维持的细胞内铁稳态在抗病毒固有免疫活化中的重要作用。

刘娟

■ 海军军医大学免疫学研究所

海军军医大学免疫学研究所暨免疫与炎症全国重点实验室教授、课题组长、博士生导师。入选国家优青（2016）、青年长江学者（2021）、首届青年人才托举工程（2015）、军队青年科技英才（2022），担任国家重点研发计划青年项目首席科学家（2023）。主要从事树突状细胞功能的代谢调控及自身免疫性疾病发病机制研究。相相关成果以第一或通讯作者在 Nature Immunology、Immunity（3 篇）、Cell Research、Cell Reports、Journal of Autoimmunity、Nature Communications、PNAS 等期刊发表 18 篇论文，影响因子总分 284 分，单篇最高 44 分，总引用 1600 余次。研究成果入选 2014 年高校十大科技进展。授权国家发明专利 4 项。担任 Natl Sci Rev 青年编委。

树突状细胞迁移的代谢调控及自身免疫

自身免疫性疾病是严重威胁国民健康的重大医学难题，树突状细胞（DC）功能紊乱被证实与多种自身免疫性疾病密切相关。然而目前对于 DC 在自身免疫性疾病发生发展中的细胞和分子机制缺乏深入了解，严重阻碍了对于疾病本质的认识及新型临床预防及治疗手段的开发。因此，阐明 DC 在疾病发生发展的免疫学机制将有助于阐明众多自身免疫性疾病的本质规律，对于推动疾病诊断治疗具有重大的理论意义及实际应用价值。本人及课题组聚焦 DC 功能调控和自身免疫性疾病分子机制研究，发现胆固醇代谢物 FPP 调控的线粒体融合对于增强 DC 迁移及活化进而促发自身免疫性疾病进展发挥重要作用。研究结果阐明了自身免疫性疾病发展过程中 DC 及其依赖的免疫微环境的功能重塑规律，为 DC 相关炎症性疾病和自身免疫性疾病提供新的机制解释和治疗思路。

贡红日

■ 南开大学生命科学学院

南开大学生命科学学院教授。从事能量生物学研究，主持国家优秀青年科学基金项目和国家重点研发计划青年科学家项目，相关研究成果发表在 Science, Molecular Cell, Nature Communications, PNAS, eLife 等杂志，先后担任自然科学基金委会议评审专家、深医专项会议评审专家、“中国科学十大进展”终选专家等。

ATP 合成酶的结构功能与药物发现

氧化磷酸化系统是维持细胞活动的主要能量来源。对于引起肺结核的结核分枝杆菌而言，氧化磷酸化系统不仅是维持自身生长必需的能量代谢系统，还起到在宿主巨噬细胞内的免疫调控作用。人源氧化磷酸化系统相关基因的表达异常、突变与肿瘤的发生发展等病理过程密切相关。近年，结核分枝杆菌的氧化磷酸化系统已经成为新兴的药物靶点，当前被世界卫生组织列为耐利福平结核病和耐多药结核病长程治疗方案的首选药物贝达喹啉正是通过靶向结核分枝杆菌 ATP 合成酶发挥杀菌活性。人源 ATP 合成酶被证实是白血病、阿尔茨海默、心肌缺血再灌注损伤等疾病的潜在药物靶点。本报告将简要地汇报结核分枝杆菌和人源线粒体氧化磷酸化系统蛋白复合物结构功能的多样性和保守性，详细地介绍课题组近年针对 ATP 合成酶开展的一些已发表和未发表的研究工作。

周洁

■ 天津医科大学

天津医科大学基础医学院教授，国家杰青，天津市免疫学会理事长。主要研究肠道及肺脏等黏膜组织的免疫调节机制，为相应炎症性疾病的免疫干预提供新策略。近年以最后通讯作者在 Immunity、Nature Medicine、Nature Metabolism、Journal of Experimental Medicine、Journal of Clinical Investigation、PNAS、Blood 等知名学术期刊发表论文 40 余篇。

髓系细胞免疫代谢与新生儿炎症

Disruption of circadian rhythm during pregnancy produces adverse health outcomes in offspring. However, the role of maternal circadian rhythm in the immune system development in early life remains poorly understood. We reported that circadian rhythms disruption (CRD) in pregnant mice profoundly aggravated the severity of neonatal inflammatory disorders, such as necrotizing enterocolitis (NEC) and sepsis. The impaired immunosuppressive function of neonatal myeloid-derived suppressor cells (MDSCs) contributed to this phenomenon. Mechanistically, breast milk derived docosahexaenoic acid (DHA) enhanced the immunosuppressive function of MDSCs via PPARγ-mediated mitochondrial oxidative phosphorylation, which was diminished upon maternal CRD. Perinatal supplementation of DHA or transfer of MDSCs caused remission of neonatal inflammation in maternal CRD model. These observations uncover previously unrecognized role of maternal rhythms in the control of neonatal inflammation.

陈晓伟

■ 北京大学

北京大学未来技术学院教授，致力研究糖脂代谢调控及其相关的心血管疾病。获得中国海外高层次人才计划（青年）、国家杰出青年基金支持；担任中国生物物理学会副监事长，中国生理学会常务理事，代谢生物学分会副秘书长；当选 Biochemical Journal 副主编及 Life Metabolism, Journal of Lipid Research, Cell Metabolism 编委。

内质网脂层平衡的代谢及免疫功能初探

由磷脂双层膜构成的生物膜是生命的根本特征，其合成与组装定位于内质网，并存在初始的“不平衡性”：磷脂分子的合成局限于单侧脂层，故必需借助高效的翻转酶实现跨膜转运，从而实现膜 - 脂平衡。我们前期发现 TMEM41B 为上述磷脂翻转酶，其缺失导致脂层失衡、代谢重塑及炎症风暴，可综合为“脂层不平衡反应”。进一步工作发现代谢应激、病毒感染、免疫和衰老等过程中，均可诱发内质网脂层不平衡，提示了磷脂翻转酶家族作为维持脂层平衡的“效应器”，或需与特定的“感应器”偶联，从而响应不同生理信号或病理应激，精准维持脂层的动态平衡。阐明该新颖通路生理功能及病理后果，或可为 NASH 等代谢性重大疾病提供潜在生物标志物和治疗靶点。

徐和平

■ 西湖大学

西湖大学研究员，实验室的研究兴趣在于解析脑膜、肠道等屏障组织中神经、代谢系统信号对免疫稳态和炎症反应的调节作用，以期为开发具有组织器官特异性靶向的精准免疫治疗奠定基础。团队近 5 年相关研究成果发表于 Science、Immunity 以及 Nature Immunology 等主流期刊。研究项目获得国家自然基金委杰出青年项目、科技部重点研发计划等项目支持。

脂滴与 2 型炎症反应

2 型炎症反应是人体抵抗寄生虫及其他胞外微生物感染的重要保护性免疫过程。然而，过度活跃的 2 型炎症也与哮喘、食物过敏等过敏性疾病的发生相关。过敏性疾病在全球发病率呈急剧上升趋势，但目前仍缺乏有效的根治手段。2 型先天样淋巴细胞（group 2 innate lymphoid cell, ILC2）是一类能够快速大量分泌 2 型炎症细胞因子的先天免疫细胞。已有研究显示，ILC2 的异常应答与过敏性疾病的发生发展有密切关联，但其活性调节机制仍待进一步阐明。我们课题组近期研究发现细胞内脂滴代谢与 ILC2 的活化及功能密切相关。本报告将首先介绍转录因子 RXR γ 通过控制细胞内的脂滴含量来调节 ILC2 的应答阈值其在肠道过敏反应中的作用，然后汇报脂滴介导 ILC2 招募下游炎性细胞浸润呼吸道的新功能。

姜长涛

■ 北京大学

北京大学教授，基础医学院副院长，免疫学系主任，国家杰青、科学探索奖获得者。从事肠道共生菌与免疫相关代谢性疾病的研究。首创“肠道菌源酶跨物种调控宿主稳态”新理论。近 5 年在 Cell（2024）、Science（2023）、Nature（2022）等杂志发表 SCI 论文二十余篇，入选 Cell Metabolism 杂志编委。获授权发明专利 7 项。获得 2023 年度中国生命科学十大进展、北京市自然科学一等奖（第一完成人）、中国青年科技奖、谈家桢生命科学创新奖、树兰医学青年奖等奖励。

肠道菌源酶：免疫相关代谢性疾病的干预新靶标

菌源酶是肠道菌群的核心功能分子，我们前期工作揭示菌源特征酶对疾病的关键作用，我们发现肠道菌群与宿主的长期共进化导致了与宿主相同功能的菌源酶的存在，提出“肠道菌源宿主同工酶”的新概念，并建立高通量同工酶筛选体系，发现其广泛存在且能跨物种调控宿主疾病进程；其中菌源 DPP4 可分泌进入体内，降解 GLP-1，诱导血糖稳态失衡。宿主 DPP4 抑制剂西格列汀无法抑制菌源 DPP4 活性，导致了西格列汀临床响应性的个体化差异，通过筛选得到高选择性菌源 DPP4 抑制剂 Dau-d4，显著改善糖尿病，为靶向肠道菌群精准干预疾病开辟了全新方向。此外，我们近期工作发现肠道菌群对胆汁酸的全新修饰类型—3- 酰基化修饰，阐明其在免疫代谢性疾病的保护作用与分子机制，并解析其全新的生物合成通路。

罗婕

■ 武汉大学

武汉大学生命科学学院教授，泰康生命医学中心 PI，免疫与代谢前沿科学中心 PI。教育部青年长江学者，湖北省杰青。主要从事胆固醇代谢调控机制及相关疾病遗传致病机制研究。研究成果发表于 Nature Cell Biology，Circulation，Journal of Cell Biology，Arteriosclerosis, Thrombosis, and Vascular Biology 等重要学术期刊。

低密度脂蛋白吸收与胞内运输

低密度脂蛋白（LDL）是人血液中胆固醇含量最多的脂蛋白颗粒，大部分会被位于肝脏及肝外组织细胞表面的低密度脂蛋白受体（LDLR）识别并内吞，从而从血浆中清除。血液过高的 LDL 水平是心脑血管疾病的关键危险因素之一。我们长期聚焦 LDL 吸收与胞内运输调控，鉴定出可诱导肝脏 LDLR 蛋白降解的新因子血浆激肽释放酶原 PK，发现抑制 PK 可有效降低血液 LDL 水平，减缓动脉粥样硬化和血栓形成。我们还通过全基因组筛选，发现线粒体磷脂酶 PLD6 可促进 LDL/LDLR 囊泡与线粒体发生融合，LDL 进入线粒体以提供胆固醇用于合成甾醇激素这一全新路径；并鉴定出脂肪酸结合蛋白家族部分成员可帮助 LDL 来源的胆固醇在细胞内运输，揭示了一类全新的甾醇转运蛋白。以上工作为免疫细胞胆固醇代谢和肿瘤细胞胆固醇重编程研究提供了新视角和思路。

李丹

■ 上海交通大学 Bio-X 研究院

上海交通大学 Bio-X 研究院教授。博士毕业于北京大学，之后在美国加州大学洛杉矶分校从事博士后研究，2017 年加入上海交通大学，主要从事神经退行性疾病和蛋白聚集研究。课题组聚焦蛋白稳态调控、相分离和聚集与疾病关系，揭示了多种神经退行性疾病关键致病蛋白质相分离的生物学功能和相变产生的淀粉样聚集的致病和调控机制。近年发表文章包括：Cell, Nat. Chem. Biol., NSMB, Nat. Commun.,Cell Res. 等，受邀为 Cell，Nature Rev. Neurosci., ALZForum 等国际一流期刊和媒体撰写专家评论、综述、展望科研发展方向等。获得中组部万人计划青年拔尖、上海高校特聘教授（东方学者）、上海市浦江人才荣誉称号。

帕金森病神经炎症中 RAGE 和 α-synuclein 纤维聚集体的相互作用

小胶质细胞介导的神经炎症和 α - 突触核蛋白（α -syn）聚集作为帕金森病（PD）的病理标志，其相互作用能够加剧多巴胺能神经元的退化和 PD 的进展。然而，它们相互作用的机制尚不清楚，这阻碍了有效地抑制 α -syn 引起的神经炎症的治疗。我们从基于结构的互作预测开始，发现 RAGE 是 α -syn 纤维在小胶质细胞上的受体。核磁共振（NMR）光谱和突变体验证了 RAGE 表面的带正电荷区域可以与 α -syn 的带负电荷 C 末端区域相结合。此外，α -syn 纤维与 RAGE 的结合可以诱导神经炎症，这一发现可以通过基因敲除和抑制剂 FPS-ZM1 的阻断作用加以验证。我们的工作显示了 RAGE 在介导小胶质细胞对 α -syn 纤维的炎症反应中的重要作用及其结构机制，这可能有助于建立有效的治疗策略，以减轻 α -syn 引起的神经炎症和神经元损伤。

任仙文

■ 昌平国家实验室

昌平实验室研究员，国家优青。主要从事基于单细胞与空间组测序的计算免疫学研究，代表性算法包括 STARTRAC、CSOmap、PhenoAligner、Redeconve 等，以通讯作者或第一作者在 Cell、Cancer Cell、Cell Research、Gut、Blood、Nature Communications 等期刊发表论文 40 多篇，曾获得中国生物信息学十大进展、高等院校优秀科学技术成果奖一等奖、北京市自然科学一等奖等、中源协和生命医学创新突破奖等荣誉。

单细胞时空重构与人体免疫图谱的绘制

人体有多种不同的组织器官构成，各自具有不同的免疫属性。例如，脾脏是专职免疫器官，脑与睾丸具有血脑屏障、血睾屏障具有免疫豁免的特征。然而，由于技术条件的限制，系统刻画人体不同组织器官的免疫组成与特征仍然是极为困难的。任仙文研究员在前期肿瘤免疫与感染免疫的研究基础上，基于自主开发的单细胞时空重构算法，通过数据整合与解析，构建了覆盖人体 30 多种不同组织器官、大于 10000 个样本、超过 1000 种不同免疫细胞类型与状态的高精度人体免疫地图。该免疫图谱不仅揭示了不同组织器官独特的免疫组成，而且刻画了不同组织器官之间的免疫联系、随年龄与性别的变化。对睾丸与肺等具体组织的精细分析，揭示了各器官独特的共性免疫特征与潜在的代谢调控因素。

王平

■ 同济大学

同济大学特聘教授，博导；国家重点研发计划项目首席科学家。先后获得国家基金委杰青、优青、“长江学者”特聘教授等。王平教授多年来从事肿瘤微环境调控机制与靶向研究，目前借助全基因组筛选及多组学技术，1）解析肿瘤细胞营养感应机制，研究营养代谢紊乱对肿瘤细胞命运的调控，如铁死亡等，并开发干预策略；2）通过研究肿瘤细胞与微环境免疫细胞相互作用，解析肿瘤逃逸免疫调控机制，开发微环境重塑新策略及干预手段；3）解析肿瘤微环境受机体宏环境调控机制，开发精准饮食治疗肿瘤新策略。先后在 Nature、Cancer Cell、Molecular Cell、J Exp. Med.、Nature Communications、Developmental Cell 等知名期刊上发表学术论文 70 余篇；申请或授权发明专利 15 项。作为项目负责人先后承担国家级、省部级、校院级项目等 30 余项。

氨基酸代谢与肿瘤微环境重塑

免疫检查点抑制剂（ICIs）的出现迅速改变了多种癌症类型的治疗模式。然而，不可忽视的是，只有少数患者实现了 ICIs 的长期、持久的反应，而耐药性是大多数患者的不幸经历。因此，如何实现免疫治疗药物的增敏性是肿瘤治疗的重要方向。cGAS-STING 信号通路在机体识别细胞质 DNA 并起始 I 型干扰素介导的抗肿瘤免疫反应中发挥重要作用。通过一系列体外和在体筛选实验，我们发现甲基化和泛素化

修饰调控 cGAS-STING 通路重塑肿瘤免疫微环境的重要机制：1）微环境甲硫氨酸促进 cGAS 甲基化导致其染色质栓系的活性自抑制，阻断干扰素信号通路，导致肿瘤免疫逃逸，并提出甲硫氨酸饮食限制或者靶向甲基化修饰酶系统能有效促进抗肿瘤免疫（Cancer Cell, 2023）；2）在体筛选发现 IFN γ 诱导泛素机器 UBE2L6-RNF19A 泛素化 cGAS 抑制其活性，在 IFN γ 抵抗和免疫治疗耐受中的生物学功能（manuscript prepared）。

马瑜婷

■ 中国医学科学院系统医学研究院

巴黎十一大学博士，北京协和医学院博导，中国医学科学院系统医学研究院执行副院长，聚焦于解析多重应激对免疫应答的调控机制，在 Nat Med、Nat Rev Immunol、Science 等学术期刊发表论文 60 篇，SCI 他引 9900 余次，入选斯坦福大学发布的全球前 2% 顶尖科学家榜单，国家万人计划科技创新领军人才、国家海外高层次人才，享受国务院特殊津贴，主持承担科技创新 2030 重大项目、国自然优青等，曾获中国青年女科学家奖、中国肿瘤青年科学家奖、钟南山青年科技创新奖等。

应激重塑神经内分泌 - 免疫多维对话

The widespread nervous system and immune system can perceive and respond to internal and external stimuli and their interaction is crucial for regulating various pathophysiological processes. We have particular interest in stress-induced neurological and endocrine alterations, which can generate a number of stress-associated immunomodulatory molecules (SAIMs) and regulate immune response against cancer and infection. SAIMs can engage corresponding receptors on immune cells to switch on signalling transduction and transcriptomic changes. Moreover, stress leads to systemic or local metabolic reprogramming and change the composition of the gastrointestinal microbiota, which indirectly modulate anti-tumour immunity via SAIMs. We have nailed down some stress-featured metabolites, their cellular or microbial sources and key sensors on immune cells. Also, we have identified some immune cell subsets as unexpected sources of SAIMs, which can reshape the immune microenvironment and macroenvironment.

邹强

■ 上海交通大学医学院

国家杰青，上海交通大学基础医学院副院长，肿瘤系统医学全国重点实验室副主任，上海市免疫学研究所资深研究员。课题组围绕肿瘤免疫的代谢调控，研究机体系统代谢对肿瘤免疫应答与耐受的调控机制，解析调控 T 细胞介导肿瘤免疫的糖代谢通路，揭示代谢产物影响肿瘤免疫的分子机理，研究成果以最后通讯作者身份发表于 Immunity、Cell Metabolism、Molecular Cell、JCI、JEM 等杂志。主持国家自然科学基金杰青、重点、优青、面上项目等，荣获上海市卫生健康系统第十九届“银蛇奖”二等奖等。

糖代谢与肿瘤免疫

围绕代谢产物乳酸对肿瘤免疫的影响，研究团队发现乳酸介导 CTLA-4 的 RNA 剪接以维持 Treg 细胞免疫抑制功能的机制。研究发现肿瘤浸润 Treg 细胞通过乳酸转运受体 MCT1 摄取乳酸，促进 Foxp3 的表达，进而促进剪接体关键组分 USP39 的转录及表达。USP39 对于 mRNA 前体(pre-mRNA)剪接和成熟至关重要，通过转录组测序分析，研究团队发现 USP39 特异性调控 Ctla4 pre-mRNA 的剪接，促进 Treg 细胞中 CTLA-4 的表达。借助多种小鼠模型及生信分析等，发现 Treg 细胞中乳酸转运受体 MCT1 特异性缺失的荷瘤小鼠无法响应 CTLA-4 单抗治疗。研

究团队进一步分析结直肠癌患者外周 Treg 细胞和肿瘤浸润 Treg 细胞发现，USP39 的表达和 CTLA4 pre-mRNA 剪接效率在 Treg 细胞浸润至肿瘤微环境后被显著上调。研究成果阐明了肿瘤浸润 Treg 细胞中“乳酸 -Foxp3-USP39-CTLA-4”信号轴介导 CTLA-4 高表达的分子机制，揭示了代谢产物乳酸影响肿瘤免疫治疗疗效的作用机制。

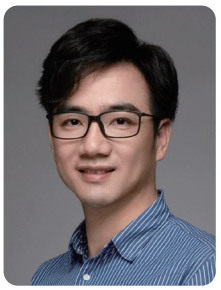
郑小虎

■ 中国科学技术大学

中国科学技术大学生命科学与医学部，免疫应答与免疫治疗重点实验室，中国科学技术大学免疫学研究所教授，独立 PI，博士生导师，国家优青，安徽省杰青。2015 年博士毕业于中国科学技术大学，毕业后留校工作至今。主要从事 NK 细胞与肿瘤免疫微环境研究，相关成果以（共）通讯发表在 Nat Immunol、Clinic Cancer Res、J Hematol Oncol、Cell Mol Immunol 等学术期刊，主持基金委专项、面上等项目，获中国免疫学会青年学者奖。

肿瘤微环境 NK 细胞失能的代谢机制

肿瘤区域独特的生态环境，比如低氧、代谢异常等因素形成肿瘤免疫应答和免疫治疗的微环境障碍，其存在会诱导浸润的效应免疫细胞出现耗竭、死亡等失能状态，肿瘤微环境障碍是目前免疫检查点治疗响应性低的重要原因。NK（Natural Killer）细胞与 T 细胞同为机体杀灭肿瘤两大主要淋巴细胞，作为天然杀伤细胞，NK 细胞具有应答迅速、抑瘤谱广、普适性好等优势，但其发现较晚，了解较少。亟需聚焦肿瘤独特生态环境，解析 NK 细胞失能的机理和关键介导分子，提出全新免疫干预策略。我们已经证实低氧、代谢失调等独特的肿瘤生态环境特征是驱使 NK 细胞失能的重要诱因；其次是发现 NK 细胞接收独特微环境信号的抑制性受体 A3AR，CD300A 等，并初步证实 Drp1 等代谢调控分子异常激活导致线粒体断裂，使得 NK 细胞走向功能失常状态。



李贵登

■ 中国医学科学院系统医学研究院

苏州系统医学研究所研究员。专注探究肿瘤 T 细胞免疫的分子机理，开发新型肿瘤免疫治疗技术和方法。曾入选国家高层次青年人才项目。近几年来作为通讯作者 / 共同通讯作者在 Nature Metabolism (2023，封面文章)、Nature Reviews Immunology (2019) 等国际期刊上发表多篇文章。目前担任中国免疫学会肿瘤免疫与生物治疗分会委员，国自然基金项目和国家重点研发计划评审专家等。

肿瘤微环境 T 细胞代谢调控机制

T 细胞免疫疗法改变了癌症的治疗模式。然而，只有少部分实体瘤患者从中获益。其中，免疫抑制性的微环境是导致 T 细胞免疫疗法受限制的主要因素。酸性肿瘤微环境是实体瘤的显著特征之一，目前已有研究表明酸性微环境能显著削弱 T 细胞的浸润能力，抑制 T 细胞的效应功能并影响其他免疫细胞活性及分化。然而，对于酸性微环境调控 T 细胞浸润的分子机制及是否参与调控 T 细胞分化，目前尚不清楚。

我们发现酸性微环境可通过抑制 METTL3 的表达 , 削弱整合素分子 ITGB1 mRNA 水平的 m6A 修饰，抑制伪足小体的形成，最终阻碍 T 细胞向肿瘤内部浸润。同时，

我们的研究还发现长期的酸性微环境暴露能够抑制 T 细胞内 MYC-SLC7A5 轴，阻碍 T 细胞的甲硫氨酸摄入，进而重编程 T 细胞内的一碳代谢及表观遗传图谱，促进线粒体代谢适应性，最终维持干性 T 细胞状态。这些研究不仅揭示了酸性微环境抑制 T 细胞浸润的分子机制，而且还发现了其在 T 细胞抗肿瘤免疫反应中扮演的新角色，从而为进一步理解酸性肿瘤微环境与 T 细胞浸润以及功能分化之间的联系提供了更深入的认识和思考。

黄宏龄

■ 厦门大学生命科学学院

厦门大学生命科学学院教授，国家青年高层次人才，福建省闽江特聘教授。长期从事 T 细胞分化及功能的分子机制研究，研究成果以第一作者或共同第一作者发表在 Cell、Nature（2022，2023）、EMBO J 等杂志。承担科技部重点研发计划（任子课题负责人）、国家基金委重大（任项目骨干）、国家基金委面上（任课题负责人）等科研项目。

T 细胞分化中的代谢调控

T 细胞是介导适应性免疫以及肿瘤免疫的核心细胞类群，其生理功能与自身的分化状态密切相关。利用多组学整合的方式，我们揭示了岩藻糖代谢通路调控记忆性 T 细胞新亚群命运分化的机制，提出了抑制代谢通路增效抗病毒免疫的新方法；发现了染色质重构复合体通过整合氨基酸 -mTOR-Myc 轴调节 T 细胞不对称分裂的现象，揭示了短暂抑制染色质重构复合体增效 CAR-T 实体瘤治疗的方案；开发了应用于肿瘤浸润 T 细胞内的单细胞 CRISPR 筛选平台，揭示了肿瘤浸润 T 细胞的新分化路径。我们的研究有助于了解免疫调控及耐受的底层机制并以此为基础开发新的免疫治疗策略。

唐科

■ 华中科技大学基础医学院

华中科技大学基础医学院生物化学与分子生物学系教授，博士生导师。长期从事肿瘤免疫中关键细胞群体（T 细胞和肿瘤干细胞）等方面的研究工作，致力于新型肿瘤免疫生物治疗技术的开发与临床转化。近五年来以第一 / 通讯作者在 Nature Immunology、Nature Cell Biology、Cellular & Molecular Immunology、Cancer Research 和 Cancer immunology research 等杂志发表多篇论文。主持国自然优秀青年科学基金项目，指南引导类“肿瘤免疫与代谢”原创探索项目和国家重点研发计划子课题等。获得中国免疫学会 " 青年学者奖”、中国科协“青年人才托举工程”和湖北省首届“青年拔尖人才”等荣誉，现为中国免疫协会肿瘤免疫与生物治疗分会委员。

记忆性 $CD8^+$ T 细胞通过尿素和瓜氨酸循环解氨促进其发育的机制研究

细胞利用 ATP 分子提供能量，葡萄糖和脂肪酸氧化是生成 ATP 的主要来源。此外，氨基酸在脱氨基后也可以被氧化以提供或调节能量生成。然而，在 ATP 生产过程中，会产生活性氧 (ROS) 和氨 (NH3) 副产品，这两种物质都可能具有细胞毒性，并限制细胞寿命。因此，长寿细胞需要发展出清除活性氧和氨的机制。记忆 T (Tm) 细胞是一种典型的长寿细胞类型。在之前的研究中，课题组已经揭示了记忆 T 细胞如何清除 ROS，然而 $CD8^+$ Tm 细胞是否能通过代谢清除有毒的氨仍然是未解之谜。

传统观念认为尿素循环只发生在肝脏，但课题组通过构建特异性抗原记忆性 T 细胞体内过继模型、同位素示踪技术和超高分辨液相质谱联用等方法首次证明了尿素循环存在于记忆 T 细胞中并发挥重要功能，并通过一系列动物模型和体外机制分析验证了尿素循环对 Tm 细胞记忆维持是必须的。在后续研究中课题组进一步发现与传统的尿素循环通过精氨酸酶 1 产生尿素不同的是，$CD8^+$ Tm 细胞利用定位于线粒体的精氨酸酶 2 催化精氨酸生成尿素，并进一步研究了精氨酸和尿素分别通过 SLC25A29 和 SLC14A1 两种溶质蛋白转运体进出线粒体。深入的机制研究还发现，$CD8^+$ Tm 细胞还利用瓜氨酸循环进行解氨作用，与尿素循环联合发挥作用。此外，课题组利用多种动物模型验证了尿素循环关键酶 Cps1 的基因表达对 Tm 细胞氨处理和记忆维持至关重要，并利用表观遗传学手段发现 Cps1 转录启动子区域 β - 羟基丁酰化是诱发 Cps1 表达的关键。最后在体内肿瘤治疗模型中，Cps1 高表达的 Tm 细胞也显示出更高效的抗肿瘤功能，为 T 细胞回输的免疫治疗提供了全新的代谢调控思路，有着明确的临床转化意义。本项研究将使我们从全新的代谢角度阐明 Tm 细胞长期存活的机制，并将提供一种全新的 T 细胞抗肿瘤思路和转化手段。

青年口头报告

海报、汇编

海选青年口头报告

Cellular spermine targets JAK signaling to restrain cytokine-mediated autoimmunity

Henan Xu[1, 2], **Xuetao Cao**[1, 2, 3]

1. Department of Immunology, Center for Immunotherapy, Institute of Basic Medical Sciences, Peking Union Medical College, Chinese Academy of Medical Sciences, Beijing, China;
2. Frontiers Research Center for Cell Responses, Institute of Immunology, College of Life Sciences, Nankai University, Tianjin, China;
3. National Key Laboratory of Immunity and Inflammation, Institute of Immunology, Navy Medical University, Shangha, China

Prolonged activation of the type I interferon (IFN-I) pathway leads to autoimmune diseases such as systemic lupus erythematosus (SLE). Metabolic regulation of cytokine signaling is critical for cellular homeostasis. Through metabolomics analyses of IFN-b-activated macrophages and an IFN-stimulated-response-element reporter screening, we identified spermine as a metabolite brake for Janus kinase (JAK) signaling. Spermine directly bound to the FERM and SH2 domains of JAK1 to impair JAK1-cytokine receptor interaction, thus broadly suppressing JAK1 phosphorylation triggered by cytokines IFN-I, IFN-II, interleukin (IL)-2, and IL-6. Peripheral blood mononuclear cells from individuals with SLE showing decreased spermine concentrations exhibited enhanced IFN-I and lupus gene signatures. Spermine treatment attenuated autoimmune pathogenesis in SLE and psoriasis mice and reduced IFN-I signaling in monocytes from individuals with SLE. We synthesized a spermine derivative, named SD1, and showed that it had a potent immunosuppressive function. Our findings reveal spermine as ametabolic checkpoint for cellular homeostasis and a potential immunosuppressive molecule for controlling autoimmune disease.

Zika Virus NS5 Protein Inhibits Type I Interferon Signaling via CRL3 E3 ubiquitin Ligase-Mediated Degradation of STAT2

Qiang Ding*

Tsinghua University
Corresponding Author E-mail: qding@tsinghua.edu.cn

The ZIKA virus (ZIKV) evades the host immune response by targeting human STAT2 for degradation through its NS5 protein, thereby inhibiting type I interferon (IFN)-mediated antiviral immunity. However, the molecular mechanism underlying this process has remained elusive. In this study, we performed a genome-wide CRISPR/Cas9 screen, revealing that ZSWIM8 as the substrate receptor of Cullin3-RING E3 ligase is required for NS5-mediated STAT2 degradation. Genetic depletion of ZSWIM8 and CUL3 substantially impeded NS5-mediated STAT2 degradation. Biochemical analysis illuminated that NS5 enhances the interaction between STAT2 and the ZSWIM8-CUL3 E3 ligase complex, thereby facilitating STAT2 ubiquitination. Moreover, ZSWIM8 knockout endowed A549 and Huh7 cells with partial resistance to ZIKV infection and protected cells from the cytopathic effects induced by ZIKV, which was attributed to the restoration of STAT2 levels and the activation of IFN signaling. Subsequent studies in a physiologically relevant model, utilizing human neural progenitor cells (hNPCs), demonstrated that ZSWIM8 depletion reduced ZIKV infection, resulting from enhanced IFN signaling attributed to the sustained levels of STAT2. Our findings shed light on the role of ZIKV NS5, serving as the scaffold protein, reprograms the ZSWIM8-CUL3 E3 ligase complex to orchestrate STAT2 proteasome-dependent degradation, thereby facilitating evasion of IFN antiviral signaling. Our study provides novel insights into ZIKV-host interactions and holds promise for the development of antivirals and prophylactic vaccines.

Key Words Flavivirus; ZIKV; NS5; Antiviral immunity; STAT2; Cullin3

琥珀酸维持 CD8$^+$ T 细胞干性并增强其抗肿瘤免疫反应

马凯丽 [1,2]，**张连军** [1,2,*]

1 免疫与炎症全国重点实验室，中国医学科学院苏州系统医学研究所

2. 中国医学科学院合成生物学调控元件重点实验室

通讯作者：张连军，zlj@ism.cams.cn

肿瘤抗原特异性 CD8$^+$ T 细胞是杀伤肿瘤的主要免疫细胞亚群，但肿瘤抑制性微环境往往诱导 CD8$^+$ T 细胞功能耗竭，极大限制了 T 细胞的抗肿瘤免疫反应。肿瘤抗原特异性 CD8$^+$ T 细胞的耗竭分化具有高度异质性，受微环境中的代谢压力调控。琥珀酸作为线粒体三羧酸（TCA）循环代谢的重要中间产物，在琥珀酸脱氢酶（SDH）失能突变的肿瘤中大量富集，但琥珀酸对 CD8$^+$ T 细胞介导的肿瘤免疫反应作用还一直存在争议。我们研究发现：SDH 突变肿瘤中 CD8$^+$ T 细胞对 PD-L1 阻断抗体疗法的响应增强，且高琥珀酸盐处理显著增强 T 细胞线粒体代谢竞争力，并诱导干性分化关键基因如 Tcf7 等附近的组蛋白甲基化修饰改变，促进 CD8$^+$ T 细胞的干性表型，进而提高其体内长效抗肿瘤能力和响应免疫检查点治疗能力，指示琥珀酸富集参与调控 T 细胞分化命运及其介导的抗肿瘤免疫反应。与此一致的是，我们观察到琥珀酸富集型肿瘤相关基因与临床上免疫检查点治疗响应效率正相关，提示琥珀酸富集可能改善免疫疗法治疗效率，为突破临床上 T 细胞免疫治疗响应率低、体内持久性差的瓶颈难题提供了新的思路。

海报

Glutamine synthetase limits tumor growth of b-catenin-mutated liver cancers by maintaining nitrogen homeostasis

Weiwei Dai*

Xi'an Jiaotong-Liverpool University
Corresponding Author E-mail: weiwei.dai@xjtlu.edu.cn

Glutamine synthetase (GS) catalyzes de novo synthesis of glutamine that facilitates cancer cell growth. In the liver, GS functions to remove ammonia waste next to the urea cycle. As dysregulated urea cycle is implicated in cancer development, the impact of GS' ammonia clearance function has not been explored in cancer. Here we show that, oncogenic activation of b-catenin leads to decreased urea cycle and elevated ammonia waste burden. While b-catenin induces the expression of GS, which is thought to be cancer-promoting, surprisingly, genetic ablation of hepatic GS accelerates the onset of liver tumors in several mouse models that involve b-catenin activation. Mechanistically, GS ablation exacerbates hyperammonemia and facilitates the production of glutamate-derived alanine, which subsequently stimulates mTORC1. Pharmacological and genetic inhibition of mTORC1 and glutamic-pyruvic transaminase (alanine transaminase) suppresses tumorigenesis facilitated by GS ablation. While HCC patients, especially those with CTNNB1 mutations, have an overall defective urea cycle and increased expression of GS, there exists a subset of patients with low GS expression that is associated with mTORC1 hyperactivation. Therefore, GS-mediated ammonia clearance serves as a tumor-suppressing mechanism in livers that harbor b-catenin activation mutations and a compromised urea cycle.

Key Words Glutamine synthetase; b-Catenin; liver cancer; ammonia; mTORC1

Engineering bacteria for Cancer Immunotherapy by Inhibiting IDO activity and Reprogramming CD8+ T cells Response

Heng Wang,Chao Wang*

Institute of Functional Nano & Soft Materials (FUNSOM), Soochow University
Corresponding Author E-mail: cwang@suda.edu.cn

Inhibiting indoleamine 2,3-dioxygenase (IDO) for anticancer therapy has garnered significant attention in recent years. However, current IDO inhibitors face significant challenges which limit their clinical application. Here, we genetically engineered a high tryptophan-expressing CB (L-Trp CB) strain that can colonize tumors strictly following systemic administration. We revealed that butyrate produced by L-Trp CB can inhibit IDO activity, preventing tryptophan catabolism and kynurenine accumulation in tumors. In addition, the large released tryptophan by L-Trp CB can provide discrete signals that support CD8+ T-cell activation and energy metabolism within the TME. We observed that L-Trp CB significantly restored the proportion and function of CD8+ T cells, leading to significantly delayed tumor growth in both mouse and rabbit multiple tumor models with limited side effects. Additionally, this effect is CD8+ T-cell dependent rather than CD4+ T-cell dependent. We here provide a synthetic biology treatment strategy for enhanced tumor immunotherapy by inhibiting IDO activity and reprogramming CD8+ T cell response in tumors.

Key Words IDO, Tryptophan, Engineering bacteria, T cell response

PVN microglia mediate hemodynamic signal transmitting and act as an early sympathetic neuronal excitation promoter in hypertension

Bo Wei [1,2], Guo Cheng [1,2], Xiaoli Liu [3], Xiao Z. Shen [1,4,5], Peng Shi [1,2]

1 Department of Cardiology of the Second Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, Zhejiang, China, 310009
2 Institute of Translational Medicine, Zhejiang University School of Medicine, Hangzhou, Zhejiang, China, 310058
3 Department of Neurology, Affiliated Zhejiang Hospital, Zhejiang University School of Medicine, Hangzhou, China, 310013
4 Brain Center, Affiliated Zhejiang Hospital, Zhejiang University School of Medicine, Hangzhou, China, 310013
5 Department of Physiology, Zhejiang University School of Medicine, Hangzhou 310058, China

Hypertension is usually accompanied with an elevated sympathetic tonicity, but how sympathetic overactivation is initially triggered has not fully understood. Recent advances reveal that microgliacentered neuroinflammation contribute to sympathetic excitation in hypertension. In this study, we investigated how microglial activation is associated with pre-sympathetic neuronal activation in the paraventricular nucleus (PVN) in the early stage of hypertension. We did a temporospatial analysis of plasma ATP, microglia and PVN pre-sympathetic neuronal activity along L-NMAE- or Ang II- hypertension development. Hypertension elicited a significant increase of ATP both in the plasma and brain parenchyma, and this blood-derived ATP promoted microglial accumulation and activation in the PVN mediated by microglial P2Y12 receptors. PVN is susceptible to the penetration of ATP released from the vasculature in response to hemodynamic disturbance after blood pressure increase. What's more, we found that the ATP ligation to microglial $P2Y_{12}$ receptor is responsible for the microglial accumulation and activation in the PVN.

Dihydroartemisinin breaks the positive feedback loop of YAP1 and GLUT1-mediated aerobic glycolysis to boost the CD8$^+$ effector T cells in hepatocellular carcinoma

Yuting Gao[1,2,†], Yi Gong[1,2,†], Junlan Lu[1,2], Yanguang Yang[1,2], Yuman Zhang[1,2], Yajun Xiong[1], Xinli Shi[1,2*]

[1] Laboratory of Integrated Medicine Tumor Immunology, Shanxi University of Chinese Medicine, Taiyuan 030000, China
[2] Department of Pathobiology and Immunology, Hebei University of Chinese Medicine, Shijiazhuang, 050200, China
*** Corresponding author**
E-mail address: shixinli@sxtcm.edu.cn (Xinli Shi).
[†]These authors contributed equally to this work.

Aerobic glycolysis is a hallmark of hepatocellular carcinoma (HCC). Dihydroartemisinin (DHA) exhibits antitumor activity towards liver cancer. Our previous studies have shown that DHA inhibits the Warburg effect in HCC cells. However, the mechanism still needs to be clarified. Our study aimed to elucidate the interaction between YAP1 and GLUT1-mediated aerobic glycolysis in HCC cells and focused on the underlying mechanisms of DHA inhibiting aerobic glycolysis in HCC cells. In this study, we confirmed that inhibition of YAP1 expression lowers GLUT1-mediated aerobic glycolysis in HCC cells and enhances the activity of CD8$^+$T cells in the tumor niche. Then, we found that DHA was bound to cellular YAP1 in HCC cells. *YAP1* knockdown inhibited GLUT1-mediated aerobic glycolysis, whereas *YAP1* overexpression promoted GLUT1-mediated aerobic glycolysis in HCC cells. Notably, liver-specific *Yap1* knockout by AAV8-TBG-Cre suppressed HIF-1α and GLUT1 expression in tumors but not para-tumors in DEN/TCPOBOP-induced HCC mice. Even more crucial is that YAP1 forms a positive feedback loop with GLUT1-mediated aerobic glycolysis, which is associated with HIF-1α in HCC cells. Finally, DHA reduced GLUT1-aerobic glycolysis in HCC cells through YAP1 and prevented the binding of YAP1 and HIF-1α. Collectively, our study revealed the mechanism of DHA inhibiting glycolysis in HCC cells from a perspective of a positive feedback loop involving YAP1 and GLUT1 mediated-aerobic glycolysis and provided a feasible therapeutic strategy for targeting enhanced aerobic glycolysis in HCC.

Keywords: dihydroartemisinin, hepatocellular carcinoma, GLUT1-mediated aerobic glycolysis, YAP1, CD8$^+$ T cells

肝星状细胞在慢性肝损伤中的异质性研究

周婉梅、施意、罗骁、赵怡、刘辉 *
广州医科大学附属第五医院
通讯作者邮箱：liuhui806@gzhmu.edu.cn

目的

慢性肝病是全球主要的疾病负担之一，严重影响患者生活质量、增加并发症和死亡率。而持续的肝脏炎症是慢性肝脏疾病进展的一个重要因素。Mallory-Denk bodies（马洛里小体，MDBs）是发生在慢性肝细胞损伤中的一种炎症聚集物。肝脏慢性炎症刺激肝星状细胞（HSC）活化，活化的肝星状细胞（aHSC）通过肝肿瘤微环境（TME）中的旁分泌串扰和基质细胞蛋白会促进肝细胞损伤，引起 MDBs 病理性形成。本文通过构建小鼠慢性肝损伤模型，运用单细胞测序探讨 HSC 在 MDBs 病理形成中的异质性和分子机制，为慢性肝病的发病机制和防治提供新思路。

方法

通过饲喂小鼠 0.1% 的 1,4- 二氢 -2,4,6- 三甲基 -3,5- 吡啶脱甲酸二乙酯（DDC）10 周构建慢性肝损伤模型，之后撤去 DDC1 月，再重新饲喂 1 周。运用单细胞核 RNA 测序对已形成 MDBs 的小鼠模型进行测序，分析 HSC 在 MDBs 病理性形成过程中的分子机制。之后通过运用生物信息学和分子生物学方法分析 HSC 在 MDBs 形成及慢性肝损伤中的异质性，最后通过体内外实验验证亚群中关键分子可能对慢性肝损伤产生的作用。

结果

为了探索肝脏 MDBs 病理形成机制，我们分析了动物模型，通过单细胞核测序结果显示，HSC 细胞在 4 组样本中共有 2792 个细胞，通过 t-SNE 识别成 4 个不同的细胞簇，依据细胞簇自身的特征命名为 aHSC、qHSC、Mmp14-Bmp2+ 和 Mmp14-IL7r+。根据

t-SNE 图得出 aHSC 和 Mmp14-IL7r+ 亚群在喂药后细胞明显增多，之后对亚群特异性基因进行分析，并通过 GO 分析表明含胶原的细胞外基质（ECM）明显增多，而 aHSC 亚群中的特异性基因 Itgbl1 上调暗示其与 ECM 形成密切相关。随后通过 KEGG 分析表明 PI3K-AKT 炎症信号通路在 aHSC 中富集增多。Western Blot 结果表明在小鼠四组样本中 AKT 和 IκB 在喂药后都显著上调，证明 PI3K-AKT 炎症信号通路在慢性肝损伤后被激活。

结论

本文首次报道了 HSC 在 MDBs 形成过程中发现了新的亚群 aHSC，并且发生了功能重塑。单细胞测序结果 KEGG 和 GO 分析显示在新发现的亚群中可能有重要蛋白和关键 PI3K-AKT 炎症信号通路调控 MDBs 病理性形成。这一发现阐明了 HSC 在肝脏 MDBs 与肝脏炎症形成的新机制，可能成为后续慢性肝损伤发病机制的新靶点，为慢性肝病的防治提供新思路。

关键字 慢性肝损伤；肝星状细胞；炎症；MDBs；

TGF-β/TGF-βR Ⅱ轴通过调控 c-JUN 激活在慢性肝损伤中的作用研究

施意、周婉梅、赵怡、罗骁、刘辉*
广州医科大学附属第五医院
通讯作者邮箱：liuhui806@gzhmu.edu.cn

目的

作为危害人类健康的主要病因之一，慢性肝病的发病机制一直是肝脏病因学研 究的难点。肝脏马洛里、小体（Mallory-Denk Bodies，MDBs）作为慢性肝损伤中与炎症相关的肝脏蛋白聚集体，存在于各种慢性肝脏疾病包括肝癌中。因此研究 MDBs 发生机制对于慢性肝病发病机制与防治具有重要意义。转化生长因子 β（TGF-β) 作为一种强大的炎症免疫反应调节器，在炎症过程中可以诱导肝巨噬细胞释放不 同的生长因子和炎症介质，起到推动炎症 反应级联放大的作用。本文通过构建二乙基 -1,4- 二氢 -2,4,6- 三甲基 -3,5- 吡啶二 羧酸（DDC）诱导小鼠肝脏 MDBs 形成的病理模型以探究 TGF- β 介导的信号在 MDBs 形成中的作用，为慢性肝脏疾病治疗和防治提供新的药物靶点和理论依据。

方法

实验小鼠通过 0.1%DDC 诱导小鼠约 10 周形成 MDBs 基础上（DDC-Fed），后撤药 1 月（DDC-Withdrawn），MDBs 消失，再重新喂药 6 到 1 天，MDBs 快速形成（DDC-Refed）。同时，对照小鼠喂养正常饮食。进一步我们将上述四组小鼠肝脏取材、制备成单细胞悬液进行单细胞核测序和生物信息学分析，随后利用小鼠组织和血清进 行 ELISA、Wetern Blot 等体内外实验进行验证。

结果

单细胞测序数据分析表明，在 MDBs 形成过程中，肝细胞 - 巨噬细胞配受体对

TGF-β/TGF-βRII 轴在 DDC-Fed、DDC-Refed 组中显著富集，且 GSVA 分析显示 TGF- β 信号通路在喂药组中也明显激活。转录因子分析结果显示 c-JUN 在 DDC-Fed 与 DDC-Refed 组中明显上调。体外实验结果表明，DDC 喂养 10w 后的小鼠血清中 TGF-β1 分泌明显增多。Western blot 结果表明，与对照组相比，在形成 MDBs 后的小鼠肝脏组织中，TGF-βRII 受体显著激活，而且 c-JUN 的蛋白水平同步上调。

结论

本文首次报道肝脏 MDB 形成过程 TGF-β/TGF-βRII 轴信号通路调控的紧密关系，且 TGF-β 信号通路及下游分子在 DDC 诱导 的肝脏 MDBs 形成过程中明显激活。这对进一步探索肝脏 MDB 形成慢性肝病发病机制与防治具 有重要意义。

关键字 慢性肝损伤；MDB；单细胞核测序

Shenqi Fuzheng Injection Modulates Tumor Fatty Acid Metabolism to Downregulate MDSCs Infiltration, Enhancing PD-L1 Antibody Inhibition of Intracranial Growth in Melanoma

Yanan Qi*

Bengbu Medical university
Corresponding Author E-mail: 357605178@qq.com

Objective: To substantiate the regulatory effects of Shenqi Fuzheng Injection (SFI) on the microenvironment of melanoma brain metastases and appraise whether SFI augments the anti-tumour effects of immune checkpoint inhibitors, with a specific focus on investigating the mechanisms underlying SFI's actions.

Methods: Initially, we established a B16-F10 brain transplant tumour model in C57BL/6 mice using a stereotaxic apparatus. The efficacy of the drug was evaluated through in vivo imaging technology, HE staining, and immunofluorescence. Mass Cytometry (CyTOF) and flow cytometry were employed to analyse the impact of SFI on immune cell subpopulations in the tumour microenvironment. Subsequently, transcriptome sequencing and metabolomics were utilised to examine the effects of SFI on melanoma-related genes and metabolism. Molecular docking, Western Blot, and ELISA assays were conducted to investigate the targets of SFI in intervening in melanoma fatty acid metabolism. Finally, the anti-tumour effects of SFI in combination with immune checkpoint inhibitors were scrutinised in the brain transplant tumour model.

Results: The pharmacological findings demonstrated that SFI inhibits the growth of melanoma brain transplant tumours in a dose-dependent manner. CyTOF, flow cytometry, and immunofluorescence results revealed that SFI significantly diminishes the levels of Myeloid-Derived Suppressor Cells (MDSCs) and Regulatory T cells (Tregs) in the tumour microenvironment while enhancing the levels of CD8+ T and CD4+ T cells. Subsequently, transcriptomic and metabolomic findings, both in vitro and in vivo, indicate that SFI significantly inhibits the arachidonic acid metabolism process in melanoma cells. Molecular docking and biological experiments showed that SFI inhibits the expression of D6D and the activity of COX-2, leading to a reduction in downstream PGE2 production. Lastly, SFI significantly enhances the anti-tumour effects of PD-L1 antibody against intracranial melanoma.

Conclusion: SFI improves the tumour immune microenvironment in melanoma by intervening in fatty acid metabolism, thereby reducing levels of MDSCs and Tregs while increasing levels of CD8+ T and CD4+ T cells. Ultimately, this augmentation leads to enhanced anti-tumour effects of the immune checkpoint inhibitor PD-L1 antibody.

Key Words Shenqi Fuzheng injection; Melanoma; Fatty acid metabolism; MDSCs; PD-L1; immune checkpoint inhibition

整合素 - 脂质代谢信号回路调控巨噬细胞参与过度炎症反应及肝衰竭的新机制

杨晶 *
江南大学
通讯作者邮箱：jingcpu@126.com

单核 / 巨噬细胞系统的过度激活是肝衰竭发病的中心环节，靶向巨噬细胞过度激活已成为肝衰竭药物开发的新方向。我们首先建立建立 ConA“二次打击”诱导的 ALF 模型，给予肝素类化合物治疗后，发现肝素类药物预处理可以显著减少肝衰竭小鼠肝脏坏死面积，降低全身炎症反应，显现出预防 / 治疗肝衰竭的潜力。接着，对肝衰竭小鼠肝组织基因组学和体外模拟肝衰竭微环境刺激巨噬细胞活化模型基因组学数据挖掘，发现巨噬细胞表面整合素家族表达量显著升高，其中 ITGB3 最为显著。荧光染色也证实 ITGB3+ 巨噬细胞是肝衰竭时肝脏巨噬细胞的优势群体。重要的是，肝素可降低肝脏 ITGB3+ 巨噬细胞数量、抑制全身炎症反应及随后的肺损伤；进一步转录组学分析发现肝素可以调控多条与脂质代谢相关的信号通路，如类固醇生物合成、脂肪酸代谢等信号通路；非靶标脂质组学显示，肝素类化合物调控多种脂质代谢产物的变化，其中胆固醇类（CE）、脂肪酸类（FA）脂质下调明显。因此，肝素类化合物可以通过调控巨噬细胞功能转化从而抑制其过度激活发挥遏制肝衰竭的作用。

关键字 肝素；肝衰竭；巨噬细胞；整合素；脂质代谢

Akkermansia muciniphila alleviates Hashimoto's thyroiditis through γδT cells

Lei Wang,Wanwei Yang,Jianfeng Shi,Zhiguo Wang,Xiaoming Yao*

Jiangsu Province Academy of Traditional Chinese Medicine
Corresponding Author E-mail: wlei@nju.edu.cn

Hashimoto's thyroiditis (HT) is the most common organ specific autoimmune disease affecting hundreds and thousands of individuals worldwide. Like other autoimmune diseases, environmental effectors, such as diet and infections, interacting with genetic predispositions are accounted for its occurring/developing with unknown mechanism.

Herein, we showed that in a HT-like mouse model, a disease-causing immune-stress induced by subcutaneous injections of pig thyroglobulin (pTG) resulted in a significant gut microbiota alteration and imbalanced gut immunity, in addition to typical HT-like leisures in testing animals. Conversely, manipulations of gut microbiota significantly ameliorated or aggravated the phenotype of the disease. Bioinformatics singled out one bacterial specie Akkermansia muciniphila (A. muciniphila) that delivered beneficial effect on HT. A. Muciniphila intervention effectively reduced the γδT cells in the mesenteric lymph nodes, peripheral blood and thyroid tissues of HT mice, The IL-17+ γδT cells of mesenteric lymph nodes in HT mice were significantly reduced whereas foxp3+γδT cells were not affected.

To further verify the crucial role of γδT cells in the pathogenesis of HT, we used Tcrd - / - mice in the B6 background to observe whether the HT model was alleviated by knocking out γδT cells. The data showed that the level of mononuclear cell infiltration, CD45 immunohistochemically staining and chemokine levels in thyroid tissues after HT were significantly lower in Tcrd - / - group than those in the HT group. In addition, serum autoantibodies were decreased obviously in the Tcrd - / - group compared with those in the HT group. Flow cytometry analysis showed that the populations of CD11c + DCs， CD80 + CD11c + DCs and CD86 + CD11c + DCs were significantly decreased in the spleen and mesenteric lymph nodes of the Tcrd - / - group compared with the HT group. We analyzed the Tfh and germinal center B cells by flow cytometry in Tcrd-/- and Tcrd+/-mice. Consistent with the decreased levels of serum antibodies, there was statistical decrease in germinal center B cell (CD19+Fas+GL-7+) and Tfh cell (CD4+PD-1+CXCR5+) proportions and numbers in the spleen and mesenteric lymph nodes between the Tcrd - / - group and the HT group. We next wanted to determine whether the gut microbiota was different between two groups, 16s rDNA analysis of intestinal contents of mice indicated that the abundance of AKK increased compared with the HT group. These results demonstrated that γδT cell subset play an important role in the pathogenesis of HT.

Our discovery has expanded the current understanding of the occurrence/development mechanism of HT, and enriched the knowledge of the interaction between the host and intestinal immunity and intestinal flora in the regulation of autoimmune diseases by A. muciniphila.

Key Words Akkermansia muciniphila ;Hashimoto's thyroiditis（HT）; γδT cells

Met-Flow: A New Method for Metabolic Detection

Juan Du*

碧迪医疗卓越中心Centre of excellence(COE)
Corresponding Author E-mail: juan.du2@bd.com

Cell metabolism refers to the collective term for all organized chemical reactions within a cell. In recent years, research on cell metabolism has been prolific. Studies indicate a close relationship between cell metabolism and the development of various diseases. Met-Flow is a novel method for detecting cell metabolism based on flow cytometry, targeting key proteins or rate-limiting enzymes in multiple metabolic pathways of cells. Coupled with multicolor flow cytometry, it allows for precise subtyping of immune cells to understand changes in metabolic states among these different cell subsets during immune responses. In this poster, we utilized flow cytometry to assess metabolic markers in peripheral blood mononuclear cell (PBMC) samples, aiming to simplify metabolic detection methodologies and fill the gap in metabolic detection techniques at the single-cell level.

Key Words Metabolism, Flow Cytometry, Single-cell

Circ_0005704 aggravates URSA via sponging miR-26a-5p to promote trophoblast autophagy

Lihua Li[1],Sha Ai[2],Xiaoxiao Fu[1],Bin Wang[2],Xiaoyan Yu[3],Qiaoqiao Han[3],Chu Chu[1],Xinkui Liu[1],Miaomiao Zhou[1],Xiaoxiao Zhu[1],Feifei Shi[1],Fang Li[1],Zhen Zhang[1],Xia Li*[1]

1. 山东中医药大学

2. 山东中医药大学附属医院

3. 上海交通大学

Corresponding Author E-mail: 60230033@sdutcm.edu.cn

Background: Recurrent spontaneous abortion refers to three or more consecutive spontaneous abortions occurring within 20 weeks' gestation, with an incidence about 3%~5% of women of childbearing age. In addition to chromosome, physiological anatomical factors and so on, there are about 50% of unexplained miscarriage, called unexplained recurrent spontaneous abortion (URSA), which means one of the most intractable clinical challenges in reproduction. Excessive trophoblast cells autophagy was found to be involved in URSA, but the underlying mechanisms remains unclear. Here, targeting the circ_0005704/miR-26a-5p/ULK1 signaling axis to regulate trophoblast cells autophagy may become an effective target and approach for the treatment of URSA.

Methods: The villus tissues of normal pregnancy and patients with URSA were collected. Transmission electron microscopy (TEM) was used to detect the autophagy of the villus tissues. Immunofluorescence (IF) method was used to detect the localization of ULK1 in the villus tissues. The expression of ULK1 mRNA in villus tissue was detected by quantitative real-time polymerase chain reaction (qRT-PCR). Western blotting was used to detect the levels of ULK1, P62, LC3II/I autophagy-related proteins in villus tissue. URSA mice models were established, and the effects of ULK1 inhibitor on trophoblast autophagy and the occurrence of URSA were observed by in vivo. The miRNA microarray kit performs whole-transcriptome high-throughput detection of RNAs extracted from PBMC, combined with bioinformatics analysis to screen the upstream regulated miRNAs of ULK1; the dual-luciferase reporter gene system was used to detect the direct relationship between miR-26a-5p and ULK1 mRNA combine. The expression of miR-26a-5p was regulated in HTR-8/SVneo, and its effect on ULK1 and autophagy was observed. Whole transcriptome high-throughput screening and bioinformatics software to predict upstream regulatory circRNAs of miR-26a-5p; combined with RNA pull-down assay, RNA Binding Protein Immunoprecipitation (RIP) and dual luciferase reporter gene system to verify that circ_0005704 directly binds to miR-26a-5p. The effects of circ_0005704/miR-26a-5p/ULK1 axis on cell migration and invasion were observed in the human trophoblast cell line HTR-8/SVneo. We verify the role and function of this mechanism through in vivo and in vitro experiments.

Results: Compared with NP group, expression and levels of ULK1 and circ_0005704 in villous tissues of URSA patients were significantly increased, while miR-26a-5p was significantly decreased, and negatively correlated with ULK1 mRNA and circ-0005704. Double luciferase reporter gene system showed that miR-26a-5p could

be directly combined with ULK1 mRNA 3'UTR, and miR-26a-5p could combined with circ_0005704. RNA pull-down and RNA immunoprecipitation (RIP) experiments confirmed the sponge adsorption of circ_0005704 and miR-26a-5p. Up-regulation of miR-26a-5p expression in HTR-8/SVneo can significantly inhibit the expression of ULK1 protein and LC3II/I ratio, and significantly promote the expression of P62, while down-regulation of miR-26a-5p had the opposite effect. Transwell assay revealed that overexpressing circ-0005704 promotes trophoblast cells autophagy via miR-26a-5p/ULK1 axis and impedes trophoblast cells migration and invasion. Up-regulation of circ-0005704 expression can significantly promote autophagy in vitro and in vivo.

Conclusion: The increased expression of circ_0005704 and the up-regulation of ULK1 expression may lead to excessive autophagy in trophoblast cells, which may be an important mechanism for the occurrence of URSA.

Key Words Unexplained Recurrent Spontaneous Abortion, circular RNA, autophagy, trophoblast

NAT10 promotes endothelial ferroptosis through increasing the ac4C modification of HMOX1 in Deep vein thrombosis

Yunhong Zhang[1],Zhen Zhang[1],Chu Chu[1],Nannan Fan[1],Tingting Zhang Zhang[1],Huiyan Zu[1],Bin Wang[1,2],Xia Li*[1]

1. Shandong University of Traditional Chinese Medicine
2. Affiliated Hospital of Shandong University of Traditional Chinese Medicine
Corresponding Author E-mail: 60230033@sdutcm.edu.cn

Deep vein thrombosis (DVT) is associated with abnormal epigenetic processes and aberrant gene expression that is a common peripheral vascular disease. In this study, ferroptosis is involved in DVT by the CHIP and 4D Label Free, but the underlying mechanism remains unclear. Here, it is revealed that N4-acetylcytidine (ac4C), a newly identified mRNA modification, aggravates ferroptosis in endothelial cells. Specifically, N-acetyltransferase 10 (NAT10) is involved in ferroptosis and is highly expressed in injured vascular tissues, but its role in thrombosis has not been determined. To investigate the role of NAT10 in endothelial ferroptosis, various detection approaches were used to determine the ferroptosis-related cellular iron content, lipid reactive oxygen species, siRNA molecules, RNA immunocoprecipitation (RIP), acRIP-sequence, ac4C dot blotting assay, and western blotting. The role of NAT10 in ferroptosis was validated in HUVECs induced with the ferroptosis activator RSL3 or FINO2 and counteracted by the NAT10 inhibitor Remodelin in vitro. Additionally, endothelial cell-specific conditional NAT10 deficiency (NAT10flox/flox/Cdh5-CreERT) mice can reduce endothelial ferroptosis and inhibit the formation and progression of DVT. In addition, NAT10 induced the ac4C modification of HMOX1, increasing its stability and translation, which subsequently repressed the anti-ferroptotic gene GPX4. Collectively, our data elucidate a new avenue through which down-regulated NAT10 reduces endothelial ferroptosis and inhibits DVT formation and progression by inhibiting HMOX1 expression.

Key Words Deep venous thrombosis, NAT10, ac4C, Ferroptosis, HMOX1

miR-126-5p protects from URSA via inhibiting Caspase-1-dependent pyroptosis of trophoblast cells

Xiaoxiao Zhu[1],Ke Xu[1],Chu Chu[1],Zhen Zhang[1],Yunhong Zhang[1],Lihua Li[1],Yonglin Liu[1],Bin Wang[2],Xia Li*[1]

1. Shandong University of Traditional Chinese Medicine
2. Affiliated Hospital of Shandong University of Traditional Chinese Medicine
Corresponding Author E-mail: 60230033@sdutcm.edu.cn

Background: Unexplained recurrent spontaneous abortion (URSA) is a distressing pregnancy complication that seriously affects the physical and psychological health of women. Normal pregnancy (NP) depends on the successful establishment and maintenance of maternal fetal immune tolerance. Trophoblast cells play an important role in the establishment of immune tolerance microenvironment. Dysfunction of human trophoblast cells leading to immunological tolerance imbalance is an important cause for the occurrence of URSA. Pyroptosis is a newly discovered programmed death of cells in recent years and excessive pyroptosis may cause unconscionable and sustained inflammatory reactions. This study intends to explore the role of miR-126-5p/Caspase-1-mediated trophoblast cells pyroptosis in the formation of URSA. The results will provide new targets and approaches for URSA treatment.

Methods: The differentially expressed genes and proteins in the villous tissue of URSA patients and NP women were analyzed by RNA seq and 4D Label free quantitative proteomics. Gene Ontology (GO) enrichment analysis was performed on differentially expressed genes and proteins. The expression of CASP1 mRNA in the villous tissues was detected by quantitative real-time polymerase chain reaction (qRT-PCR). The expression of Caspase-1 total protein and activation level, Gasdermin D (GSDMD) and active fragment GSDMD-N protein in the villous tissues was detected by Western blot. The expression of interleukin-1β (IL-1β) and interleukin-18 (IL-18) in serum was detected using Enzyme-linked immunosorbent assay (ELISA). RNA seq was used to detect miRNAs in villous tissue of 3 NP women and 3 URSA patients, and combined with biological information analysis to screen the upstream regulatory miRNAs of CASP1. Double luciferase reporter gene system were used to confirm the direct binding of miR-126-5p with CASP1 mRNA 3'UTR. In vivo experiments were conducted to observe the effects of pyroptosis inhibitor, Caspase-1 inhibitor, mouse Caspase-1 overexpression plasmid, miR-126-5p mimics, miR-126-5p inhibitor and negative control on trophoblastpyroptosis and URSA. qRT-PCR, Western blot and ELISA were used to analyze the effect and molecular mechanism of miR-126-5p/Caspase-1/GSDMD signal axis on URSA.

Results: In this study, RNA seq and 4D Label free quantitative proteomics revealed that both the mRNA and protein levels of CASP1 and the level of pyroptosis were upregulated in the villous tissues of URSA patients. Inhibited cell pyroptosis by pyroptosis inhibitor and Caspase-1 inhibitor can reduce embryo resorption rate of URSA mice, while promoting Caspase-1 expression in NP mice can upregulate embryo resorption. We also found that miR-126-5p expression significantly decreased in URSA patients and negatively correlated with CASP1 mRNA. Overexpression of miR-126-5p suppressed trophoblast pyroptosis via inhibiting Caspase-1/GSDMD signaling pathway by direct binding to CASP1 3'-UTR and vice versa. Moreover, experiments in vivo

substantiated that upregulation of miR-126-5p effectively suppressed Caspase-1-mediated pyroptosis in placental tissue and significantly reduced embryo resorption rate.

Conclusion: The diminished of miR-126-5p plays a crucial role in URSA by enhancing trophoblast pyroptosis through activating Caspase-1/GSDMD signaling pathway. Consequently, miR-126-5p possess great prospects as a potential diagnostic marker and therapeutic target for URSA.

Key Words Unexplained recurrent spontaneous abortion, Pyroptosis, miR-126-5p, Caspase-1, Trophoblast

高脂饲养小鼠结肠癌免疫治疗效果受限的机制研究

王淑艺[1]，袁豪华[1]，陈双会[1]，周生文[1]，聂瑛洁[2*]，李林照[1*]
1 贵州省贵阳市贵州大学医学院，贵州 贵阳 550025
2 香港大学深圳医院，广东 深圳 518053

1. 背景

随着现代社会的发展、人们生活水平的提高和生活方式的变化，肥胖的发生率逐年升高，截止 2019 年，我国成年人中近一半的人群（48.9%）患有超重或肥胖。已有研究发现，结直肠癌（CRC）等一系列恶性肿瘤的发病率与肥胖存在显著关联，同时，BMI 与免疫治疗效果之间的关系在不同的癌症类型中存在差异。我们前期研究发现，在高脂饲养小鼠的结肠癌模型中，肿瘤免疫治疗效果受到显著抑制。基于此，我们将探索肥胖与结肠癌免疫治疗之间的关系，研究其可能存在的机制，为未来癌症的精准治疗提供理论支撑。

2. 材料与方法

本研究通过高脂饲养 C57 BL/6J 小鼠，构建肥胖模型，监测体重、进食量、空腹血糖、胰岛素、胆固醇等生理指标。高脂饲养 8 周后，通过腹腔糖耐量实验检测其葡萄糖代谢情况，同时通过糖水偏好实验（SPT）、旷场试验（OFT）、强迫游泳实验（FST）检测行为学变化。通过酶联免疫吸附测定（ELISA）检测外周血糖皮质激素、血清素水平，明确肥胖状态下相关激素变化情况。饲养 10 周后，通过注射 MC38 结肠癌细胞建立皮下荷瘤模型，待肿瘤体积长至 200 mm3 后，采用课题组前期开发的纳米药物 CDNP（包裹 R848）进行治疗，该方案通过 R848 诱导巨噬细胞 M1 型极化，促抗肿瘤免疫。探究免疫治疗效果在肥胖小鼠中是否存在差异，并检测外周血相关激素水平变化。

3. 结论

本研究探究代谢 - 神经内分泌 - 肿瘤免疫之间潜在机制，初步阐明机体肥胖状态引起代谢紊乱、并伴随慢性应激状态的发生，此过程中存在相关激素水平的改变可能影响了结肠癌免疫治疗效果。

代谢紊乱表征包括肥胖小鼠的体重明显增加、空腹及餐后 2h 血糖、外周血胰岛素、胆固醇含量偏高，糖耐量受损等；行为学实验表明其具有抑郁样行为、快感缺失、自主探索行为减少等；此外，肥胖小鼠肿瘤生长速度更快且免疫治疗效果受到抑制，相关激素（例外周血糖皮质激素、血清素）水平增高，且在肿瘤发展（HFD-T vs. HFD）中有进一步升高趋势，即表明肥胖小鼠应激反应增强、具有焦虑及抑郁样行为，该状态与免疫治疗效果受损间存在的具体机制有待进一步探索。

未来我们将采用免疫治疗与糖皮质激素抑制剂或 5-HT 再摄取抑制剂联合治疗，将巨噬细胞重编程与代谢水平调控相结合，强化肿瘤免疫治疗效果，为肥胖患者提供更有效、更安全的肿瘤免疫治疗新方案。

汇编

Ggpps deficiency in adipocyte promotes white adipose tissue atrophy remodeling through activating macrophages IL18 signaling in mice

xian zhang*,Yanting Xu,Jian Liu

Hefei University of Technology
Corresponding Author E-mail: zhangxian0426@hotmail.com

Adipose tissue macrophages (ATMs) have important adaptive functions in lipid homeostasis and insulin sensitivity of adipose tissue. As a key metabolic enzyme in the mevalonate pathway, geranylgeranyl diphosphate synthase (GGPPS) can regulate the prenylation modification of proteins, thereby regulating downstream signaling pathways. Previous studies have shown that GGPPS regulates intracellular vesicle transport, which may dynamically affect adipokine secretion and related white adipose tissue (WAT) remodeling. However, the role of GGPPS in WAT remodeling and ATM inflammation have not been reported. Here, we showed that GGPPS was primary expressed in adipocytes of adipose tissue and was required to maintain the expansion of adipose tissue. Specific deficient of Ggpps in adipocytes promoted WAT atrophy remodeling, ectopic lipid deposition in liver and insulin resistance in mice. Meanwhile, RNA sequencing analysis revealed that adipocyte specific Ggpps deficiency inhibited adipogenesis, lipogenesis and lipolysis, and promoted inflammation, macrophage activity and chemotaxis in WAT. Ggpps deficiency also enhanced the accumulation and M1 polarization of ATMs and induced the expression of inflammation cytokines and the number of dead adipocytes and crown-like structures (CLSs) in WAT. Mechanism study showed that adipocyte Ggpps deficiency promoted IL18 expression in macrophage and IL18r and Na-Cl cotransporter (NCC) expression in adipocyte, thereby accelerating adipocyte death, exacerbating lipid homeostasis and insulin sensitivity in WAT. Collectively, Ggpps deficiency in adipocyte promotes atrophy remodeling, exacerbates lipid metabolism and insulin sensitivity in WAT through activating macrophages IL18 signaling in mice.

Key Words White adipose tissue, GGPPS, Macrophage, IL18 signaling, Atrophy remodeling

藏药二十五味鬼臼丸对绝经后骨质疏松模型大鼠骨代谢平衡的干预作用

江宇楠 *
青海大学
通讯作者邮箱：jiang20220221@163.com

目的

探讨藏药二十五味鬼臼丸通过减轻氧化应激反应防治绝经后骨质疏松症的作用机制。

方法

将 40 只 3 月龄健康雌性 SD 大鼠手术去势，随机分为 Sham 组、OVX 组、GJ 组、RLX 组。通过一般情况观察及比色法、ELISA 法检测血清中 ROS、T-SOD、MDA、GSH-Px 与 BGP、β-CTx、β- 半乳糖苷酶含量，免疫组化观察成 - 破骨细胞活性，荧光硬组织切片及扫描电镜观察股骨、腰椎病理和微结构变化。结果 与 Sham 组相比，OVX 组大鼠出现明显骨质疏松且体重增加，骨微结构破坏明显，骨体积分数与骨骺线面积和血清 SOD、GSH-Px、BGP 及骨组织成骨细胞活性显著降低（$P < 0.05$，$P < 0.01$），ROS、MDA、β-CTx、β- 半乳糖苷酶及破骨细胞活性显著上升（$P < 0.05$，$P < 0.01$）；与 OVX 组相比，GJ、RLX 组大鼠骨质疏松症状有所改善，骨吸收陷窝减少，骨小梁间距减小且排列有序，骨胶原纤维、骨体积分数与骨骺线面积和血清 SOD、GSH-Px、BGP 及成骨细胞活性显著增加（$P < 0.05$，$P < 0.01$），ROS、MDA、β-CTx、β- 半乳糖苷酶及破骨细胞活性显著下降（$P < 0.05$，$P < 0.01$）。结论 藏药二十五味鬼臼丸可减轻氧化应激反应，有效改善绝经后骨质疏松大鼠模型骨代谢水平与骨微结构变化。

关键字 藏药二十五味鬼臼丸；绝经后骨质疏松；氧化应激；骨代谢平衡

Unveiling a novel pathway through machine learning-derived CD8+ T cell-associated genomic signature for prognosis improvement in late-stage high-grade serous ovarian cancer

Liu Xinkui,Zhang Zhen,Wei Ran,Fan Nannan,Shi Feifei,Niu Liangzhong,Zhou Miaomiao,Qin Liping,Zhang Yunhong,Li Xia*

Shandong University of Traditional Chinese Medicine
Corresponding Author E-mail: 60230033@sdutcm.edu.cn

Background: Despite increasing evidence suggesting that high-grade serous ovarian cancer (HGSOC) is immunogenic and holds potential for immunotherapy, the effectiveness of PD-1 or PD-L1 blockade in HGSOC remains significantly limited. Thus, there is an urgent need for novel therapeutic and prognostic biomarkers related to CD8+ T cells to enhance the clinical diagnosis and treatment of HGSOC.

Methods: Retrospective analysis was performed using four independent cohorts of late-stage HGSOC. The immune cell infiltration levels were estimated by ssGSEA, and consensus clustering was used to categorize the HGSOC patients into distinct immune infiltration subgroups. WGCNA was used to screen CD8+ T cell activation-related genes, and a CD8+ T cell-associated signature was developed using machine learning methods. The prognostic predictive performance of our signature was validated by comparing it with published signatures. Furthermore, the signature genes were further investigated through pan-cancer analysis and single-cell transcriptomic analysis.

Results: A 10-gene prognostic signature (GBP2, CCL18, CD69, SLC28A3, ISG20, CTSC, PLEK2, NFKB1, IFNGR1, and VSIG4) associated with CD8+ T cell activation in late-stage HGSOC was developed. The established signature served as an independent prognostic factor for overall survival, demonstrating robust accuracy and consistent performance in predicting prognosis across diverse datasets. Additionally, this signature demonstrated superiority over traditional clinicopathological features (such as stage and grade) and previously established models. The low-risk group of HGSOC patients exhibited elevated levels of activated CD8+ T cell and cytotoxic signature scores within tumor environment, indicating their potential benefit from chemotherapy and immunotherapy. Pan-cancer analysis revealed that GBP2, CCL18, CD69, SLC28A3, ISG20, CTSC, and VSIG4 exhibited a significant positive correlation with CD8+ T cell infiltration in over 15 cancer types, while PLEK2, NFKB1, and IFNGR1 showed no significant association with CD8+ T cell infiltration in the majority of analyzed cancer types.

Conclusion: This study presents a precise prognostic signature associated with CD8+ T cells, enabling accurate identification of patients at high risk of mortality in late-stage HGSOC. Meanwhile, this study could offer innovative insights into the identification of potential therapeutic targets to improve the clinical outcomes of late-stage HGSOC.

Key Words high-grade serous ovarian cancer, tumor environment, CD8+ T cell, machine learning

MIR937 amplification potentiates ovarian cancer progression by attenuating FBXO16 inhibition on ULK1 mediated autophagy

Zhen Zhang[1],Chu Chu[1],Wei Li[1],Haoyu Sun[1],Yunhong Zhang[1],Lihua Li[1],Nannan Fan[1],Feifei Shi[1],Xinkui Liu[1],Liang Chen[2],Xia Li*[1]

1. Innovative Institute of Chinese Medicine and Pharmacy, Shandong University of Traditional Chinese Medicine
2. Department of Radiation Oncology, Shandong Cancer Hospital and Institute, Shandong University
Corresponding Author E-mail: 60230033@sdutcm.edu.cn

Background: Epithelial ovarian cancer (EOC) is one of the most lethal cancer worldwide. Early diagnosis and effective therapeutic strategies are still in urgent need for EOC treatment. Genetic studies have revealed that gene copy number alterations (CNA) frequently occurred in EOC pathogenesis, however the function and mechanism for certain CNA are still not fully understood.

Methods: CNA data from TCGA ovarian cancer patients were analyzed by cbioportal and bioinformatics tools. The copy numbers of miR937 from clinical patients were determined by Taqman PCR analysis. The expression of miR937, miR-937-5p, and miR-937-3p was detected by quantitative real-time polymerase chain reaction (qRT-PCR). The miR937 CNA model was built by CRISPR-Cas9 guided gene deletion. The cell proliferation and viability was monitor by CCK8, colony formation assay, and EdU incorporation analysis. OV tumor cells were injected subcutaneously or intraperitoneally into the nude mice (NOD-Scid) to establish the xenograft model, and visualize the function of miR937 on OV progression. Dual-luciferase reporter analysis was used to confirmed the targeting of FBXO16 by miR-937-5p. Co-IP and ubiquitination assay was performed to detect the interaction between FBXO16 and ULK1, and FXBO16 facilitated ubiquitionation of ULK1. Immunohistochemistry analysis was used to determine the abundance changes of ULK1 protein in clinical samples upon miR937 genomic amplification. Data for survival analysis were downloaded from Kaplan plotter and re-analyzed with graphpad software.

Results: In this study, we found that miR937 genomic locus frequently amplified in EOC patients, and the expression for miR937 positively correlated with its gene copy numbers. By generating miR937 copy number variation models, we determine the promotion effects of miR937 on OV progression both in vitro and in vivo. Rescue assay further confirmed the functional product for miR937 in OV promotion is miR-937-5p, but not miR-937-3p. Mechanistically, miR-937-5p could bind to the 3'UTR of FBXO16 transcript, and result in the down-regulation of FBXO16 protein expression. Subsequently, the abundance of FBXO16 bound to ULK1 was decreased, and the K48 linked poly-ubiquitination of ULK1 was attenuated, which was facilitated by CUL1/FBXO16 complex. In clinic, miR937 amplification patient samples exhibit low FBXO16 expression, while high levels ULK1 protein and autophagy. Survival analysis demonstrated that FBXO16 (high) ULK1 (low) favors long survival for EOC patients.

Conclusion: The results suggested that miR937 amplification in EOC patients attenuates FBXO16 expression, relieve the K48 linked poly-ubiquitination on ULK1, and increase ULK1 mediated autophagy, which finally accelerate OV progression. FBXO16/ULK1 targeting might serve as a promising strategy of precise intervention for EOC patients with miR937 amplification.

Key Words Epithelial ovarian cancer, miR937 amplification, FBXO16, ULK1, Autophagy

Date / /

Date / /

Date / /

Date / /

Date / /

Date / /

Date / /

Date / /