



2023 CSSCR 干细胞研究与转化 踏遍青山 中国干细胞第十三届年会

The 13th Annual Meeting of CSSCR

论文汇编

2023
10.12-15th | 浙江·杭州
Hangzhou, Zhejiang

主办单位：中国细胞生物学学会干细胞生物学分会

承办单位：浙江大学医学院附属第一医院

协办单位：浙江省免疫学会



目录

帕金森病的细胞治疗—从基础到临床.....	13
陈跃军.....	13
干细胞赋能细胞治疗：新型免疫细胞智造平台	14
黄河.....	14
Lung Regeneration, Impaired Repair, and Disease Progression	15
汤楠.....	15
基因编辑技术及临床应用	16
李大力.....	16
Deciphering the underlying mechanisms of mammalian placentation and early embryogenesis.....	17
Hongmei Wang.....	17
Chromatin reader and cell fate determination.....	18
郝乔然.....	18
人 CS12-21 胚胎发育的近—远端特化进程.....	19
曹尚涛、冯辉坚、易红艳、潘梦婕、林立惠、张焱、冯子彧、汪捷、裴端卿、马燕琳、陈捷凯....	19
解析人胚胎干细胞特性维持的转录后调控机制健康研究院	20
金颖.....	20
Preventing Post-Implantation Embryonic Development Defects Caused by Alcohol Exposure Through Restoration of the CREB/ KDM2B Axis.....	21
Hang Liu、Feifei Zuo、Qian Li、Cailing Lu、Xudong Wu.....	21
Peri-implantation embryogenesis and regulation	22
Qingyuan Zhu、Jitao Ge、Ying Liu、Fan Zhou	22
Fast Chemical Reprogramming of Somatic Cells to Pluripotency.....	23
祝赛勇.....	23
靶向 DNA 修复提高干细胞质量的探索研究.....	24
毛志勇.....	24
Functional study of the transient hepatic steatosis in liver regeneration	25
丁秋蓉.....	25
造血干细胞与微环境.....	26

程辉	26
Tissue derived organoid s and regeneration	27
安亚春、连佳贝、郭立强、范玉佳、杜浩然、毛雨诺、胡慧丽	27
基于小分子和表型大数据的细胞命运调控新策略	28
赵扬	28
解析人脑中间神经元多样性和腹侧类 器官	29
时颖超	29
基于微肿瘤 3D 模型开展耐药机制研究	30
席建忠	30
小肠类器官与干细胞命运调控	31
尹晓磊	31
人源神经类器官的构建与应用	32
向阳飞	32
细胞治疗在消化道肿瘤中的应用	33
沈琳	33
新型基因编辑技术开发	34
王皓毅	34
Next generation of DNA base editors and their applications.....	35
Tong Li、Huawei Tong、Dingyi Han、Qingquan Xiao、Yingsi Zhou、Hui Yang.....	35
MSC 细胞外囊泡在眼组织损伤修复中 的作用机制及转化研究	36
柳夏林	36
基因编辑与创新性细胞治疗	37
刘明耀	37
hPSC-derived cardiac line age cells for repair of infarcted hearts.....	38
杨黄恬	38
哺乳动物再生机路径与转化	39
李伟	39
iPSC 分化胰岛细胞药物开发经验分享	40
刘彤日	40
Targeting stem-like persistent cells in lymphoma treatment	41

赵维莅	41
亚微米分辨率三维获取完整器官的精准形态	42
龚辉	42
Development of programmable RNA technology and its potential applications in biomedicine.....	43
钱永军	43
Studying ALS/FTD Pathomechanisms using Induced Pluripotent Stem Cell Models	44
Ke Zhang, Ph.D.....	44
不同位点造血干细胞发育的调控	45
李专	45
Single cell spatiotemporal transcriptomic landscape of developing tendon reveals cellular differentiation and interaction	46
Zi Yin	46
Reconstruction of single-cell and spatial multi-omics for enhanced understanding of cell identities and disease phenotypes.....	47
Dongqing Sun、Xin Dong、Ya Han、Xiaoying Shi、Zhanhe Chang、Chenfei Wang.....	47
SWI/SNF complexes and stem cell identities.....	48
朱哲鑫	48
The stem cells underlying cancer bone metastasis	49
Weijie Zhang	49
Epigenetic Control of Epithelial-Mesenchymal Plasticity and Cancer Stemness	50
Yun Zhang, Ph.D.....	50
Single-cell lineage tracing reveals stem cell fate in development and disease.....	51
裴唯珂	51
Towards better eggs and embryos.....	52
Chun So	52
Unveiling pluripotent state transitions during somatic cell reprogramming and early human embryonic development.....	53
刘晓东	53
探究异倍体与 P53 的互作对肿瘤发生发展的影响	55
卢明飞、张美丽、黄粤	55
间充质干细胞介导纳米放射增敏剂用于非小细胞肺癌的靶向放疗	56

曾丽娟、肖靖芳、田甘、卞修武	56
Allogeneic hematopoietic stem cell transplantation for the treatment of acute lymphoblastic leukemia: single-center, retrospective study and ALL transplant-specific prognostic scoring system	57
高铭阳、高蕾	57
Favourable outcomes between HLA-haploid and matched sibling donor hematopoietic stem cell transplantation: multi-centre, retrospective study and severe aplastic anemia transplant-specific prognostic scoring system.....	58
高铭阳、高蕾	58
利用小鼠胚胎干细胞探究异倍体促进畸胎瘤转移的分子机制	59
肖蓉、许德澍、张美丽、陈章华、白凡、黄粤	59
Effects and mechanisms of various Mesenchymal stem cell targeting Ferroptosis on inflammatory diseases	60
李强、任博媛、吴祖泽、靳继德	60
脑小血管病的细胞治疗	61
于念叶	61
Discovery and Application of Postnatal Nucleus Pulposus Progenitors Essential for Intervertebral Disc Homeostasis and Degeneration.....	62
高博	62
lncRNA CARMN 通过 Wnt 信号调控乳腺及乳腺癌干细胞功能.....	63
李明洋、王超尘、王腾、刘铭镐	63
Human dopaminergic neuron organoids derived from pluripotent stem cells.....	64
王馨悦、孙高英、王传玥、胡宝洋	64
hUCMSCs improve autophagy and promote testosterone synthesis via AMPK-mTOR pathway in aging mice	65
杨鸿宇、薛函、余丽梅、何志旭	65
Umbilical Cord Mesenchymal Stem Cells Rescued Cardiac Function via Up-regulating Mitophagy in D- galactose induced Oxidative Damage	66
刘娟、吴雨瞳、徐尚福、刘滔滔、薛函、冉昕、于泓、何志旭、余丽梅	66
Neural aging and regulation research	67
李达	67
PGE2 驱动 hESC-RPE 线粒体低毒兴奋效应以增强视网膜退行性疾病移植治疗效果	68
程政航	68

缺血性脑卒中小鼠模型的单细胞转录组图谱揭示小胶质细胞介导的外周免疫细胞脑部浸润.....	69
管其标.....	69
干细胞与再生医学发展概述	70
李子 and	70
Precise Correction of Lhcgr Mutation in Stem Leydig Cells by Prime Editing Rescues Hereditary Primary Hypogonadism in Mice	71
夏凯、项鹏.....	71
Therapeutic Potential of Double-Negative T (DNT) Cell Infusion in Alleviating Alzheimer's Disease Symptoms	72
谢苑芷、刘京、侯宗仁、刘凯伦、李灿、张真豪、王强	72
下丘脑环路调控慢性应激中免疫红细胞的生成	73
刘伯男、王琪、婷婷、骆斯佳、张璟祎、卢盈妃、王思远、胡宝洋	73
Regulation of human amniotic mesenchymal stem cells on follicular developmental and inflammatory cytokines for therapy of cis-platinum induced ovarian insufficiency mice	74
王圆圆、余丽梅、罗娇、刘璐、王钰莹、范振海、杨鸿宇	74
中枢神经系统的免疫应答通路的探究	75
李逸凡、胡宝洋.....	75
Comparison of chemicals-induced 2-cell like state in mouse embryonic stem cells.....	76
于永芹、刘林.....	76
AFG3L2 突变引起常染色体隐性遗传的脊髓小脑共济失调的致病机理研究	77
李虹雨、马晴雯、鲍莉雯、龚秀丽、曾凡一	77
Predictive Value of Pre-Treatment ctDNA Genomic Landscape in Relapsed or Refractory Multiple Myeloma Patients Undergoing anti-BCMA CAR-T Therapy: Insights from Tumor Cells and T Cells	78
陈蓉蓉.....	78
一种有效筛选出能够制备出嵌合体小鼠的 iPSCs 的方法	79
杨冠恒、郭歆冰、龚秀丽、桑晓、陈雁雯、郭传亮、鲍莉雯、张敬之、曾凡一	79
transient activation of PIEZO1 mechanosensitive channel facilitates ex vivo expansion of hematopoietic stem cells.....	80
王琪炜、李金鑫、姜玲俐、钱鹏旭	80
IGFBP7 预防牙髓间充质干细胞衰老的作用和潜在机制研究	81
李晓钰、胡磊、王松灵	81

Microplastics dampen the self-renewal of hematopoietic stem cells by disrupting the gut microbiota-hypoxanthine-Wnt axis.....	82
姜伶俐、叶逸山、韩颖丽、王琪炜、鲁欢、Jinxin Li、钱文畅、曾欣、张召茹、赵妍敏、施继敏、罗依、黄河、钱鹏旭	82
Sialin (SLC17A5) 通过调控线粒体代谢维持间充质干细胞功能稳态.....	83
李晓钰、王松灵	83
NAT10 regulates the stability of HSC-specific mRNAs to control hematopoiesis.....	84
李卫倩、霍悦、张召茹、钱鹏旭、王芳、余佳	84
mESCs 分化为 TEPs 及 Aire 敲低对胸腺 T 细胞发育与分化的影响.....	85
李远迪、高杰、胡蓉、何志旭、苏敏	85
基因编辑造血干细胞移植治疗 β 654 地中海贫血小鼠	86
鲁丹、龚秀丽、郭歆冰、陈燕雯、朱怡文、方彧聃、蔡勤、许淼、杨华、曾凡一.....	86
RNA binding protein HuR regulated by OIP5-AS1 may be involved in maternal transcript degradation during the human maternal-to-zygotic transition	87
魏豪、刘艳娜、张月华、邱家俊、曾凡一、颜景斌	87
Small extracellular vesicles derived from acute myeloid leukemia cells promote leukemogenesis by transferring miR-221-3p	88
Mengyu Li、Guohuan Sun、Jinlian Zhao、Yajie Wang、Shangda Yang、Tao Cheng、Hui Cheng	88
成纤维细胞生长因子 4 抑制大鼠睾丸间质干细胞分化但刺激其增殖	89
王义炎、王梦云、乔薪颐、叶蕾、王洪、杨进、郑柯、崔榕、葛仁山	89
Mesenchymal Stromal Cells Alleviate Depressive and Anxiety-like Behaviors via a Lung Vagal-to-Brain Axis in Male Mice	90
张小然、黄晶、黄玮俊、项鹏	90
The adipose-neural axis is involved in cardiac arrhythmias	91
范玉宝、黄珊珊、李苏华、吴冰原、黄里、赵琦、郑振达、谢旭晶、刘佳、黄玮俊、孙佳琦、王茂生、朱秀龙、朱洁明、项鹏、李伟强	91
红系特异性启动子与 BCL11A 三代慢病毒干扰在 β 地中海贫血基因治疗中的研究	92
李燕、何志旭、张鹏	92
Nuclear pore interactome reveals domain mediated mRNA export fate by FXR1 in human embryonic stem cells.....	93
杨嘉宾、陈仲扬、赫佳音、马艳妮、余佳	93
高度可重复性类器官平台的建立及其应用	94

张晓姗、刘雅文、汪阳明	94
基于 MH 序列多态性的新型细胞交叉污染检测方法的建立	95
伍义行、张彤彤、朱羽婕、周彦铸、庄安琪、陈艳、陈善梅	95
Ang-(1-7)/MasR 与 Ang- II /AT1R 平衡在 hUMSCs 抗人源化 ACE2 小鼠肺纤维化的作用研究	96
莫楠、范振海、李博涵、王艳阳、何志旭	96
Development of a humanized mouse model with functional human maternal–fetal interface immunity... ..	97
董帅、付聪、舒畅、谢敏、李艳、邹俊、孟一姊、徐鹏、单延红、田慧敏、何津、杨永广、胡正	97
间充质干细胞来源 IGF2 分泌缺失诱导肝脏枯否细胞 M1 型极化	98
周彩平、桂薇薇、林细华	98
Multi-Gene Engineered iPSC-Derived CAR-NK cells Display Robust Anti-Tumor Effects in Acute Myeloid Leukemia	99
王艺芸、王林钦、邵谧、何向军、岳亚男、周怡璇、王东睿、胡永仙、杨璐菡、黄河	99
PDCD4 缺失的间充质干细胞促进皮肤损伤修复的作用及机制研究	100
刘丽媛、姜杨、郑成云	100
过表达白介素 1 受体拮抗剂的间充质干细胞治疗出血性膀胱炎的疗效及机制研究	101
宋佳霖、姜杨、郑成云	101
The ATF4-RPS19BP1 axis modulates ribosome biogenesis to promote erythropoiesis	102
Zheng Zhaofeng、 Yang Shangda、 Gou Fanglin、 Tang Chao、 Zhang Zhaoru、 Jiang Penglei 、 Qian Pengxu、 Zhu Ping、 Cheng Hui、 Cheng Tao、 郑昭烽	102
A programmed intracellular fabrication of high-functioning mitochondria supplies energy for osteoarthritis therapy.....	103
陈旭日、欧阳宏伟	103
Converging bioprinting and organoid towards advanced tumor microenvironment (Review)	104
王晓宇、罗依雪、马源锴、王鹏逾、姚睿	104
成纤维细胞对人毛囊干细胞来源毛囊类器官结构的影响及其作用机制	105
连尉伶、曾炫皓、臧青、张琦、林尽染、吴文育、徐金华	105
Development of a pig bioreactor supporting robust human hematopoiesis for large-scale production of functional human immune cells	106
胡正、邹俊、汪正铸、许凯、海棠、李子义、李伟、周琪、杨永广	106
利用诱导多能干细胞构建 bardet-biedl 综合征肾脏模型探索 BBS7 复合杂合突变影响肾脏发育的机制研究	107

肖蓉、闵婕	107
Modeling human anti-pig xenoimmune responses in a pig artery tissue grafted humanized mouse model	108
方铭慧、邹俊、徐飞、王雪、杨永广、胡正	108
CD19 CAR-T 细胞治疗 R/R NHL 后中枢神经系统复发	109
赵梦雨、杨婷婷、董叶恬、周凌辉、孔德麟、黄河、胡永仙	109
Spatial transcriptome analysis explores human fetal vaginal epithelial stem cell	110
赵光锋、叶紫英、胡娅莉	110
表观遗传编辑调控 B2M 超级增强子构建通用型干细胞	111
徐婧怡、王飞、柳华	111
The culture system of porcine embryonic-derived pluripotent stem cells was screened according to the transcriptome characteristics of porcine E7-8 epiblast	112
余卓然、王红兴、颜廷胜、刘忠华	112
Low-intensity pulsed ultrasound improves osteogenesis under oxidative stress in periodontal ligament stem cells via Akt-FOXO1	113
唐丽、杨珂	113
BRD4 通过募集 EHMT1/2 抑制终末红细胞生成	114
张蒙、陈谊金、黄朦朦、孟夜、张杰、罗黔、霍大伟、郑海琼、徐玉林、钱鹏旭、黄河	114
Nrf2 regulates immunosuppressive ability of umbilical cord mesenchymal stromal cells on the therapeutic effect of experimental bronchopulmonary dysplasia	115
章杰、杨珂	115
Bifunctional nanoparticles regulate directional differentiation of neural stem cells and polarization of microglia	116
王树萍、张朔、刘琦、孙春辉、任娜、王金刚、刘宏	116
Effect of 1 μ M BPA on human neural stem cells via ERR α and TGF- β 1 signaling	117
孙吉坤、贾紫璇、张婧、潘慧心、王清路	117
基于 H3K4me3/H3K9me3 参与成纤维细胞生长因子 9 (FGF9) 刺激 Leydig 干细胞自我更新和分化的机制研究	118
全荷花、鲍肃好、何佳怡、王义炎、葛仁山、李晓珩	118
RNA 结合蛋白 YBX1 调控胚胎干细胞多能性退出的研究	119
郭传亮、洪磊、杨冠恒、蔡勤、张少清、龚秀丽、李文秀、郭昕冰、薛燕、曾凡一	119

ALKBH5 Modulates Hematopoietic Stem and Progenitor Cell Energy Metabolism through m6A Modification-Mediated RNA Stability Control.....	120
高义萌、Joshua T. Zimmer、Radovan Vasic、刘诚扬、Rana Gbyli 、郑书剑、 Amisha Patel、刘纬、齐志红、李亚萍、Raman Nelakanti 、宋远斌、Andrew Z. Xiao、Sarah Slavoff 、Richard Kibbey 、Richard A. Flavell、Matthew D. Simon、Toma Tebaldi、李华兵、Stephanie Halene.....	120
The inhibition of ULK1 promotes human erythroid progenitor proliferation and inhibits differentiation by upregulating AHR signaling	121
陈谊金、郑海琼、罗黔、张朦朦、张杰、张蒙、钱鹏旭、黄河	121
Naringenin promotes exosomes of immature dendritic cells derived from induced pluripotent stem cells to alleviate the rejection of transplantation	122
黄晓燕、靳占奎、李研、赵向绒、冯杨萌、封青、李亚萍、徐翠香、田普训	122
诱导人多能干细胞定向分化为视网膜祖细胞及其机制研究	123
刘逸凡、徐国彤、金彩霞	123
人脐带间充质干细胞通过调节 T 细胞反应治疗实验性过敏性结膜炎	124
李东丽、徐国彤、海滨	124
骨髓巨噬细胞参与骨髓增生异常肿瘤的无效造血	125
李陈元、邢通、姚伟丽、赵红艳、王婧、张圆圆、吕萌、许兰平、张晓辉、黄晓军、孔圆.....	125
Correction of a APDKD point mutation using adenine base editors in hiPSCs and kidney organoids.....	126
王菁文、邱燕玲、张磊、周欣瑶、胡思慧、刘倩宜、刘思邈、武学清、黄军就	126
人脐带血造血干细胞诱导分化的表观遗传调控机制研究进展	127
贾炳豪、刘春亚、唐琴、任立成	127
人脐带间充质干细胞外泌体联合 ATRA 应用于脐带血造血干细胞体外扩增研究.....	128
贾炳豪、刘春亚、唐琴、任立成	128
Deciphering biophysical cues in cell fate conversion.....	129
王鹏元	129
左归丸促进人脐带间充质干细胞迁移和归巢的分子机制研究	130
焦存、芦现杰	130
功能化干细胞源性凋亡小体纳米囊泡通过“找-吃”策略 靶向内皮细胞.....	131
钱姝桐、毛佳怡、赵秋羽、卢博伦、赵彬帆、张柳成、毛曦媛、张余光、王丹茹、孙晓明、崔文国	131
肝脏干细胞的衰老与逆转	132
王敏君、陈费、刘清桂、胡以平	132

联合疗法诱导产生肠道胰岛素的细胞并降低糖尿病小鼠的血糖	133
杜雯	133
转录组分析 hESC-MSCs 治疗早期矽肺小鼠中的关键信号通路	134
胡文锋、杨佳丽、刘晓明	134
MSCs-sEV 通过激活 DPCs 中 AKT 通路促进毛囊再生的作用与机制	135
田瑞云、李富荣	135
小鼠滋养层类器官的构建及功能筛选	136
林照博、毛倩	136
人多能干细胞的巨噬细胞分化与细菌感染模型	137
孙仕成、Elizabeth S Ng、Andrew G Elefanty、Sohinee Sarkar、Edouard G Stanley	137
人多能干细胞的血液与淋巴免疫分化	138
孙仕成、Ali Motazedian、Jacky Li、Kevin Wijanarko、Jacqueline V Schiesser、Yi Yu、Elizabeth S Ng、 Andrew Elefanty 、Edouard Stanley	138
脂肪干细胞来源的类神经干细胞球通过调节免疫微环境修复大鼠骶神经损伤	139
李君洋、王玉、尚爱加	139
DHH 通路在小鼠睾丸间质干细胞发育中的机制研究	140
李慧涛、苏铭、林杭、王义炎、李晓珩、朱琦琦、朱阳、葛仁山	140

报告人摘要合集





陈跃军，中国科学院脑科学与智能技术卓越创新中心，高级研究员。主要从事人多能干细胞的神经分化和神经退行性疾病的细胞治疗，开发了能够在体外或体内分别进行高通量发育谱系示踪的新技术 SISBAR 和 CREST，解析了多巴胺能神经分化的单细胞谱系，在此基础上开发了更安全有效的帕金森病细胞治疗新策略；解析了帕金森病细胞治疗中移植细胞环路整合和作用的新机制。研究成果以通讯作者（含共同）发表在 Cell Stem Cell（4 篇），Nature Methods, Journal of Clinical Investigation, Brain 等杂志，并基于以上研究成果启动临床转化。

帕金森病的细胞治疗—从基础到临床

陈跃军

中国科学院脑科学与智能技术卓越创新中心

【摘要】 帕金森病（PD）的主要原因是中脑黑质多巴胺能（DA）神经元的退行性变和丢失，移植外源 DA 神经细胞是最具潜力的 PD 治疗策略。然而移植用供体细胞中目的 DA 神经细胞和非目的细胞在分化过程中是如何产生的？其移植后是如何整合入宿主神经环路的？如何获得效率更高，更稳定的移植治疗效果？这些问题都是 PD 细胞治疗在临床上更广泛应用亟待解决的关键问题。针对以上问题，我们建立了能够在体外和体内进行高通量单克隆谱系示踪的新技术-SISBAR（You et al. 2023 Cell Stem Cell）和 CREST（Xie et al. 2023 Nature Methods），揭示了目的 DA 神经细胞和非目的细胞的分化谱系和路径；发现和鉴定了能够特异性表征 DA 神经前体细胞的表面标记分子，通过表面标记分子分选的前体细胞移植后，可以得到 DA 神经元高度富集（最高达到 80%），细胞组成明确、稳定的移植结果（Xu et al. 2022 JCI）；在环路层面，我们发现移植的 DA 神经细胞可以在结构和功能上特异性整合入宿主大脑，调控宿主神经环路。（Chen et al. 2016 Cell Stem Cell；Xiong et al. 2021 Cell Stem Cell）。



黄河，浙江大学求是特聘教授，973首席科学家，主任医师，博士生导师。现任浙江大学医学院附属第一医院院长、党委副书记，浙江大学血液学研究所所长，干细胞与细胞免疫治疗浙江省工程中心主任。任国家重点研发计划“干细胞及转化研究”重点专项专家组成员，全国医学专业学位研究生教育指导委员会委员，中华骨髓库专家委员会副主任委员，中华医学会血液学分会常务委员，亚洲细胞治疗组织学术委员会副主席，亚太血液与骨髓移植学会执行委员会委员，欧洲血液与骨髓移植学会国际学术委员会委员等学术职务。

主要研究方向为干细胞基础研究与造血干细胞移植临床应用、细胞免疫治疗前沿技术与转化研究。先后于2003年及2015年2次荣获国家科技进步奖二

等奖。作为负责人承担973，863，国家自然科学基金重点项目，国家自然科学基金国际合作与交流项目等27项，以通讯作者在Nature, Cell Research, Lancet Haematology, Blood等期刊发表SCI论文241篇，获省部级以上科技奖项15项，授权发明专利21项。近5年在国际大型会议担任主席、特邀报告和口头报告百余次。作为大会主席分别于2005年和2014年在杭州主办亚太国际骨髓与造血干细胞移植大会。主编人民卫生出版社出版的国内首部CAR-T细胞治疗学专著《CAR-T细胞免疫治疗学》，主编人民卫生出版社全国研究生《血液内科学》教材，参编著作及教材11部。任国际造血干细胞移植领域权威杂志Bone Marrow Transplantation, Journal of Hematology and Oncology编委。

干细胞赋能细胞治疗：新型免疫细胞智造平台

黄河

浙江大学

【摘要】 以CAR-T为代表的细胞免疫治疗在难治复发恶性血液病中取得重大突破，展现出了巨大的临床应用前景，目前全球和中国分别有7款和3款CAR-T产品获批上市。国际著名科学家Michel Sadelain和Carl June教授因在“细胞免疫治疗领域的突出贡献”获得2023年“科学突破奖”。近年来我团队专注于功能增强、新靶点和通用型的新型CAR-T细胞研发及临床转化研究并取得系列成果：国际首次报告非病毒转染、PD1定点整合功能增强型CAR-T细胞治疗淋巴瘤，完全缓解率87.5% (Nature 2022)；国际首次报告靶向CD7通用型CAR-T细胞治疗T系恶性血液病，总体反应率82% (Cell Research 2022)；国内首次报告靶向GPC5D新靶点CAR-T细胞治疗骨髓瘤临床研究，总体反应率100% (Lancet Haematology 2023)；受邀在Lancet Haematology发表“中国CAR-T细胞治疗：快速进展和光明未来”综述。但CAR-T治疗仍面临治疗靶点局限、复发率高、制备成本高等难题，我团队与杭州启函生物科技有限公司合作，共同研发多能干细胞来源的免疫细胞并开展临床转化研究，目前已建立多能干细胞来源NK细胞、靶向CD19 CAR-NK细胞、靶向CD33 CAR-NK细胞、靶向CLL1 CAR-NK细胞和靶向CD70 CAR-NK细胞的诱导分化及培养体系，其中靶向CD19、CD33、CLL1三种CAR-NK细胞正在开展IIT临床研究。干细胞来源的免疫有望克服传统细胞免疫治疗的局限，成为未来细胞免疫治疗的典范。



汤楠博士，1993 年获西安交通大学医学学士学位。2000-2005 年在美国加州大学圣地亚哥分校 Randall Johnson 博士实验室开展博士研究，获分子病理学博士学位。2006-2012 年在美国加州大学旧金山分校 Gail Martin 博士的实验室开展博士后研究。2012 年在北京生命科学研究所以建立实验室，现为北京生命科学研究所以高级研究员。

汤楠博士一直致力于肺发育、肺再生和肺部疾病的研究，在肺泡发育，肺泡再生，和肺纤维化

疾病的机制上有重要发现。已发表学术论文 30 余篇，研究成果入选中国医学科学院“中国 2020 年度重要医学进展”。根据肺泡再生及相关肺部疾病机制的科学发现，汤楠博士目前主持和参与针对肺部疾病的医学转化和临床试验研究。汤楠博士获得了多项国内外奖项，包括“北京市海外高层次人才（海聚人才）工程”，“中青年科技创新领军人才”，“万人计划”，“顾孝诚讲座奖”等。汤楠博士积极推动国际科学合作，2018 年起担任 Development Cell Editorial Board，受邀担任 2023ISSCR 组委会成员。

Lung Regeneration, Impaired Repair, and Disease Progression

汤楠

北京生命科学研究所以

【摘要】 Lung diseases are the leading causes of morbidity and mortality worldwide. The lung epithelium is not only essential for lung gas exchange function, it also acts as an important barrier to protect our body from harm. In response to injuries, the lung epithelium is able to rapidly repair and regenerate to restore an intact epithelial barrier and recover normal lung function. Using a convergence of mouse genetics, cell biology, intravital live imaging, and state-of-the-art sequencing technology, we aim to investigate the genetic and cellular mechanisms underlying the complex orchestration of lung regeneration. We demonstrate pulmonary alveolar development and regeneration are synergistically controlled by mechanical forces, local growth factors, and niche cell interactions. We have established a direct mechanistic link between impaired alveolar regeneration, mechanical tension, and progressive lung fibrosis. Our studies will provide insights to develop therapeutic strategies to induce lung tissue repair and regeneration in diseased lungs.



李大力，博士，华东师范大学生命科学学院研究员，博士生导师，教育部青年长江学者、杰出青年基金获得者，上海市基因编辑与细胞治疗前沿科学基地主任。2004 年至 2007 年在美国德州农工大学访学，2007 年获湖南师范大学遗传学博士学位，毕业后在华东师范大学工作至今。多年来以基因编辑技术创新为基础，开发了多种高效动物模型构建的新方法，围绕罕见病的模型构建和基因治疗，开展了深入研究，并成功利用基因编辑技术治愈 β 地中海贫血和非霍奇金淋巴瘤患者，在 Nature, Nature Biotechnology, Nature Medicine 和 Nature Genetics 等高水平期刊发表论文 100 多篇，作为课题组长主持科技部重点研发课题，国家自然科学基金委重点项目，获教育部高等学校科学研究优秀成果奖自然科学奖一等奖、第 16 届谈家桢生命科学创新奖和中国教师及发展基金会首届“卓越青年研究生导师奖励基金”。

基因编辑技术及临床应用

李大力

华东师范大学

【摘要】目前全球已知罕见病超过 7000 种，80%以上与基因突变直接相关，严重影响患者健康和生命，给家庭带来沉重负担。遗传疾病的致病基因鉴定和治疗都是领域的难题，而基因编辑技术的出现对于罕见病的诊治都有很好的前景。我们首先利用 TALEN 和 Cas9 体系建立了 5 周内快速构建人类遗传疾病致病突变的小鼠模型的技术体系。发现 SYK 基因新发杂合突变导致人类多发免疫缺陷，并通过小鼠模型进行了验证，通过骨髓移植证明可以在小鼠模型和病人中治愈该疾病。正如 SYK 单点突变导致疾病，人类 58%的遗传致病变异都是点突变，因此碱基编辑技术对于纠正遗传疾病有重要意义。通过对碱基编辑器的优化与改造，开发了一系列性能优越的碱基编辑器，包括超高活性的胞嘧啶碱基编辑器 HyCBEmax、几乎无脱靶活性且仅编辑 1-2 个碱基的 ABE9、由 TadA 脱氨酶改造的高精度胞嘧啶编辑器 Td-CGBE/CBEs 以及同时编辑 A、C 碱基的双碱基编辑器 A&C-BEmax 等新工具。此外还开发了实现腺嘌呤颠换的碱基编辑器 AXBE 和 ACBEs，丰富了碱基编辑技术的适用范围。利用基因编辑技术开发了治疗 β 地中海贫血的基因疗法，在临床研究中治愈了全部十余名患者，有望实现一次治疗终身治愈。



王红梅，中国科学院动物研究所研究员，干细胞与生殖生物学国家重点实验室主任，中国动物学会生殖生物学分会主任委员。国家杰出青年基金获得者，国家百千万人才工程有突出贡献中青年专家，“万人计划”科技创新领军人才。英国剑桥大学胎盘研究中心（CTR）学术委员会成员。1995 年于北京师范大学生物系获得学士学位，2002 年于中国科学院动物研究所获得理学博士学位，2003-2005 年在加拿大渥太华健康研究所从事博士后研究。王红梅课题组研究方向包括：（1）哺乳

动物早期胚胎和胎盘发育；（2）干细胞与生育力的维持和重建。在 Science, Nature, Cell, Nat Genet, Cell Res, Dev Cell 等期刊发表研究论文及综述 80 余篇。

Deciphering the underlying mechanisms of mammalian placentation and early embryogenesis

Hongmei Wang 1,2,3

- 1.State Key Laboratory of Stem Cell and Reproductive Biology, Institute of Zoology, Chinese Academy of Sciences, Beijing 100101, China
- 2.University of Chinese Academy of Sciences, Beijing 100049, China
- 3.Beijing Institute for Stem Cell and Regenerative Medicine, Beijing 100101, China

【摘要】 Placenta is a transient organ to connect the fetus and the pregnant woman during pregnancy. A functional placenta is important for the growth of the fetus and the health of the pregnant woman. Abnormal placental development and function can lead to defects in embryonic development and pregnancy complications and diseases. Wang lab has focused on unraveling the mechanisms underlying mammalian (human, macaque, mouse) placenta development and function throughout gestation. This includes mapping the cellular and molecular atlas of different mammalian placentas by single-cell multi-omics studies, revealing the origin and differentiation trajectory of different placental cells, dissecting the mechanisms underlying trophoblast cell-cell fusion, epithelial-mesenchymal transition, the interaction between trophoblasts and the uterine endometrium, and hematopoiesis within the placental villous core. Based on the understanding of placenta, Wang lab also tries to develop various culture systems to support ex-uterus embryogenesis and reveal the features of mammalian early embryo development.



郝乔然，博士，副教授。2004 年获美国纽约大学医学院博士，2006-2013 于美国斯隆凯特琳癌症研究中心从事博士后研究，2013 年全职回国，在清华大学生命学院任副教授至今。主要研究领域：TGFβ 信号通路在癌症和早期发育中的表观遗传调控机制。以第一作者或通讯作者身份在 Cell, Nature Cancer, Cell Stem Cell 等杂志发表 30 余篇研究论文。

Chromatin reader and cell fate determination

郝乔然

MOE Key Laboratory of Protein Sciences, State Key Laboratory of Molecular Oncology, School of Life Sciences, Tsinghua University Beijing 100084, China

【摘要】 During early development, chromatin readers interact with the epigenome to fine-tune cell fate decisions by interpreting and responding to epigenetic marks on DNA and histones. 2-cell-like cells (2CLCs)—which comprise only ~1% of murine embryonic stem cells (mESCs)—resemble blastomeres of 2-cell-stage embryos and are used to investigate zygotic genome activation (ZGA). Here, we discovered that TRIM66 and DAX1 function together as negative regulators of the 2C-like state in mESCs. Chimeric assays confirmed that mESCs lacking TRIM66 or DAX1 function have bidirectional embryonic and extraembryonic differentiation potential. TRIM66 functions by recruiting the co-repressor DAX1 to the Dux promoter, and TRIM66's repressive effect on Dux is dependent on DAX1. A solved crystal structure shows that TRIM66's PHD finger recognizes H3K4-K9me3, and mutational evidence confirmed that TRIM66's PHD finger is essential for its repression of Dux. Thus, beyond expanding the scope of known 2CLC regulators, our study demonstrates that interventions disrupting TRIM66 or DAX1 function in mESCs yield 2CLCs with expanded bidirectional differentiation potential, opening doors for the practical application of these totipotent-like cells.



陈捷凯，中国科学院广州生物医药与健康研究院研究员，博士生导师，国家自然科学基金杰出青年基金获得者。主要从事干细胞、细胞谱系及细胞命运调控研究。目前累计发表论文 79 篇，其中以通讯/共同通讯作者在 Nature、Cell、Molecular Cell、Cell Research 等杂志发表论文 17 篇，h 指数 41；已授权发明专利 9 项(PCT 2 个)。作为项目负责人主持包括国家重大科学研究计划、国家重点研发计划等多项重要科技项目。研究成果入选国家“十三五”科技创新成就展，获得国家自然科学二等奖、中国科学院杰出科技成就奖、第一届中国科学院五四青年奖章等奖项。

人 CS12-21 胚胎发育的近——远端特化进程

曹尚涛^{3,10,*}，冯辉坚^{1,4,6,10}，易红艳^{2,7,10}，潘梦婕^{1,10}，林立惠^{1,10}，张焱^{4,10}，冯子或^{1,5,10}，汪捷¹，裴端卿^{7,9,*}，马燕琳^{2,8,*}，陈捷凯^{1,9,*}

¹中国科学院广州生物医药与健康研究院中国科学院再生生物学重点实验室，广州，510530；²海南医学院第一附属医院海南省人类生殖与遗传重点实验室，海口，571101；³广州实验室，广州，510200；⁴生物岛实验室细胞谱系中心，广州，510000；⁵广州医科大学附属第五医院，广州，510700；⁶中国科学院大学，北京，101408；⁷西湖大学生命科学学院，杭州，310024；⁸海南医学院生殖健康及相关疾病研究与转化教育部重点实验室，海口，571101；⁹中国科学院香港创新研究院再生医学与健康创新中心，香港，999077

*通讯作者：cao_shangtao@gzlab.ac.cn; peiduanqing@westlake.edu.cn; chen_jiekai@gibh.ac.cn;

mayanlinma@hotmail.com

【摘要】肺是人类重要的呼吸器官，其近端气道和远端肺泡分别负责空气的传导和气体交换。然而，在早期胚胎发育中，肺近-远端结构是如何特化形成的仍存在很多未知。为此，我们应用单细胞 RNA-seq 技术解析人受精后胚胎 4-8 周 (Carnegie 阶段 12-21) 的早期肺发育过程，共捕获 169,686 个单细胞并绘制肺发育图谱。分析发现肺近-远端的特征基因在 4 周的肺内胚层上皮细胞中已经呈现差异表达，说明肺的近-远端特化早在 4 周的肺芽阶段就已经启动，早于过去认为的 5 周时才发生近-远端特化。我们进一步发掘了新的调控肺近-远端特化的转录因子，如近端的 THRB 和 EGR3 及远端的 ETV1 和 SOX6。此外，细胞互作分析显示上皮细胞的发育与所处的微环境密切相关，如上皮细胞与间充质细胞存在大量显著的配体-受体相互作用，我们发现其中一类间充质细胞，其分泌的信号因子 BDNF 能够促进肺上皮的生长和分支。最后，我们描绘了气道平滑肌和血管平滑肌细胞命运分离的动态过程。总而言之，本研究扩展了我们对胚胎期肺发育过程的认识，全新发现的转录因子和微环境有望为器官重建和再生医学开辟了新的途径。



金颖，研究员，博士生导师。上海交通大学特聘教授，上海市生殖医学重点实验室主任，中国科学院上海营养与健康研究所多能干细胞研究组课题组长。

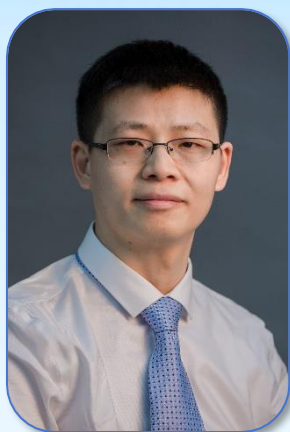
她从事胚胎干细胞和胚胎发育早期细胞命运分子调控机制的研究二十余年，在多能干细胞系的建立、发育多能性及自我更新的分子调控方面有多项原创性成果，发表了一系列高质量的学术论文，包括 Cell Stem Cell, Development Cell, PNAS 等，培养了多位优秀的干细胞研究青年人才，并先后获得教育部自然科学奖二等奖和中国干细胞研究创新奖等。

解析人胚胎干细胞特性维持的转录后调控机制健康研究院

金颖

Shanghai Jiaotong University School of Medicine/Shanghai Nutrition and Health Institute, CAS

【摘要】 Human embryonic stem cells (hESCs) have great potential for developmental biology and regenerative medicine. However, extensive apoptosis and DNA damage often occur when hESCs respond to various stresses or injuries. Understanding the molecular control and identifying new factors associated with hESC survival are fundamental to ensure the high quality of hESCs. Cell identity is determined by cell type-specific gene transcription programs that are modulated at both transcriptional and posttranscriptional levels. Relative to the transcriptional regulation, the posttranscriptional regulation is less known, although it plays critical role in cell fate determination. Among multiple posttranscriptional events, pre-mRNA splicing and modification are two critical processes in gene expression regulation. Particularly, alternative splicing (AS) provides a mechanism to expand mRNA and protein diversity from the same genomic template. Understanding how pre-mRNA AS and modification participate in supporting hESC survival and identifying new factors are fundamental to ensure the high quality of hESCs. Here, we describe two new factors required for hESC survival. Both PRPF8 and PRPF6 are pre-mRNA splicing factors and important components of tri-snRNP in spliceosomes. Knockdown of either PRPF8 or PRPF6 results in hESC apoptosis. Our studies reveal that PRPF8 controls AS of PIRH2, a gene coding a ubiquitin E3 ligase of p53. PRPF8 knockdown specifically increases the transcript level of the PIRH2B isoform, which lacks a RING domain and E3 ligase activity, in turn, activates the p53 pathway and cell death. As for PRPF6, its knockdown in hESCs gives rise to severe DNA damage in addition to apoptosis. To elucidate how PRPF6 maintains genome integrity of hESCs, we conduct a series of experiments and bioinformatics analysis. Our results indicate that PRPF6 can bridge spliceosomes and m6A writers through forming nuclear condensates to support genomic stability and survival of hESCs. These findings highlight that pre-mRNA splicing and m6A modification machineries coordinate robustly to ensure dynamic and precise regulation of gene expression and guard genomic stability in hESCs.



吴旭东，天津医科大学基础医学院细胞生物学学系主任、教授、博士生导师，天津市医学表观遗传学重点室主任，中国医学科学院血液学研究所兼职研究员，入选国家级青年拔尖人才。2004年毕业于华中科技大学同济医学院，2009年获得北京协和医学院博士学位，2014年开始在天津医科大学组建实验室。主要研究方向为表观遗传学：探索表观遗传信息建立及交互作用的分子基础，明确组蛋白修饰的动态调控机制及其生物学和病理生理学意义。目前在 Mol Cell、Cell Res、Nat Commun 等杂志发表研究论文 20 多篇；获批国家发明专利一项；主持国家重点研发计划、国家自然科学基金重点国合与面上项目、天津市杰青等科研项目。

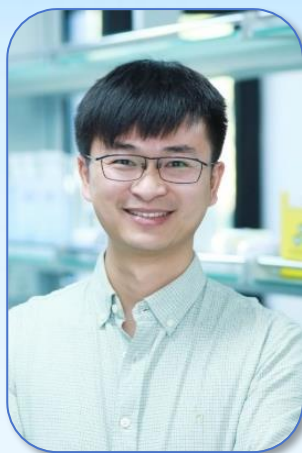
Preventing Post-Implantation Embryonic Development Defects Caused by Alcohol Exposure Through Restoration of the CREB/ KDM2B Axis

Hang Liu¹, Feifei Zuo¹, Qian Li¹, Cailing Lu², Xudong Wu¹

¹Department of Cell Biology, Tianjin Medical University

²Department of Genetics, National Research Institute for Family Planning, Beijing, China

【摘要】 Peri-implantation establishment of Polycomb group (PcG) proteins at promoters is critical for the post-implantation development, which requires the long isoform of KDM2B (KDM2BLF). Nevertheless, the mechanisms governing the spatiotemporal induction of KDM2BLF expression or its disruption under pathological conditions, remain elusive. Here we find that CREB (cAMP response element-binding protein) activity is indispensable for induction of KDM2BLF expression and exit from naïve pluripotency. When embryos are exposed to ethanol during the pre-implantation stage, CREB inactivation and increased risks of post-implantation defects are observed, accompanied with KDM2BLF insufficiency and impaired PcG establishment in epiblasts. Consistently, treatment of mouse embryonic stem cells with acetaldehyde, the primary metabolic product of ethanol, affects exit from naïve pluripotency, which can be rescued by constitutive active CREB or CREB agonist Rolipram at the presence of intact KDM2BLF. Moreover, Rolipram successfully restores the post-implantation embryonic development. Therefore, our study highlights the crucial functions of CREB signaling in chromatin configuration and embryonic development, providing insights into the teratogenic effects induced by ethanol and proposing potential prevention strategies.



周帆，清华大学生命科学学院、清华-北大生命联合中心研究员，博导。2016 年博士毕业于军事医学科学院，2016 年在北京大学从事博士后研究，2020 年加入清华大学和组建实验室。致力于整合体内功能鉴定、组学挖掘和遗传学操控等体系，研究围着床胚胎发育中的细胞命运规律与调控机制，研究工作发表在 *Developmental Cell* (2023)、*Cell Stem Cell* (2023)、*Nature* (2019、2016) 等期刊。2016 年获吴瑞奖，2017 年入选中国科协青年人才托举工程，解析人类胚胎着床研究入选 2019 年中国生命科学十大进展，2022 年获科技部国家重点研发计划资助。

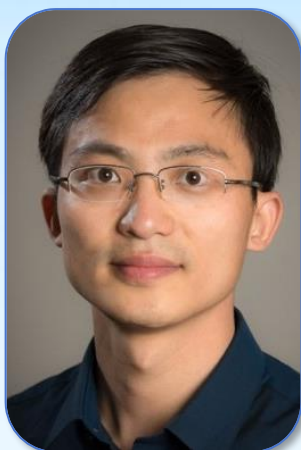
Peri-implantation embryogenesis and regulation

Qingyuan Zhu¹, Jitao Ge¹, Ying Liu¹, Fan Zhou^{1*}

¹Tsinghua-Peking Center for Life Sciences, School of Life Sciences, Tsinghua University, Beijing, 100084

*Correspondence: zhoufanlove@tsinghua.edu.cn

【摘要】 Connecting preceding blastocyst formation and following gastrulation respectively, peri-implantation embryogenesis is a key biological event during mammalian development. The embryo undergoes a series of cellular and molecular regulatory processes from pre- to post-implantation transition (PPT). In this presentation, we will discuss in vitro and in vivo models, omics measurement and molecular marker identification to explore the ingenious linkages among molecular program, lineage specialization, and polarity formation from a perspective of multidimensional molecular regulation. Relevant studies potentially provide clues to understand cell fate and regulation of embryo development, as well as the possible causes of habitual abortion and infertility.



祝赛勇, 浙江大学生命科学研究院研究员, 国家青年人才项目入选者。研究方向长期聚焦在干细胞化学生物学、再生医学等前沿领域, 近期研究成果包括细胞快速化学重编程 FCR-iPSC、胰岛前体细胞高效扩增及分化 ePP-islet 等, 相关研究成果发表在 Nature、Nature Cell Biology、Cell Stem Cell、Nature Communications、Science Advances、EMBO J、PNAS 等国际知名期刊, 并已获得 10 多项专利。

Fast Chemical Reprogramming of Somatic Cells to Pluripotency

祝赛勇

浙江大学

【摘要】 Reprogramming somatic cells towards pluripotent stem cells (PSCs) not only provide essential approaches for regenerative medicine, but also have revolutionized our understanding of cellular plasticity. The resulting iPSCs resemble embryonic stem cells (ESCs) molecularly and functionally. Notably, induced pluripotency provides a biochemically and genetically trackable system to dissect molecular mechanisms controlling cell fates. Chemical approaches can provide novel and effective small molecules that can be used to control cell fates, states, and functions, and be developed as a potential therapy strategy. Recent advances on cellular reprogramming by only small molecules hold enormous potentials for regenerative medicine. However, chemical reprogramming remains a slow process and labour intensive, hindering its broad applications and the investigation of underlying molecular mechanisms. Here, we develop a fast chemical reprogramming (FCR) system, which significantly improves the kinetics of cell identity rewiring. These iPSCs generated by FCR are morphologically, molecularly and functionally similar to ESCs, indicating successful reprogramming by the FCR platform. Next, we find that FCR rapidly goes through an interesting route for pluripotent reprogramming, uniquely transitioning through a developmentally diapause-like state. Furthermore, FCR critically enables comprehensive characterizations using multi-omics technologies, and has revealed unexpected important features including key regulatory factors and epigenetic dynamics. Particularly, activation of pluripotency-related endogenous retroviruses via inhibition of heterochromatin significantly enhances reprogramming. Our studies provide critical insights into how only environmental cues are sufficient to rapidly reinstate pluripotency in somatic cells, and make notable technical and conceptual advances for solving the puzzle of regeneration.



毛志勇，同济大学教授，博导，同济大学附属第一妇婴保健院转化医学研究中心主任，国家杰青、优青、海外高层次青年人才、上海市优秀学术带头人。

学术兼职：中国细胞生物学会衰老细胞生物学分会常务委员，中国生物物理学会衰老生物学专业委员会常务委员，中国老年医学学会基础与转化医学分会常务委员。主持国家基金委杰出青年基金、优秀青年基金项目、重大研究计划集成项目、科技部 973 青年项目及重点研发计划子课题等科研基金。

研究方向：从事衰老及干细胞与基因组稳定性研究，阐明了衰老及干细胞相关 DNA 修复变化及调控机制，建立了一系列研究衰老相关 DNA 修复的细胞和动物模型，以通讯（含共同）或第一作者在 Science、Nature、Nature Cancer、PNAS、Nucleic Acids Research、eLife 等国际期刊发表高水平学术论文。

靶向 DNA 修复提高干细胞质量的探索研究

毛志勇

同济大学

【摘要】 干细胞耗竭及基因组不稳定均是衰老的重要特征。在衰老的个体内，干细胞池无法高效更新及分化，导致组织器官功能衰退，最终引发器官及个体衰老乃至衰老相关疾病的发生。因此，基于多能干细胞的细胞疗法是延缓衰老、治疗衰老相关疾病的重要途径，而获取病人自身来源的干细胞进行疾病建模、药物筛选亦是未来进行个性化医疗的必然要求。然而，上述设想的实现不可避免地涉及年老个体来源体细胞的重编程及诱导多能干细胞的体外培养。导入 Yamanaka 因子或体细胞核移植 (SCNT) 是诱导多能干细胞的两大途径，而我们的前期研究发现：年老个体来源诱导的多能干细胞及 SCNT 获取的多能干细胞均存在基因组稳定性的显著下降；此外，在体外连续传代过程中，诱导多能干细胞亦会发生 DNA 损伤的进一步积累。机制研究揭示：SIRT6 表达下降介导了年老个体来源的诱导多能干细胞的非同源末端连接 (NHEJ) 修复受损，进而导致细胞多能性下降；而同源重组 (HR) 修复受损则会导致 SCNT 效率下降，这限制了基于干细胞的细胞疗法的临床转化。为克服上述困境，我们利用 SIRT6 别构激动剂 MDL-800 成功提升年老个体来源诱导多能干细胞的 NHEJ 修复效率及基因组稳定性，并改善其分化潜能；我们还基于自主研发的高通量药物筛选平台，获取了特异性激活 HR 修复的天然小分子杜鹃素，并揭示其可直接结合并激活去泛素化酶 UCHL3 从而促进 HR 关键因子 RAD51 的招募，提升 HR 修复能力，最终促进 SCNT 效率。我们的研究为未来基于多能干细胞进行衰老及相关疾病的干预提供了新的可能。



丁秋蓉，博士，中国科学院上海营养与健康研究所研究员，博士生导师。国家海外高层次人才引进计划（青年），中国科学院百人计划，上海市优秀学科带头人。致力于结合干细胞生物学和基因编辑技术，探索肝纤维化、肝硬化等严重肝病的致病机理及新的治疗方案。主要研究成果以通讯作者在 Nat Metab, Mol Cell, J Hepatol, Nat Commun, Cell Disc, Cell Rep 等杂志发表论文 20 余篇。作为项目负责人承担国家自然科学基金重点、国家重点研发计划课题、中科院先导子课题等项目。

Functional study of the transient hepatic steatosis in liver regeneration

丁秋蓉

中国科学院上海营养与健康研究所

【摘要】 The early phase lipid accumulation is essential for liver regeneration. However, whether this transient steatosis can serve as signals to direct liver regeneration rather than simply providing building blocks for cell proliferation remains unclear. Through in vivo CRISPR screening, we identify MIER1 as a key epigenetic regulator that bridges the acute steatosis and chromatin remodeling and cell proliferating in liver regeneration. Physiologically, the transient steatosis in early regeneration causes acute stress to hepatocytes, activating the EIF2S pathway, and consequently attenuating MIER1 translation. MIER1 downregulation in turn promotes cell cycle gene expression and regeneration through affecting chromatin remodeling. Consistently, affected liver transient steatosis due to adipose-specific Lipe knockout led to compromised MIER1 regulation and impaired regeneration, which can be rescued by liver MIER1 depletion; whereas pre-treatment with an acute high-fat diet before surgery can significantly improve liver regeneration. Furthermore, the signaling function of the acute lipid accumulation is impaired in animals with chronic liver steatosis; whereas MIER1 depletion greatly improves regeneration in these animals. Taken together, our studies reveal how the energy and the biomaterials— e.g. supplied by lipids, and the epigenetic events are intimately intertwined to impact liver regeneration, and suggest a potential strategy to boost liver regeneration.



程辉博士。中国医学科学院血液病医院（血液学研究所）研究员，协和准长聘助理教授、博导，中以联合实验室副主任。研究方向为造血干细胞与微环境。在 Cell Stem Cell、Nat Cell Biol、Blood、Leukemia、J Clin Invest、J Exp Med、Nat Commun 等杂志上发表论文 40 余篇。国家重点研发计划（中以专项）首席。获国家优青、天津市杰青等人才项目。获国家自然科学基金二等奖（2020）、天津市自然科学特等奖（2022）和一等奖（2015）。获国内外发明专利 5 项。中国生理学会青年委员、中国生理学会血液生理学会专委会委员和天津市血液与再生医学学会理事。

造血干细胞与微环境

程辉

中国医学科学院血液病医院

【摘要】 Hematopoietic differentiation is controlled by intrinsic regulators and the extrinsic hematopoietic niche. ATF4 plays a crucial role in the function of fetal and adult hematopoietic stem cell (HSC) maintenance; however, the precise function of ATF4 in the bone marrow niche and how ATF4 regulates adult hematopoiesis remain largely unknown. Here, we employ four cell-type-specific mouse Cre lines to conditionally knock out Atf4 in Cdh5+ endothelial cells, Prx1+ bone marrow stromal cells, Osx+ osteo-progenitor cells, and Mx1+ hematopoietic cells, and uncover the role of Atf4 in niche cells and hematopoiesis. Intriguingly, depletion of Atf4 in niche cells does not affect hematopoiesis; however, Atf4-deficient hematopoietic cells exhibit HSC function and erythroid differentiation defects, which lead to hypoplastic anemia. Mechanistically, ATF4 directly regulates the transcription of Rps19bp1 which is in turn involved in 40S ribosomal subunit assembly to coordinate ribosome biogenesis and promote erythropoiesis. Finally, we demonstrate that under conditions of 5-fluorouracil-induced stress, Atf4 depletion impedes the recovery of hematopoietic lineages, which requires efficient ribosome biogenesis. Taken together, our findings highlight the indispensable role of the ATF4-RPS19BP1 axis in the regulation of erythropoiesis.



胡慧丽教授，山东大学基础医学院系统生物医学系主任。2014 年山东大学博士毕业，2015-2018 年在荷兰皇家科学院 Hans Clevers 教授实验室完成博士后研究。主要建立三维类器官模型并与生物信息学、遗传筛选技术相结合，深入探究细胞命运可塑性和疾病发病机制，并探讨类器官在疾病干预中的应用。代表性成果以第一作者或通讯作者身份在 Cell (ESI 高被引论文)、Cancer Cell 等共发表论文 30 余篇。课题组获 Cell Stem Cell 报到。承担国家优秀青年基金，国家重点研发计划青年科学家项目。

Tissue derived organoids and regeneration

安亚春¹，连佳贝¹，郭立强²，范玉佳¹，杜浩然¹，毛雨诺¹，胡慧丽^{1*}

1 教育部实验畸形学重点实验室，山东大学基础医学院系统生物医学系，山东大学基础医学院干细胞与再生医学中心，济南，250012

2 山东大学齐鲁医院，济南，250012

*通讯作者，huhuili@sdu.edu.cn

【摘要】干祖细胞体外三维重建模拟了发育、稳态或损伤再生过程，为生理或病理条件下细胞命运调控新机制阐述和疾病干预策略提供了重要体外研究模型。如何驱动成体细胞高效建立组织来源的类器官并维持其长期扩增，是实现体外器官再造的关键科学问题。我们一方面运用组织来源的类器官、结合小鼠模型与生物信息分析、基因编辑技术，解析异质性肝脏类器官中细胞命运调控新机制，建立新型类器官并初步探究其在衰老干预、疾病治疗和仿生器官构建中的应用。另一方面探究精准模拟疾病和干预策略的多细胞新型类器官。

运用前期建立的肝脏类器官模拟了肝脏再生过程，结合单细胞转录组测序分析，我们发现异质性类器官中新细胞亚群改变在肝细胞类器官的增殖中和体内肝再生当中的促进作用，发现了促进肝脏再生的转录因子和调控网络。通过空间转录组测序我们初步探究了这些新机制在再生过程中引起的空间变化，为构建高仿生类器官提供了分子依据。同时我们也建立了模拟肾脏再生和疾病的类器官模型，为小分子药物筛选提供了平台。



赵扬，2003 年本科毕业于北京大学生命科学学院，2009 年于北京大学获博士学位。现任北京大学未来技术学院分子医学研究所“细胞重编程和再生医疗研究室”主任 (PI)，博士生导师，北大清华生命科学联合中心、天然药物及仿生药物国家重点实验室研究员。入选国家“万人计划”青年拔尖人才，国家自然科学基金委“优青”，担任国家重点研发计划的课题负责人。赵扬曾在诱导多能干细胞、细胞重编程等领域取得多项突破，相关成果在 Science、Cell、Cell Stem Cell 等杂志发表论文 20 余篇，SCI 总引用次数达 6000 余次，相关成果曾获评“2013 年度中国科学十大进展”、“2013 年度中国高校十大科技进展”、细胞出版社“2015 中国年度论文”、“2015 年中国生命科学领域十大进展”等。

基于小分子和表型大数据的细胞命运调控新策略

赵扬

北京大学

【摘要】 Cellular reprogramming and pluripotent stem cells (PSC) differentiation into diverse functional cell types provide promising solutions to support drug discovery, disease modeling, and regenerative medicine. Phenotypic screening methods have greatly accelerated the study of mechanisms involved in cell fate reprogramming and PSC differentiation, and additionally has enabled the development of new chemical tools for stem cell research. In our studies, we developed two transcriptional profile-based phenotypic screening platforms, DRUG-seq2 (a modified DRUD-seq method) and PHDs-seq (Probe Hybridization based Drug screening by sequencing) to overcome some limitations inherent in previous phenotypic screening methods. We showed their suitability for screening chemical compounds that induce cell reprogramming and revealing the underlying molecular mechanisms. In addition, by harnessing live-cell bright-field imaging and machine learning (ML), we realize real-time cell recognition in the entire iPSC differentiation process, e.g., cardiomyocytes (CMs), cardiac progenitor cells (CPCs), PSC clones, and even misdifferentiated cells. This enables non-invasive prediction of iPSC differentiation efficiency, purification of ML-recognized CMs and CPCs for reducing cell contamination, early assessment of the CHIR99021 dose for correcting the misdifferentiation trajectory, and evaluation of initial PSC colonies for controlling the start point of differentiation, all of which provide a more invulnerable differentiation method with resistance to variability. Moreover, with the established ML models as a readout for the chemical screen, we identify a CDK8 inhibitor that can further improve the cell resistance to the overdose of CHIR99021. Together, these studies showed examples that small molecules and phenotyping profiles (transcriptomics and imageomics) can empower the development and optimization of methods for stem cell research, providing a better understanding and rational modulation of cell fate transition processes for cell manufacturing or pharmaceutical regenerative medicine.



时颖超，广东省智能科学与技术研究院神经细胞图谱与认知环路研究组组长，研究员；中国科学院青年创新促进会会员。于 2018 年在中国科学院生物物理研究所获理学博士学位。主要从事单细胞多组学测序及类脑器官的三维培养方面的研究，2020-2021 年期间，以共同一作第一位及第一作者的身份在 Science , PLoS Biology 及 Current Opinion in Neuroscience 杂志上发表了探究人脑中间神经元发育规律及类脑器官优化培养的学术论文共 3 篇。除此之外，以往的研究工作发表在了 Science, Neuron, Scientific Reports 等国际期刊上，并授权专利 1 项。

主持国家自然科学基金面上项目 1 项，作为项目骨干参与国家科技部科技创新 2030-“脑科学与类脑研究”重大项目 1 项。

解析人脑中间神经元多样性和腹侧类器官

时颖超

广东省智能科学与技术研究院

【摘要】中间神经元是大脑中最重要神经元类型之一，主要通过释放 GABA 调节脑神经活动。中间神经元功能异常会打破脑神经网络中的兴奋-抑制平衡，从而导致癫痫、自闭症、精神分裂等多种神经精神疾病。中间神经元在形态、基因表达、环路连接以及神经电生理活动模式等方面表现出了极其丰富的多样性，而中间神经元的多样性是大脑能够实现复杂而精细功能的基础。然而，目前关于人脑中间神经元的多样性形成机制尚不清楚。我们的研究系统地解析了人脑中间神经元发育和多样性形成的分子调控机制，并通过与小鼠中间神经元的发育规律进行比较揭示了人脑中间神经元发育在进化上的保守性和特异性。我们对人脑中间神经元发育机制的研究确定了一系列关键的调控分子。基于前期的工作基础，我们进一步构建了腹侧类器官，以期作为模拟人脑中间神经元发育以及探究中间神经元发育相关疾病的体外模型。



席建忠，北京大学教授，国家特聘教授长江学者，国家杰出青年基金获得者，重点研发项目首席科学家，北京大学未来技术学院副院长。目前担任中国生物医学工程学会类器官和器官芯片分会副主任、中国医药生物技术协会基因检测分会副主任、中国化学会化学生物学专业委员会委员、中国医药生物技术协会生物芯片分会常务委员、中国生物医学工程学会生物医学测量分会委员、中国医师协会临床精准医疗专业委员会等职务，是 Science、JACS、Biomaterials 等多个国际知名杂志的审稿人。

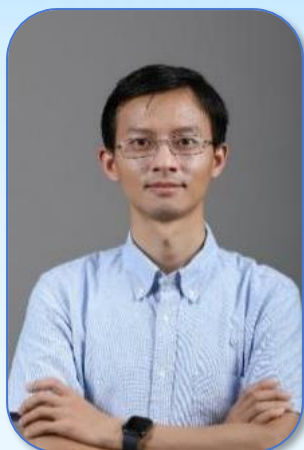
在化学、生物、微电子加工等多个领域，有良好的海内外教育与工作经历，是前沿交叉研究领域难得的领军人才。主要从事肿瘤精准医学、基因编辑、生物芯片等研发及应用，在新药靶点、肿瘤体外模型、高通量功能筛选等方面，取得了突出成绩，在 Nature, Nature Biotechnology, Nature Cell Biology, Nature Communication, PNAS, Angew. Chem. Int. Ed. 等专业杂志，发表 70 余篇高水平学术论文，申报 10 项国家发明专利，其中 4 项授权。主持或承担过国家级课题 17 项。

基于微肿瘤 3D 模型开展耐药机制研究

席建忠

北京大学

【摘要】化疗及靶向治疗是治疗恶性肿瘤的主要手段之一。但是，只有 30% 的癌症病人可以找到对应药物，绝大部分患者不得不一次次去试药，至少有一半的病人无药可用。患者不仅浪费大量的金钱，更重要的是耽误治疗最佳时间，甚至加重了病情。这是全球癌症治疗的实情，也是精准医疗行业的痛点！因此，为肿瘤患者快速准确地找到最适合的治疗方案，是医院和患者的当务之急需解决的问题。最近，我们团队开发出一种全新精准个体化药效评估技术—微肿瘤芯片。微肿瘤模型由肿瘤细胞、成纤维细胞及免疫细胞等自组装和增殖形成，能准确地预测胃肠癌等临床病人的药效反应（90% 以上）。微肿瘤模型很好地再现肿瘤患者的病理、分子以及临床治疗的特征，不仅有助于肿瘤异质性分子机制的解析，而且对新药研发具有深远的意义。



尹晓磊，同济大学生命科学与技术学院教授，博士生导师，同济大学附属东方医院特聘研究员。入选国家青年高层次人才计划。国家重点研发计划“干细胞及转化研究”重点专项首席科学家。

本科和博士均毕业于北京大学，其后于麻省理工学院和哈佛大学医学院进行博士后和讲师阶段的研究。长期从事干细胞命运调控及再生医学研究。已在 Cell Stem Cell, Nature Methods 等杂志上发表论文 20 余篇，引用 5000 余次。

小肠类器官与干细胞命运调控

尹晓磊

同济大学

【摘要】 成体干细胞衍生的类器官在再现组织结构、细胞组成和功能方面表现出卓越的能力，使其成为研究体外发育和疾病的一个极具吸引力的平台。但目前的类器官系统还存在异质性强，细胞类型有限，可扩展性低等挑战。例如，许多组织的类器官为维持干细胞自我更新和扩增而优化，这导致功能细胞多样性较低；相反，促进类器官的分化和成熟往往导致类器官停止增殖或增殖能力下降。我们认为，维持类器官中干细胞自我更新和分化之间的平衡是获得具有细胞多样性的类器官的关键。在本研究中，我们利用小分子来增强人肠道类器官中干细胞的干性，从而增强它们的分化潜能，进而增加类器官内的细胞多样性。我们进一步利用信号通路的组合使自我更新和分化之间的平衡发生偏移，获得富含肠道干细胞或特定肠道功能细胞类型的类器官。这一优化的培养体系可以提高小肠类器官系统在高通量筛选等应用中的可扩展性和实用性。



向阳飞，上海科技大学干细胞与神经生物学实验室负责人，国家人才计划（青年）、上海市人才计划获得者，中国神经科学学会发育与再生分会委员。从事脑类器官技术研究近十年。主要内容包括基于人类多能干细胞的脑区特异类器官、复杂脑类器官构建技术开发及应用。相关工作被 Nature、Cell、Cell Stem Cell 等杂志的评述文章强调，被 Nature、Cell 类器官主题收录，被 Nature Methods 编辑部作为重点关注研究方向（“Methods to Watch”）介绍。实验室于 2020 年、2021 年获干细胞领域著名期刊 Cell Stem Cell 介绍。作为课题负责人参与国家重点研发计划、国家自然科学基金、上海市科委等项目。

人源神经类器官的构建与应用

向阳飞

上海科技大学

【摘要】 神经类器官是体外模拟人类大脑及神经系统其他结构的三维模型。

神经类器官以干细胞为基础，通过在三维悬浮培养条件下的自发或定向分化、依赖细胞间的自组织而形成。我们在过去十年的研究中聚焦干细胞定向分化，构建了多种人脑区特异的类器官，同时，通过整合多脑区或多细胞谱系，探索建立了更为复杂的人脑类器官技术，为便利地在体外研究人源遗传背景下的脑发育、功能、疾病、药物作用等提供了新模型。作为一种新的前沿技术，神经类器官依旧面临诸多技术挑战有待攻克。本次报告将介绍我们在人源神经类器官精细化构建方面的探索，包括如何构建具备人脑核团特征的类器官。



沈琳教授，北京大学肿瘤医院，消化肿瘤内科主任、I期临床试验病房主任。历任北京大学肿瘤医院副院长、北京市肿瘤防治研究所副所长，北京学者，北京市突出贡献专家。中国抗癌协会肿瘤精准治疗专业委员会主任委员，中国抗癌协会肿瘤药物临床研究专业委员会首届主任委员，中国临床肿瘤学会临床研究专家委员会主任委员，中国临床肿瘤学会胃癌专家委员会候任主任委员，中国抗癌协会大肠癌专业委员会副主任委员，北京癌症防治学会理事会轮值理事长。

细胞治疗在消化道肿瘤中的应用

沈琳

北大肿瘤医院

【摘要】晚期消化系统肿瘤的治疗以化疗、分子靶向治疗等药物治疗为主，但面临化疗疗效有限、分子靶向药物适用人群少，总体治疗效果已达瓶颈的问题。近年来以抗 PD-1/PD-L1 抗体为代表的免疫检查点抑制剂在食管癌、胃癌等治疗中获得成功，一定程度上改善了晚期消化道肿瘤的预后。与此同时，以 CAR-T (Chimeric antigen receptor T cell, 嵌合抗原受体 T 细胞) 疗法为代表的细胞治疗在血液系统恶性肿瘤治疗也取得令人瞩目的成功，其在实体肿瘤的应用也备受关注。随着技术的进步及观念的更新,越来越多的细胞治疗产品在消化系统肿瘤中开展早期探索性研究, 尤其是以 CLDN18.2、Gucy2C、GPC3 等为靶点的 CAR-T 细胞已经展现出巨大的潜力。



王皓毅，中国科学院动物研究所干细胞与生殖生物学国家重点实验室副主任、基因工程技术研究组组长。

2009 年于美国华盛顿大学获得分子细胞生物学博士学位，开发了基于转座子的 Calling Card 技术；在麻省理工学院 Whitehead 研究所 Rudolf Jaenisch 实验室进行博士后研究，从事全能性干细胞和小鼠中基因编辑技术的开发和应用。

在近年研究中取得多项成果，包括开发新型 TnpB 和 Argonaute 靶向核酸酶工具；应用基因编辑构建抗耗竭 CAR-T 细胞；建立胚胎电转构建基因编辑小鼠模型方法；基于 naive 胚胎干细胞实现人类 X 染色体随机失活的模拟；建立原位基因表达调控技术 CRISPR-on 和 Casillio 系统等。

新型基因编辑技术开发

王皓毅

中国科学院动物研究所

【摘要】以 CRISPR/Cas 为代表的基因编辑技术革命性的改变了生物学以及相关产业。但现有工具相对较大的尺寸使其较难递送，因此限制其应用。另外，现有技术在有些物种和细胞类型中大片段 DNA 整合的效率仍然较低。因此，我们聚焦开发了具有小尺寸和整合大片段 DNA 能力的新型基因编辑工具。基于数据驱动的模式，采用进化基因组学的方法，我们对原核生物转座子 IS605 家族的 TnpB 蛋白和 102 个真核基因组中的 DNA 转座子进行了系统研究，并鉴定出多种尺寸极小且在人类细胞中具有高活性的 TnpB 基因编辑工具和具有大片段基因整合活性的 DNA 转座子工具。这些成果丰富了基因工程工具箱，并且为转座子生物学研究提供了重要的功能数据和理解。

将这些基因编辑技术应用于细胞治疗有助于提高其有效性和安全性，因此我们也针对 CAR-T 细胞治疗实体肿瘤所面临的诸多挑战进行了基因改造，从而显著提升了 CAR-T 细胞抗耗竭能力和体内体外功能，为未来的临床应用提供了重要的基础。



杨辉，中国科学院脑科学与智能技术卓越创新中心研究员，辉大基因创始人、首席科学顾问，国家杰出青年基金获得者，上海市青年拔尖人才、优秀学术带头人，何梁何利科学与技术进步奖、中源协和生命医学创新突破奖、药明康德生命化学研究奖杰出成就奖获得者。

长期专注于基因编辑领域研究，在基因编辑技术开发、安全性评价以及基因治疗遗传性疾病的临床转化研究中取得了一系列原创性成果。首创了更灵敏的基因编辑脱靶检测技术 GOTI，并首次证明单碱基编辑工具存在严重的 DNA 脱靶效应和 RNA 脱靶效应；开发了多种具有底层专利的小尺寸 RNA 编辑工具和 DNA 编辑工具，并获得中美国家授权；首创不依赖于脱氨酶的由糖苷化酶介导的 DNA 单碱基编辑系统。

研究成果刊登于 Science、Nature、Cell、Nature Methods、Nature Biotechnology、Nature Cell Biology、Cell Research 等国际顶级期刊。其中，“单碱基基因编辑造成大量脱靶效应及其优化解决方法”研究成果入选“2019 度中国生命科学十大进展”。

Next generation of DNA base editors and their applications

Tong Li¹, Huawei Tong¹, Dingyi Han², Qingquan Xiao¹, Yingsi Zhou¹, Hui Yang^{1,2*}

¹HuidaGene Therapeutics Co., Ltd., Shanghai 200131; ²Institute of Neuroscience, Center for Excellence in Brain Science and Intelligence Technology, Chinese Academy of Sciences, Shanghai 200030

*Correspondence: huiyang@ion.ac.cn

【摘要】 Base editors have great potential in both basic research and gene therapy. Existing base editors are constructed by fusing nCas9 with the adenine or cytidine deaminase domain, which initiates deamination reactions on A or C bases, activating the base excision repair mechanism, consequently enabling base substitutions such as A-to-G, C-to-T, and C-to-G. However, there is currently no base editor capable of achieving adenine transversion or direct guanine base editing. Additionally, due to the large size of Cas9, base editors based on nCas9 struggle to be efficiently packaged and delivered using a single AAV vector, severely limiting their in vivo gene editing applications. Here, we significantly enhanced the activity of N-methylpurine DNA glycosylase (MPG), which possesses hypoxanthine base (Hx) excision activity, through multiple rounds of engineering. By fusing the optimized MPG variant with ABE8e, we developed an efficient adenine base editor named AYBE, which achieved up to 72% adenine-to-Y (Y = C or T) editing efficiency at endogenous cellular sites, with lower off-target effects compared to ABE8e. Moreover, by engineering MPG to have high guanine excision efficiency in vitro, we created an MPG variant that, when fused with nCas9, resulted in a guanine base editor called gGBE, which does not rely on deaminases and is based on glycosylase activity. gGBE achieved high guanine editing efficiency, reaching up to 81.2% at endogenous cellular sites, with 94% G-to-Y editing product ratio and minimal off-target effects. In addition, we also developed miniature base editors derived from the IscB nuclease. The reprogrammable nucleases IscB and Cas9 share similar structural domains, but IscB is less than half the size of SpCas9, offering significant delivery advantages. Through multiple rounds of engineering of the OgeulIscB protein and its corresponding ω RNA, we obtained an IscB system that is highly efficient in mammalian systems, named enIscB (496 aa). Furthermore, by fusing cytosine or adenosine deaminase with enIscB nickase, we generated miniature IscB-derived base editors (miBEs), exhibiting robust editing efficiency (up to 92%) to induce DNA base conversions, with specificity similar to SpG Cas9. The development of AYBE and gGBE provides editing tools for 27% T(and C)-to-A SNPs and 5% T-to-G SNPs among all human pathogenic SNPs, which are uneditable using current base editors, while the development of miBEs further provides versatile tools for genome editing.



柳夏林，眼科学教授、主任医师、博士生导师，眼科学国家重点实验室PI，广东省医学领军人才，国自然重点及重大项目评审专家。

长期从事视网膜疾病等难治性致盲眼病的基础和临床研究，在干细胞及其衍生物调控免疫功能，促进眼组织再生修复等领域取得了多项成果。曾作为项目负责人承担干细胞外囊泡领域国家重点研发计划项目、国自然重点项目等多项国家级科研项目。牵头组织发布国内首个干细胞外囊泡团体标准（中国细胞生物学学会发布），在 Science Advances, PNAS, PloS Med, Cell Death and Differ, IOVS 等发表 SCI 论文 100 多篇。

MSC 细胞外囊泡在眼组织损伤修复中的作用机制及转化研究

柳夏林

中山大学

【摘要】围绕间充质干细胞来源的细胞外囊泡（MSC-sEV）促进眼表组织及视网膜神经组织损伤后修复的作用及机制开展研究。1) 发现 MSC-sEV 可通过 miR-204 有效调控巨噬细胞从 M1 促炎活化表型转化为 M2 抑炎表型，改善眼表微环境，促进眼表组织修复，缓解干眼症状；并且研发了脐带来源间充质干细胞外囊泡滴眼液应用于临床试验，可有效缓解难治性移植物抗宿主病相关性干眼患者的症状和体征。2) 发现 MSC-sEV 通过一种新的 G-CSF-to-Ly6Clow Mo/M Φ 信号轴促进视网膜神经节细胞的存活和轴突再生。眼内注射的 MSC-sEV 主要被视网膜血管周细胞及小胶质细胞吞噬，诱导集落刺激因子 G-CSF 的释放。这导致 Ly6Clow 单核细胞/单核细胞来源的巨噬细胞(Mo/M Φ)的招募，显著促进视神经损伤后 RGC 存活和轴突再生。这一研究表明特定的修复性免疫细胞亚群在眼组织神经损伤修复中的重要作用，同时揭示了血管周细胞从循环中招募修复性免疫细胞到促进眼组织修复的作用。



刘明耀，国家首批特聘教授，华东师范大学生命医学研究所所长，上海市调控生物学重点实验室主任。刘明耀教授致力于 G 蛋白偶联受体在个体发育和重大疾病发生发展中的功能、机理及靶向药物研发，同时在基因编辑和细胞治疗的技术应用转化中做出卓越研究。回国后作为首席科学家先后主持国家 973 和重大科学研究计划、国家自然科学基金重点项目、国家重大新药创制课题等。已在 Science、Nature、Nature Medicine、Nature Biotechnology、Nature Cell Biology、PNAS 等国际知名学术刊物上发表 SCI 论文 400 多篇，论文引用 2 万 8 千多次，H-Index 85，连续多年被评为高被引学者，申请专利 200 多项，授权 100 余项。2012 年至 2020 年担任华东师范大学生命科学学院院长、华师大-以色列海法大学科学与技术转化研究院院长。2012 年和 2017 年分别获得国家科学技术进步一等奖和上海市科技进步一等奖，2014 年获得上海市白玉兰纪念奖，2017 年起担任中国细胞生物学学会肿瘤细胞分会会长，2020 年起任教育部科技委员会委员，2021 年获得华东师范大学首届杰出学术贡献奖。

基因编辑与创新性细胞治疗

刘明耀

华东师范大学

【摘要】团队将基因编辑技术与 CAR-T 细胞治疗以及干细胞治疗有机结合，开发非病毒定点整合 CAR-T 细胞治疗技术，在国际上首次将基因编辑定点整合技术应用于非霍奇金淋巴瘤的临床治疗，相关研究论文发表在 2022 年 Nature 杂志，受到 CAR-T 细胞治疗产业的广泛关注，为基因编辑技术在 CAR-T 细胞治疗中的产业化应用提供基础和转化新模式。团队还利用基因编辑技术改造造血干细胞，有效恢复 β 地中海贫血患者红细胞中胎儿血红蛋白的表达，恢复其正常的红细胞功能，实现彻底治愈重度遗传性 β 地中海贫血，目前该技术已成功治愈 15 名 β 地中海贫血患者，也是国际上首次利用基因编辑技术治愈 β^0/β^0 重症地中海贫血患者，最早两例相关研究发表在 2022 年 Nature Medicine 杂志上。



杨黄恬 医学博士，中国科学院上海营养与健康研究所 特聘研究员；Fellow of the ISHR (国际心脏研究学会). 聚焦于 hPSCs 心肌谱系细胞分化、线粒体及活性物质在心肌缺血损伤修复中的作用、机制及应用转化研究。先后承担科技部、国自然、中科院和上海市多个项目。在国际知名期刊发表论著百余篇；获 2020 年度国家科学技术进步奖二等奖。任 ISHR 中国分会副主席、中国细胞生物学学会资深会员、中国药理学会心血管专委会常务理事、中国病生学会理事和心血管和信号转导专委会、中华医学会心血管病学分会基础学组和组织修复与再生分会心脏再生组委员、AHA/ASA Professional Membership 等；J Mol Cell Cardiol 和 Pflügers Archiv-Eur J Physiol 副主编；生理学报常务编委；Cell Death Disease, Acta Pharmacol Sinica, Cardiovascular Drugs and Therapy, Current Opinion in Physiology 等期刊编委。

hPSC-derived cardiac line age cells for repair of infarcted hearts

杨黄恬

中国科学院上海营养与健康研究所

【摘要】 心肌梗死(心梗是疾病死亡的重要要原因，其死亡率在我国呈逐年上升趋势。心梗导致大量心肌细胞死亡，由于心肌细胞有限的再生能力，丢失的心肌细胞被纤维瘢痕替代，进而导致心律失常和心力衰竭。现有治疗方法无法补偿心梗后丢失的心肌细胞和破坏的心肌组织、逆转心力衰竭的进程，因此，亟需发展缓解心肌细胞减容、促进梗死心脏组织和功能重建的治疗方法。

基于人多能干细胞 (hPSCs) 衍生心血管细胞移植治疗的探索显示了其可能的应用前景。我们研究证实移植 hPSCs 衍生心血管细胞前体细胞、心肌细胞和心外膜细胞可显著改善小鼠、猪或非人灵长类动物梗死心脏心功能和病理性重构。机制研究发现其分泌的胞外囊泡 (EVs) 和细胞因子通过调节局部炎症微环境、促进心肌细胞存活和增殖、血管新生；同时部分移植细胞发挥替代作用，进而改善梗死心肌心功能和局限疤痕。进一步我们比较了 hPSCs 衍生不同心血管细胞和移植方式提升心肌修复的疗效和机制，为细胞和细胞产物的临床转化应用提供临床前研究依据。



李伟，中国科学院动物研究所研究员，干细胞与生殖生物学国家重点实验室副主任。主要从事基因工程和干细胞等创新生物技术的研发，并利用这些新技术和模型揭示哺乳动物生殖与再生的基础调控规律，开发重大疾病的基因治疗。在包括 Cell、Nature、Science 在内的学术刊物发表通讯作者论文 40 余篇，获得基金委杰出青年科学基金、中国科学院青年科学家奖等资助和奖励。

哺乳动物再生机路径与转化

李伟

中国科学院动物研究所

【摘要】 Stem cells have versatile applications owing to their unique features, such as rapid and unlimited proliferation capacity and broad differentiation potential. They can serve as a model for developmental study, as well as the perfect seed cells for regenerative medicine. Moreover, stem cells have amazing potential to be engineered for novel phenotypes and functions. Here we introduce several novel stem cell tools or platforms we have developed during the past several years and discuss their potential applications. The haploid embryonic stem cells (ESCs) are derived from the haploid blastocyst, which provide a convenient approach for large-scale genetic screen and rapid generation of genome-modified animals. Another novel stem cell type is the mammalian allodiploid ESCs, which contain stable allodiploid genome of two evolutionarily distant related species, and can self-renew indefinitely and differentiate into all three germ layers. These features make them a useful tool for the identification of genetic basis of phenotypic differences between species. Our studies hence show that stem cell engineering is promising to generate novel tools for biological research.



刘彤日，牛津大学生物化学博士（2018 年 9 月 30 日）；北京大学生命科学&经济学双学士（2014 年 10 月 1 日）；国家留学基金委全额奖学金获得者；

主要经历：意胜生物创始人、CEO；iPSC 创新药公司海外首席代表，英国分公司总经理；英国伦敦干细胞学会会员、英国基因和细胞疗法再生医学学会会员；2022 年大兴区“新国门”领军人才；Hicool 2022 全球创业大赛优胜奖；多年海外 iPSC 干细胞领域科研及注册、公司运营及生物医学产业经验；

iPSC 分化胰岛细胞药物开发经验分享

刘彤日

北京意胜生物科技有限公司

【摘要】北京意胜生物科技有限公司成立于 2021 年 8 月，是多能干细胞（iPSC 与 ESC）分化细胞药物研发和生产的生物医药企业，专注于胰岛方向药物研发和产业化，以及通用型多能干细胞平台建设。到目前阶段，多能干细胞细胞分化胰岛细胞的全流程研发技术开发已完成，意胜生物自研的分化方案已可以成功将干细胞在体外细胞培养条件下成功分化为胰岛细胞，并可以检测到最终的胰岛细胞合成、分泌胰岛素（降血糖的有效成分），且在外界不同浓度的葡萄糖刺激下进行反馈调节，分泌不同量的胰岛素。同时意胜生物已完成细胞库建库、分化生产 CMC、临床前研究设计、临床方案设计等产业转化储备和相应人才配置，为实现糖尿病的细胞疗法治疗开发和临床试验而努力。

报告内容将围绕以下几个方面：

糖尿病及胰岛移植简介

Diabetes and Islet Transplantation

干细胞分化胰岛进展

Derivation of Islet from Stem Cell

从研发到产业转化

Tech Transferring from Research to Product Development

意胜生物简介

Essentia Introduction



赵维莅，主任医师，教授，博士生导师。国家杰出青年科学基金获得者，教育部长江学者特聘教授，科技部万人计划领军人才，百千万人才工程国家级人选。上海交通大学医学院附属瑞金医院副院长，上海市重中之重临床医学中心主任，上海血液学研究所所长。中华医学会血液学分会副主任委员，淋巴细胞疾病学组组长，中国病理生理学会理事，实验血液学专委会秘书长
中国临床肿瘤协会抗淋巴瘤联盟副主。

致力于淋巴细胞恶性疾病的临床和基础研究，以通讯/第一作者在《CANCER CELL》、《NATURE GENETICS》、《BLOOD》《LANCET HAEMATOL》、《SIGNAL TRANSDUCT TARGET THER》、《J HEMATOL ONCOL》、《MOLECULAR CANCER》等国际权威杂志发表文章 110 余篇，总影响因子超过 1500，30 分以上文章 14 篇，10 分以上文章 44 篇。相关成果以第一完成人获国家科学技术进步奖二等奖 1 项，省部级一等奖 6 项，获国家发明专利 14 项，主持国家科技部重点研发计划、863 重大项目、国家自然科学基金重点项目多项。先后荣获“全国卫生系统先进工作者”、“全国三八红旗手”、中国青年女科学家奖、EBMT 青年领袖奖、谈家桢生命科学奖、上海市科技精英等多项荣誉。

Targeting stem-like persistent cells in lymphoma treatment

赵维莅

上海瑞金医院

【摘要】持久性肿瘤细胞指的是常规抗肿瘤治疗后仍持续存活的一类肿瘤细胞亚群，是当今癌症治疗后复发耐药的关键难题，这群细胞具有生长缓慢或停滞、能量代谢灵活、细胞表型和肿瘤微环境高度可塑、对细胞凋亡抵抗以及对铁死亡敏感等生物学特征。因此，深入了解这群细胞的生物学特征及其产生的分子机制，有利于制定潜在的靶向治疗策略来打破癌症持久性，实现最大化避免肿瘤复发，从而提升癌症治疗后复发耐药患者的生存。



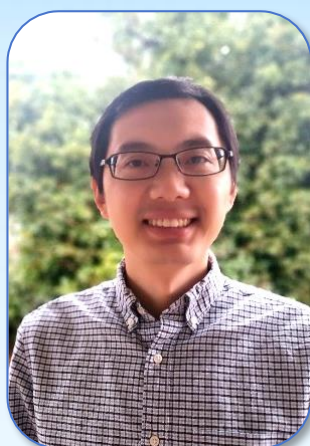
龚辉，华中科技大学武汉光电国家研究中心生物医学光子学功能实验室、兼任苏州脑空间信息研究院副院长。主要从事完整器官亚微米分辨率的三维精准光学成像（MOST、FMOST）及构建哺乳动物全脑神经环路、血管网络和高分辨图谱等研究。主持和完成了多项国家和省部级科研项目，包括科技创新 2030-“脑科学与类脑研究”重大项目、国家 973 项目课题、国家自然科学基金重大项目课题等。研究成果以第一作者或通讯作者发表于 Science, Nature Methods, Nature Neuroscience 等学术期刊 50 余篇，获 2014 年国家技术发明奖二等奖，2020-2021 年度黄家驷生物医学工程奖技术发明类一等奖。

亚微米分辨率三维获取完整器官的精准形态

龚辉

华中科技大学

【摘要】生物体是既复杂又精密的系统，是由相互联系、相互作用的器官组成的具有特定结构和功能的有机整体。要想全面系统地揭示生物体或器官的工作机理、了解组织器官的发育、衰老和再生情况，则先要明晰其中各类细胞的精细形态及其在组织中准确的空间方位。我将介绍自主研发的显微光学切片断层成像（MOST）和荧光显微光学切片断层成像（fMOST）技术原理、性能和相应的样本标记和处理方法，并展示利用 MOST/fMOST 成像技术以亚微米分辨率三维获取和可视化多种完整器官内的单细胞精细形态结构和位置信息，探讨大范围亚细胞水平三维成像和图像大数据计算新技术助力干细胞研究和应用的可能性。



钱永军，北京大学未来技术学院，北京大学未来技术学院研究员，北大-清华生命科学联合中心研究员，博士生导师。2016 年在北京大学生命科学学院获得博士学位。2018 至 2023 在冷泉港实验室及杜克大学医学院进行博士后研究。2023 年 7 月任职北京大学未来技术学院助理教授、研究员，同时加入北大-清华生命科学联合中心。实验室研究兴趣在于开发基于 RNA 的新工具、新方法；发展下一代细胞类型、细胞状态的监测和操纵技术；探索将新型 RNA 技术应用于神经生物学、干细胞生物学以及转化医学，推进“可编程医学”的发展。

Development of programmable RNA technology and its potential applications in biomedicine

钱永军

北京大学

【摘要】当前生物和医学研究中一个重要的瓶颈，是缺乏高度模块化和可编程的技术，以监测和操纵特定细胞类型和细胞状态。RNA 处在遗传信息传递的中心，并在细胞类型和细胞状态的多样性中起着重要作用。尽管近年来通过 RNA 测序积累了大量的转录组数据，但是在生物学和医学研究中，通过监测特定 RNA 来观察、操纵和编辑细胞仍然是一个巨大挑战。我将介绍我们最新发明的 CellREADR 技术：一种可编程的、序列特异的活体 RNA 监测的新方法。CellREADR 利用 ADAR（作用于 RNA 的腺苷脱氨酶）介导的 RNA 编辑，将细胞特异 RNA 的检测与效应蛋白的翻译耦合起来。通过病毒载体，CellREADR 实现了对小鼠、大鼠和猕猴大脑以及离体人脑组织中特定细胞类型的靶向。此外，CellREADR 还实现了对活体小鼠神经元类型的实时记录和控制。因此，CellREADR 技术显示出了基于 RNA 的细胞的监测和编辑的潜力；具有特异、简单和通用的特点；有望广泛应用于生命科学、生物技术和可编程 RNA 医学的研究。



张轲，2005 年获得清华大学生物学学士学位，2013 年获得贝勒医学院博士学位，2013 以后在美国先后担任博士后，助理教授/独立 PI，2022 年全职回国加入深圳湾实验室神经疾病所任特聘研究员。课题组主要研究 ALS/FTD 的分子机理 (Science Translational Medicine 2022; Cell 2018; Nature 2015)，聚焦应激颗粒在这些疾病中的作用以及作为药物靶点的可能。擅长运用果蝇和病人诱导干细胞作为模型研究神经退行性疾病的机理。

Studying ALS/FTD Pathomechanisms using Induced Pluripotent Stem Cell Models

Ke Zhang, Ph.D.

Junior PI, Shenzhen Bay Laboratory

【摘要】 Amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD) are two related neurodegenerative disorders without curative treatments. The major challenge to their therapeutic development is our incomplete understanding of their pathomechanism. To this end, animal and cellular models have been used to dissect ALS/FTD pathomechanism and identify potential therapeutic targets. While studies in animal models have identified potential factors contributing to pathogenesis, whether these findings can be translated to patients is unclear, especially giving the huge variability among individual patients. Thus, a human-related model is key to successful translation to clinics.

Neurons derived from patient induced pluripotent stem cells (iPS neurons, or iPSNs) provides a powerful tool to model ALS and FTD. Using this model, we and others have previously recapitulated many key disease features in cultured neurons, including excitotoxicity, impaired protein quality control, defects in subcellular organelles, etc. Together with animal models, we performed genetic screens in ALS/FTD patient-derived iPSNs and identified novel modifier genes of neurodegeneration. These studies confirmed previous findings that RNA-processing defects are key to ALS/FTD pathogenesis and suggested potentially novel therapeutic targets for these devastating diseases.



李专, 博士, 南方医科大学基础医学院教授, 博士生导师。广东省“珠江学者”青年学者, 南方医科大学基础医学院发育生物学教研室副主任, 2018 年以南方医科大学“第三层次人才”引进回国。主要从事造血干细胞发育及调控, 研究成果发表于 Cell Stem Cell, Blood, Haematologica 等杂志 10 余篇, 引用超过 500 余次。先后主持国家自然科学基金项目 4 项, 以课题负责人和项目骨干参与国家科技部重点研发计划 2 项。

不同位点造血干细胞发育的调控

李专

南方医科大学

【摘要】 The first adult repopulating hematopoietic stem cells (HSCs) are found in the aorta-gonad-mesonephros (AGM) region, produced from hemogenic endothelial cells. Our previous study has shown that the embryonic head is the other site for HSC development. However, the regulation of HSC emergence from different sites remains incomplete. In the AGM region, we have found that autophagy is involved in the pre-HSC emergence and maturation, and wild-type p53-induced phosphatase 1 (Wip1) plays roles in the cell cycle on pre-HSCs. In addition, Wip1 affects the function of microglia in the embryonic head, but not in the AGM region. Interestingly, microglia, as a positive regulator, regulate the erythropoiesis and HS/PC expansion and/or maturation in hematopoietic developments through secreting proinflammatory factors in the embryonic head. Our work illustrates the regulatory mechanism of hematopoiesis from intrinsic and extrinsic aspects in the AGM region and embryonic head.



茵梓，浙江大学医学院教授，干细胞与再生医学专业和运动医学专业 博士生导师。

研究方向：肌腱干细胞与再生医学，致力于探索肌腱组织工程的核心要素肌腱干细胞亚群识别鉴定、分化调控和再生应用的研究。成果共发表 60 余篇肌腱研究领域 SCI 文章，H 指数 31，全部在国内完成。其中以第一作者通讯作者(含共同)在 Science Advances、Advanced Science 、Biomaterials、Cell Reports 等发表 SCI 论文 20 余篇，篇均他引 50 余次，包括一篇 ESI 前 1%高引用论文。获得授权专利 3 项。主持国家自然科学基金青年项目、优青项目和面上项目，国家重点研发计划干细胞专项青年科学家项目。

Single cell spatiotemporal transcriptomic landscape of developing tendon reveals cellular differentiation and interaction

Zi Yin

Zhejiang University School of Medicine

【摘要】 Background: Tendon injuries cause prolonged disability and never recover completely. Developmental biology is the template for investigating tissue regeneration. Understanding tendon development is therefore of considerable clinical relevance. Some progress has recently been made in this through single-cell RNA sequencing (scRNA-seq). However, it is still lack of topographical transcriptomic information that can help understanding cellular trajectories and interactions during tendon development.

Methods: Spatial enhanced resolution omics-sequencing (Stereo-seq), a spatial transcriptomic technology, achieved finer resolution, higher sensitivity, and larger view. In this study, P7 and P14 of mouse Achilles tendon-bone were subjected to scRNA-seq and Stereo-seq for generating the spatiotemporal transcriptomic data. The single-cell and spatial transcriptomics were integrated for spatial cellular deconvolution, pseudotime trajectory and cell-cell communication analysis.



Schematic showing study design for spatiotemporal analysis of mouse tendon development

Results: Unsupervised clustering of scRNA-seq and stereo-seq data revealed various subpopulations and we identified spatial modules for specific tissue organizations. Next, the integrated analysis of the scRNA-seq and stereo-seq data was performed. We revealed the spatiotemporal hierarchical relationship of tendon cell differentiation process. By cell type deconvolution, we identified tendon subpopulation distribution, and found that tendon stem/progenitor cell (TSPC) population existed at tendon sheath and persistent throughout tendon development and maturation. Spatial differentiation trajectories predicted a transition from TSPC to enthesis cell. Finally, we investigated the spatial ligand-receptor pairs and identified potentially important interactions during tendon development.

Discussion and Conclusion:

In this study, we have combined single-cell and spatial transcriptomics to explore the developing mouse tendon at high spatial resolution. We identified a stem cell population as long-term tendon sheath stem cells and revealed the potential microenvironment cues. Furthermore, we predicted that TSPCs may contribute to enthesis development and demonstrated that fgf signaling is an important regulator. In general, our study constitutes a fundamental reference for further studies aiming to understand tendon development.



王晨飞, 2012 及 2017 年于同济大学生命科学与技术学院获得生物信息学学士及博士学位, 2017-2020 年分别在同济大学、美国哈佛大学 Dana-Farber 癌症研究所从事博士后研究, 2020 年受聘于同济大学生命科学与技术学院, 历任特聘研究员、教授, 获得国家优青、吴瑞奖学金、博士后创新人才支持计划、上海市科技启明星等荣誉支持。研究方向为开发单细胞及空间多组学整合分析的智能算法, 研究免疫疾病及衰老过程中细胞身份转变的调控机制。以通讯/第一作者(含共同)身份在 Nature、Nat. Cell Biol.、Cell Stem Cell、Genome Biol.、Genome Med.、EMBO J.、Cancer Immunol. Res.、Nucleic Acids Res. 等杂志发表二十余篇论文, 累计引用 2000 余次, 担任 Nat. Rev. Genet.、

Nat. Methods、Nat. Commun.、Cell Genom.、Cell Syst.、Genome Biol.等领域内杂志审稿人。

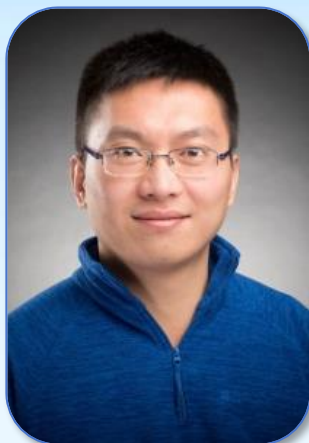
Reconstruction of single-cell and spatial multi-omics for enhanced understanding of cell identities and disease phenotypes

Dongqing Sun^{1,2}, Xin Dong^{1,2}, Ya Han^{1,2}, Xiaoying Shi^{1,2}, Zhanhe Chang^{1,2}, Chenfei Wang^{1,2*}

¹ Key Laboratory of Spine and Spinal Cord Injury Repair and Regeneration of Ministry of Education, Department of Orthopedics, Tongji Hospital, School of Life Science and Technology, Tongji University, 200092, China

² Frontier Science Center for Stem Cells, School of Life Sciences and Technology, Tongji University, Shanghai 200092, China

【摘要】 Single-cell sequencing techniques have been widely used to study the cellular heterogeneity of biological systems including immune disorders such as tumor, developmental processes, and aging systems. Recent technological advancement of single-cell sequencing has expanded from transcriptomics to multi-omics as well as with spatial resolutions, deepening the understanding of molecular mechanisms such as regulation of gene expression, and intercellular interactions within complex systems. However, many current single-cell and spatial multi-omics technologies can only generate one type of sequencing data at a time, and there is a lack of effective tools to integrate multi-omics data to understand the mechanisms of gene regulation and cellular cross-talks at multiple levels. Meanwhile, most spatial and multi-omic techniques have technical limitations to achieve single-cell resolution. To address these problems, we have developed a series of single-cell and spatial multi-omics data integration tools: MultiSpace can reconstruct spatial chromatin accessibility and DNA methylation signal by integrating spatial transcriptomics (ST) with single-cell multi-ome data. SCRIP and SCRIPro integrate single-cell or spatial multi-ome data with a large scale of epigenome and TF binding ChIP-seq references, enabling precise analyzing of single-cell TF enrichment, building gene regulation networks (GRNs), and reconstructing the dynamics of GRNs along time and space axes. STRIDE can enhance low-resolution ST to single-cell resolution by integrating ST with scRNA-seq using topic modeling. CELLIST enables the accurate segmentation of high-resolution ST data through multi-modal integration, which enhanced downstream spatial clustering, cell sub-typing, and CCI analyses. We hope that by accurately integrating and resolving single-cell and spatial multi-omics data, we can systematically understand the definition and dynamics of cell identities and their causal relationships to disease phenotypes from an integrated view.



朱哲鑫，合肥综合性国家科学中心大健康研究院高级研究员。2008 年本科毕业于中国海洋大学生物科学专业。之后在中科院上海生命科学研究院金颖研究员实验室对人胚胎干细胞的自我更新机制进行了系统的研究并取得发育生物学博士学位。2016-2017 年在英国剑桥 Wellcome Trust Sanger Institute 刘澎涛教授实验室研究 Extended potential stem cells (EPSCs)。2017-2023 年在美国 St Jude Children's Research Hospital Charles W.M Roberts 实验室，并通过与 Douglas R. Green 实验室合作，系统研究了染色质重塑子在干细胞对称分裂和 T 细胞不对称分裂中的作用。研究成果以第一作者和通讯作者身份发表在 Cell Stem Cell 和 Nature。其发表在 Cell Stem Cell (Zhu et al., 2017)的工作被 F1000 以 Exceptional Recommendation 形式进行了专题报告；发表在 Nature (Zhu et al., 2023)的工作被 Nature Reviews Molecular Cell Biology (IF: 94.4)以 research highlight (Zlotorynski et al., Nat Rev Mol Biol (2023))的形式进行了高度评价和详细解读。

SWI/SNF complexes and stem cell identities

朱哲鑫

合肥综合性国家科学中心

【摘要】 For cells to initiate and sustain a differentiated state, it is necessary that a 'memory' of this state is transmitted through mitosis to the daughter cells. Mammalian switch/ sucrose non-fermentable (SWI/SNF) complexes (also known as Brg1/Brg-associated factors, or BAF) control cell identity by modulating chromatin architecture to regulate gene expression, but whether they participate in cell fate memory is unclear. Here we provide evidence that subunits of SWI/SNF act as mitotic bookmarks to safeguard cell identity during cell division. The SWI/SNF core subunits SMARCE1 and SMARCB1 are displaced from enhancers but are bound to promoters during mitosis, and we show that this binding is required for appropriate reactivation of bound genes after mitotic exit. Ablation of SMARCE1 during a single mitosis in mouse embryonic stem cells is sufficient to disrupt gene expression, impair the occupancy of several established bookmarks at a subset of their targets and cause aberrant neural differentiation. Thus, SWI/SNF subunit SMARCE1 has a mitotic bookmarking role and is essential for heritable epigenetic fidelity during transcriptional reprogramming.



张伟杰, 2022.11-至今 研究员, 博士生导师, 浙江大学生命科学研究院, 2016.9-2022.10 博士后, 贝勒医学院, 2009.9-2015.6 博士研究生, 中国科学技术大学, 2005.9-2009.7 本科, 中国科学技术大学, 2022 年国家自然科学基金海外优秀青年基金获得者。从事乳腺癌转移和耐药机制的研究, 在 *Cell*、*Cancer Discovery*、*Cancer Cell*、*Nature Cell Biology*、*Nature Cancer* 等期刊发表了多篇研究文章。主要成果包括: 首次报道并证实骨微环境促进肿瘤细胞继发扩散形成多器官转移 (*Cell* 2021); 首次报道 NG2+ 间充质干细胞调控骨的重塑活性和骨转移起始的细胞分子机制 (*Cancer Discov* 2023); 发现雌激素受体阳性早期骨转移中雌激素受体表达的下调和内分泌治疗抗性的联系 (*Dev Cell* 2021); 首次报道内质网相关蛋白降解机器维持造血干细胞骨髓内定位和功能的分子机制 (*Nat Cell Biol* 2020)。

The stem cells underlying cancer bone metastasis

Wei jie Zhang^{1, 2}

¹Zhejiang Provincial Key Laboratory of Cancer Molecular Cell Biology, Life Sciences Institute

²Department of Orthopaedic Surgery, the Second Affiliated Hospital, School of Medicine
Zhejiang University, Hangzhou, Zhejiang 310058, China

【摘要】 Bone is commonly affected by metastatic disease. Tumor cells may spread to bone early and remain quiescent for a long time. How these early disseminated tumor cells (DTCs) break out of dormancy, evade the adjuvant therapies and evolve into lethal disease is poorly understood. Bone resident DTCs exhibit enrichment of stemness in both mouse models and human samples, but the underlying mechanism remains elusive. Using murine bone metastasis models, we proved that interaction with bone microenvironment induces the emergence of cancer stem cells (CSCs) through a EZH2-mediated epigenetic reprogramming process in cancer cells. In ER+ breast cancer, this process is accompanied with ER α loss and acquisition of basal phenotype, contributing to endocrine resistance in early-stage bone metastasis. Furthermore, the stem cell-like population is more capable of seeding secondary metastasis. Genetically or pharmaceutically blockade of EZH2 re-sensitizes bone metastasis to adjuvant endocrine therapies and significantly diminishes the further dissemination of bone metastasis. Early-stage bone metastasis was later found to be in close proximity to perivascular niches covered by NG2+ stromal cells. Genetic depletion of NG2+ cells dramatically decreases the incidence of bone metastasis. NG2+ bone marrow stromal cells express stem-cell markers and enrich mesenchymal stem cells that are capable of trio-lineage differentiation in vitro. However, NG2+ cells are solely responsible to osteogenesis in both homeostatic and fractured bones in vivo. NG2+ cells are recruited to the remodeling areas, differentiated into osteoblastic cells, thus creating a supportive niche for bone metastasis initiation. Mechanistically, N-cadherin is highly expressed on NG2+ cells and further increased upon their osteogenic differentiation. N-cadherin interacts with E-cadherin on tumor cells to form heterotypic adherent junctions that activate mTOR signaling and promote tumor cell proliferation and migration. Selective knockout of N-cadherin in NG2+ cells abolished these effects in vitro, and phenocopied NG2+ cell depletion in vivo, decreasing both bone metastasis and bone remodeling. These findings uncover the origin of stemness in bone marrow DTCs as well as the critical role of NG2+ mesenchymal stem cells in regulating bone metastasis.



张赟，国家癌症中心/中国医学科学院肿瘤医院研究员，北京协和医学院博士生导师，分子肿瘤学全国重点实验室课题组长。本科毕业于北京大学，在美国杜克大学王小凡教授指导下获博士学位，在美国麻省理工学院怀特海德研究所 Robert A. Weinberg 教授实验室进行博士后研究。获国家海外高层次人才计划青年项目支持。主要从事肿瘤转移的分子机制研究，目前实验室主要关注肿瘤微环境调控癌细胞表型状态的分子机制及其对肿瘤转移和耐药性的影响。

Epigenetic Control of Epithelial-Mesenchymal Plasticity and Cancer Stemness

Yun Zhang, Ph.D.

State Key Laboratory of Molecular Oncology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100021, China

【摘要】 Activation of an epithelial-mesenchymal transition (EMT), a latent cell-biological program involved in development and wound healing, has been linked to the formation of both normal and neoplastic stem cells. In their various manifestations, EMT programs enable epithelial cells to enter into a series of intermediate states arrayed along the E-M phenotypic spectrum. At present, we lack a coherent understanding of how carcinoma cells control their entrance into and continued residence in these various states, and which of these states associate with stem-like properties and thus favor the process of metastasis. Here we characterize a layer of EMT-regulating machinery that governs E-M plasticity (EMP). This machinery consists of two chromatin-modifying complexes, PRC2 and KMT2D-COMPASS, which operate as critical regulators to maintain a stable epithelial state. Interestingly, loss of these two complexes unlocks two distinct EMT trajectories. Dysfunction of PRC2, but not KMT2D-COMPASS, yields a quasi-mesenchymal state that is associated with stem-like properties, highly metastatic capabilities and poor survival of patients with breast cancer. These findings identify epigenetic factors that regulate EMP, determine specific intermediate EMT states and, as a direct consequence, govern cancer stemness and the metastatic ability of carcinoma cells.



裴唯珂，西湖大学研究员、博士生导师，国家重点研发计划（青年）项目负责人。2018 年获德国海德堡大学最优等荣誉博士学位(summa cum laude)，师从德国最高科学奖(Leibniz Prize)得主 Hans-Reimer Rodewald 院士。2018 至 2020 年在德国癌症研究中心进行博士后训练，研究造血干细胞分化命运调控以及免疫系统发育。2020 至 2021 年在哈佛医学院/布莱根妇女医院担任 Research Fellow，研究免疫调节与肿瘤免疫治疗。

裴唯珂实验室致力于开发新一代单细胞示踪技术，解码造血干细胞发育与衰老机理，研究肿瘤、感染等条件下免疫系统的应答机制。并与其他实验室紧密合作，探究复杂实体器官（如大脑、胚胎）发育的时空调控规律。

研究工作发表在 Nature, Cell Stem Cell, Nature Protocols, Cell Research 等期刊，曾获 CRI Irvington fellowship，入选 Eugene V. Weissman Fellow，《麻省理工科技评论》35 岁以下科技创新 35 人（中国）。

Single-cell lineage tracing reveals stem cell fate in development and disease

裴唯珂

西湖大学

【摘要】血液系统的发育由造血干细胞开始，经历一系列细胞命运决定事件，最终形成谱系组成复杂的多细胞体系。‘细胞的命运是如何被决定的’一直以来都是发育生物学的核心问题。我们的研究围绕谱系示踪新工具的开发与应用，在生理条件下在体解析成体干细胞的分化命运。我们开发了基于 DNA 条形码的高分辨率谱系示踪技术，首次定量解析了自然状态下造血干细胞发育命运的异质性，揭示了血液系统的“二叉树”发育路径。为进一步在单细胞精度揭示干细胞命运决定机制，我们开发了基于 RNA 条形码的单细胞谱系示踪技术 PolyExpress，并应用该技术鉴定了维持造血干细胞静息的调控基因 Hoxb2，为在体解码细胞命运的转录调控机制提供了强有力的新工具。



苏俊，先后于 2016 年获得香港中文大学细胞及分子生物学一级荣誉学士学位和 2019 年获德国哥廷根大学生物及复杂系统物理最优等 (summa cum laude) 博士学位。

修读期间获得裘槎博士生奖学金、马普裘槎博士后研究奖学金等超过 15 个奖项及奖学金。

在德国马克斯普朗克生物物理化学研究所 (现多学科科学研究所) 进行博士及博士后训练，师从德国国家科学院院士、莱布尼茨奖得奖者 Melina Schuh 博士。作为第一或共一作者的研究成果发表在 Science(2019、2022)、Trends Cell Biol.、Nat. Protoc.、J. Cell Physiol. 等国际权威杂志，申请国际专利 1 项，并获德国细胞生物学会颁发的尼康年轻科学家奖 (Nikon Young Scientist Award)、德国马克斯普朗克学会颁发的奥托哈恩奖牌 (Otto Hahn Medal) 及奥托哈恩大奖 (Otto Hahn Award; 自 2006 年设立第二位华人得奖者) 予以肯定。2022 年入选国家高层次青年人才、《麻省理工科技评论》中国“35 岁以下科技创新 35 人”。

Towards better eggs and embryos

Chun So

National Institute of Biological Sciences, Beijing

【摘要】 Human oocytes are prone to assembling meiotic spindles with unstable poles, which can favor aneuploidy in human eggs. The underlying causes of spindle instability were previously unknown. We found that NUMA (nuclear mitotic apparatus protein)-mediated clustering of microtubule minus ends focused the spindle poles in human, bovine, and porcine oocytes and in mouse oocytes depleted of acentriolar microtubule-organizing centers (aMTOCs). However, unlike human oocytes, bovine, porcine, and aMTOC-free mouse oocytes have stable spindles. We identified the molecular motor KIFC1 (kinesin superfamily protein C1) as a spindle-stabilizing protein that is deficient in human oocytes. Depletion of KIFC1 recapitulated spindle instability in bovine and aMTOC-free mouse oocytes, and the introduction of exogenous KIFC1 rescued spindle instability in human oocytes. Thus, the deficiency of KIFC1 contributes to spindle instability in human oocytes. Lastly, we will also present recent data to show that the introduction of exogenous KIFC1 improves the fidelity of spindle assembly in human zygotes.



刘晓东，西湖大学生命科学院研究员，诱导干细胞与发育再生医学实验室负责人。2011 年获得澳大利亚莫纳什大学理学荣誉学士学位。2019 年获得澳大利亚莫纳什大学博士学位，2019-2021 年在莫纳什大学和澳洲再生医学研究所从事表观遗传学和重编程相关博士后研究，2021 年在英国弗朗西斯·克里克研究所进行基因编辑与人类胚胎发育等方向博士后研究。曾获得 Carmela and Carmelo Ridolfo Prize in Stem Cell Research，国际干细胞大会科学优秀奖，并入选英国 1851 研究奖学金展览皇家委员会和欧洲分子生物学组织 (EMBO) postdoc

fellowship。

Unveiling pluripotent state transitions during somatic cell reprogramming and early human embryonic development

刘晓东

西湖大学

【摘要】 Human development is a highly-coordinated process, with any abnormalities during the early embryonic stages can often have detrimental consequences. The complexity and nuances of human development underpin its significance in stem cell and embryo research. By studying the molecular mechanisms underpinning the reprogramming process of human somatic cells into pluripotency, we unveil a dynamic cell fate decision that led to the derivation of induced trophoblast stem cells. We also describe the reprogramming of fibroblasts into in vitro three-dimensional models of the human blastocyst, termed iBlastoids. Characterization of iBlastoids shows that they model the overall architecture of blastocysts, presenting an inner cell mass-like structure, with epiblast- and primitive endoderm-like cells, a blastocoel-like cavity and a trophectoderm-like outer layer of cells. Cells undergo a major epigenome reconfiguration when reprogrammed to human induced pluripotent stem cells (hiPS cells). Using the knowledge gained from our previous studies, we developed a transient-naive-treatment (TNT) reprogramming strategy that emulates the embryonic epigenetic reset. We show that the epigenetic memory in hiPS cells is concentrated in cell of origin-dependent repressive chromatin marked by H3K9me3, lamin-B1 and aberrant CpH methylation. TNT reprogramming corrects epigenetic memory and aberrations, producing hiPS cells that are molecularly and functionally more similar to hES cells than conventional hiPS cells. We foresee that these technologies will allow studies of early developmental diseases and screening for treatments, and as such has tremendous potential for understanding infertility, early pregnancy loss and advancing the use of stem cells in biomedical and therapeutic applications.

在线投稿摘要合集



探究异倍体与 P53 的互作对肿瘤发生发展的影响

卢明飞、张美丽、黄粤

重大疾病共性机制研究全国重点实验室，医学遗传学系，基础医学研究所，中国医学科学院
&北京协和医学院

【摘要】 异倍体 (Aneuploidy)，即细胞内染色体数目发生非整倍性变异，是肿瘤细胞的重要特征之一。异倍体与癌症相关基因突变在不同类型的人类肿瘤细胞中都广泛存在，但在肿瘤发生发展中异倍体与癌症相关基因突变是如何相互作用的尚有待研究。本研究以四株背景一致的，6 号、8 号、11 号和 15 号染色体分别三体 (Trisomy, Ts) 的小鼠异倍体胚胎干细胞 (ESC) 作为研究模型，利用 CRISPR 基因编辑技术对抑癌基因 Trp53 进行纯合敲除，建立多株异倍体-癌症相关基因变异的 ESC 株系。体外研究发现 Trp53 的敲除并不影响野生型 ESC 的增殖能力，而一些 Trp53 敲除的 6 号染色体三体 (Ts6) 的异倍体 ESC 克隆的增殖能力增强。在自我更新的培养条件下，Trp53 敲除不影响野生型 ESC 和 Ts6 异倍体 ESC 的自我更新能力和克隆形成能力。而在分化条件下与野生型 ESC 相比，Trp53 敲除能明显提高 Ts6 异倍体 ESC 未分化和部分分化的细胞比例，从而使异倍体 ESC 更多地停留在干细胞阶段。在体内的畸胎瘤形成实验中，Trp53 敲除能显著增强异倍体 ESC 在免疫缺陷鼠皮下的畸胎瘤形成能力。当接种较低的起始细胞数量时，与野生型 ESC 相比，Trp53 敲除能明显提高异倍体 ESC 在体内形成畸胎瘤的效率、畸胎瘤的生长速度以及瘤重。综上所述，我们的工作揭示了在 ESC 形成畸胎瘤的过程中，异倍体与 P53 蛋白缺失起一定程度的协同作用，为肿瘤形成机制的研究提供新的见解。

【关键字】 异倍体，癌症相关基因突变，P53，胚胎干细胞，畸胎瘤

间充质干细胞介导纳米放射增敏剂用于非小细胞肺癌的靶向放疗

曾丽娟、肖靖芳、田甘、卞修武

中国人民解放军陆军军医大学第一附属医院

【摘要】目的：研究脂肪来源间充质干细胞（AD-MSCs）作为纳米放射增敏剂的靶向递送载体增强肿瘤放射治疗的效果。

方法：选用硒化铋（ Bi_2Se_3 ）纳米放射增敏剂为模型，针对该纳米粒对肿瘤缺乏特异性，将其负载于间充质干细胞中，设计 AD-MSCs/ Bi_2Se_3 纳米体系用于非小细胞肺癌（NSCLC）的靶向放疗。分别在细胞和荷瘤小鼠层次评估 AD-MSCs/ Bi_2Se_3 纳米体系对肿瘤的靶向能力和放射治疗效果。

结果：优化的细胞内负载策略几乎不会影响 AD-MSCs 的细胞活力、特异性表面标志物或迁移能力，而且 Bi_2Se_3 纳米放射增敏剂可以从 AD-MSCs 有效地运输到肿瘤细胞。体内生物分布测试表明，通过 AD-MSCs 介导的输送， Bi_2Se_3 纳米放射增敏剂在肿瘤中的积累增加了 20 倍。AD-MSCs/ Bi_2Se_3 与 X 射线照射同步给药很好地控制了荷 A549 小鼠的肿瘤进展。

结论：间充质干细胞与非辐照肿瘤细胞相比更容易迁移到辐照肿瘤细胞中，而且间充质干细胞在全身给药后会优先在肺组织内聚集，因此肿瘤靶向间充质干细胞/NPs 系统用于 NSCLC 的靶向放疗是可行的，也是有前景的。

【关键字】 间充质干细胞；纳米放射增敏；靶向递送

Allogeneic hematopoietic stem cell transplantation for the treatment of acute lymphoblastic leukemia: single-center, retrospective study and ALL transplant-specific prognostic scoring system

高铭阳、高蕾

中国人民解放军陆军军医大学第二附属医院

【摘要】 Background: Acute Lymphoblastic Leukemia (ALL) is a malignant tumor occurring during the development of white blood cells, characterized by abnormal proliferation of lymphoblastic cells in the blood. Patients with all survived for only a few months before the 20th century, with 20% all survival achieved with single agent chemotherapy and 50% all survival achieved with multiagent combination + radiotherapy. With recent advances in all treatment options and continuous optimization of allogeneic hematopoietic stem cell transplantation (allo-HSCT), the current complete remission (CR) rate of childhood all is 90%, and the long-term disease-free survival (EFS) rate reaches 80%. However, adults (> 15 years old) are less clinically effective than children, with CR rates of 70% - 90%, EFS of only 30% - 40%, and long-term survival rates above 60 years old are only 10-15%. Allogeneic hematopoietic stem cell transplantation (allo-SCT) is an important therapy for ALL and is indicated as part of first-line therapy for adults with high-risk ALL and as the only treatment for relapsed and refractory ALL. Studies have shown that the long-term leukemia free survival (LFS) rate of allo-HSCT with myeloablative preconditioning therapy can reach 45% to 75%. Objective: To investigate the efficacy of allo-HSCT in the treatment of ALL, and to explore the risk factors of allo-HSCT in ALL patients. Study Design: This is a disease-specific, single-center and retrospective study. We retrospectively studied 220 consecutive patients with ALL who underwent allo-HSCT in our center over the past decade. Results: Between January 2011 and December 2021, 220 consecutive patients with ALL who underwent HSCT at our transplant center were enrolled in this study. The median follow-up time was 47 months (range, 2-140 months). All of the patients achieved hematopoietic reconstitution. The median time intervals to achieve neutrophil engraftment and PLT engraftment were 15.0 days (range, 10-56 days) and 18 days (range, 10-119 days). The cumulative incidence of acute graft versus host disease (GVHD) and grade III-IV acute GVHD at 90 days were 22.6% (17.6%-28.8%, 95% CI) and 2.6 % (0.8%-6.4%, 95% CI), respectively. The 5-year cumulative incidence of chronic GVHD and moderate-severe chronic GVHD were 27.7% (21.9%-34.5%, 95% CI) and 15.9% (11.1%-22.3%, 95% CI), respectively. The overall incidence of infection was 78.6%. There were 52 patients occurred relapse. The 5-year CIF of relapse was 23.5% (18.2%-29.8%, 95% CI). Of these, 44 patients belonged to the high-risk group. There were 38 patient deaths by December 2021. The 5-year overall survival (OS) was 80.4% (95% CI, 73.7-85.6%). The 5-year leukemia-free survival (LFS) was 72.6% (95% CI, 66.0%-78.1%). We developed the nomogram to predict the OS and LFS of different patients. According to the ROC boundary value of the nomogram score (score=92), we obtained the scoring system of OS: low-risk (score \leq 92) and high-risk (score>92). The 5-year OS was 88.2% (95% CI, 80.2-93.1%) and 61.7% (95% CI, 47.7-73.0%) for the low-risk group (n=153) and high-risk group (n=67), respectively (p = 0.000, HR =4.12, 95% CI 2.14-7.91). Using the same method, the scoring system of LFS was obtained: low-risk (score \leq 70) and high-risk (score>70). The 5-year OS was 87.5% (95% CI, 80.1-92.3%) and 54.0% (95% CI, 43.2-63.6%) for the low-risk group (n=120) and high-risk group (n=100), respectively (p = 0.000, HR =4.23, 95% CI 2.35-7.61). Conclusions: The transplantation mode in our center has achieved good therapeutic effects in treating ALL. In this treatment mode, it was also perform an integrated prognostic scoring system for ALL after allo-HSCT, which accurately and conveniently predicts OS and LFS in patients with ALL after allo-HSCT. In addition, the bridging of allo-HSCT with novel cellular immunotherapy contributes to ALL.

【关键字】 Acute Lymphoblastic Leukemia, allo-HSCT, cellular immunotherapy contributes

Favourable outcomes between HLA-haploid and matched sibling donor hematopoietic stem cell transplantation: multi-centre, retrospective study and severe aplastic anemia transplant-specific prognostic scoring system

高铭阳、高蕾

中国人民解放军陆军军医大学第二附属医院

【摘要】 Background: In recent years, haploidentical hematopoietic stem cell transplantation (haplo-HSCT) treatment for hematological malignant diseases has made great progress due to the advent of novel conditioning regimens, optimized graft manipulation, improved graft-versus-host disease (GVHD) prophylaxis, and advances in supportive care. It also showed very favorable outcomes in severe aplastic anemia (SAA) patients in recent studies, with comparable outcomes to those of patients receiving immune suppressive therapy (IST) and allogeneic HSCT from an matched sibling donor (MSD) or matched unrelated donor (MUD). However, most of the previous studies relied on single-center data analysis, and the conditioning regimen, GVHD prophylaxis and supportive care were relatively singular. We do not know whether there are differences in the survival of SAA patients after haplo-HSCT and MSD-HSCT under conditions involving different transplant centers, conditioning regimens and GVHD prophylaxis.

Objective: The primary aim is to assess the curative effect of haplo-HSCT compared with MSD-HSCT in the treatment of SAA. The secondary aim is exploratory to analyze the risk factors of overall survival (OS) of SAA patients.

Study Design: This is a disease-specific, multi-center and retrospective study. We retrospectively studied 156 consecutive patients with SAA who underwent haplo-HSCT or MSD-HSCT at four transplant centers in China.

Results: Among 156 enrolled patients, 39 in MSD-HSCT group and 117 in haplo-HSCT group. The date of the last follow-up for all surviving patients was April 30, 2022. The median follow-up time was 26.5 (range, 2–117) months. There was no difference in patient age and gender, ABO blood type, donor age and donor gender between the two groups. There were differences in time from AA diagnosis to HSCT between the two groups : 2 (range, 1–72) months in the MSD-HSCT group and 4 (range, 1–122) months in the haplo-HSCT group ($p=0.021$). There are also differences in Conditioning regimen ($p=0.040$), GVHD prophylaxis ($p=0.000$), CD34+ cells ($p=0.021$) between the two groups. The median age of participants at the time of transplantation was 27 (range, 10–45) years in the MSD-HSCT group and 24 (range, 2–57) years in the haplo-HSCT group. The 2-year OS rate was 87.5% in the haplo-HSCT group and 89.7% in the MSD-HSCT group. Time to hematopoietic reconstitution, incidence of GVHD, infection and graft failure rates were not significantly different between the two groups. According to the median score of the nomogram, we obtained the SAA prognostic scoring system: low-risk (score=0) and high-risk (score>0). The 2-year OS was 96.4% and 80.4% for the low-risk group and high-risk group, respectively ($p = 0.004$). According to the ROC method boundary value of the nomogram score, we obtained another scoring system: low-risk (score<72) and high-risk (score>72). The 2-year OS was 95.2% and 73.7% for the low-risk group and high-risk group, respectively ($p = 0.001$).

Conclusions: Haplo-HSCT achieves outcomes comparable to those of MSD-HSCT for SAA patients. Haplo-HSCT should be considered an effective alternative for patients with SAA without a matched sibling donor. The SAA transplant-specific prognostic scoring system proposed in this study can conveniently predict the OS for SAA patients following MSD-HSCT or haplo-HSCT.

【关键字】 severe aplastic anemia, haploidentical, HSCT, nomogram, prognostic scoring system

利用小鼠胚胎干细胞探究异倍体促进畸胎瘤转移的分子机制

肖蓉 1、许德澍 2、张美丽 1、陈章华 2、白凡 2、黄粤 1

1. 重大疾病共性机制研究全国重点实验室，医学遗传学系，中国医学科学院-北京协和医学院基础医学研究所，北京 100005
2. 北京大学，BIOPIC，北京 100871

【摘要】目的：异倍体是指细胞内染色体数目的非整倍性变异，是大多数肿瘤细胞的共同特征。高度异倍性常常与肿瘤患者的不良预后密切相关。但是，异倍体在肿瘤转移中的作用尚不明确。方法：本研究利用标记荧光素酶报告基因的具有相同遗传背景的野生型和异倍体小鼠胚胎干细胞（mESC）作为研究模型，利用小动物活体光学成像系统追踪异倍体 mESC 形成的畸胎瘤是否发生远端器官转移。再通过全基因组测序（WGS）分析原位畸胎瘤与转移瘤的基因拷贝数变异（CNV）情况，通过全外显子组测序（WES）分析基因突变的情况，通过单细胞转录组测序分析比较原位瘤和转移瘤的基因表达谱，揭示异倍体促进畸胎瘤转移的分子机制。结果：与野生型 mESC 不同，异倍体 mESC 在小鼠皮下形成的畸胎瘤普遍地出现多种远端器官转移，包括肺、肝脏、肠、胸腔纵膈等。WGS 和 WES 分析表明，异倍体畸胎瘤转移过程中未出现新的 CNV 和基因变异。单细胞转录组测序分析发现异倍体原位瘤和转移瘤中均存在大量的具有干细胞特征的细胞。拟时序分析表明异倍体畸胎瘤分化早期蛋白酶体活性相关亚基表达水平显著下调，内质网应激通路显著激活。进一步的研究表明，蛋白酶体激活剂 Oleuropein 和内质网应激抑制剂 4-PBA 能有效地抑制异倍体畸胎瘤转移，并且敲低未折叠蛋白反应（UPR）三个通路的关键基因也能显著降低异倍体畸胎瘤的转移效率。结论：异倍体普遍地促进畸胎瘤转移。蛋白酶体活性不足和内质网应激过度活化是异倍体促进畸胎瘤转移的潜在分子机制，这为理解肿瘤转移的机制提供了新的视角。

【关键字】畸胎瘤，转移，异倍体，胚胎干细胞，蛋白酶体，内质网应激

Effects and mechanisms of various Mesenchymal stem cell targeting Ferroptosis on inflammatory diseases

李强、任博媛、吴祖泽、靳继德

Beijing Institute of Radiation Medicine

【摘要】 Inflammatory disease is a major global health problem, which is closely related to the occurrence and development of many diseases. Multiple Mesenchymal stem cell cells (MSCs) , as a promising therapeutic approach, have attracted extensive research interest in recent years. In particular, recent studies have shown that MSCs have the ability to regulate iron metabolism and ameliorate inflammatory diseases by targeting Ferroptosis. Ferroptosis is a special cell death caused by iron accumulation in cells, which is closely related to the occurrence and development of many inflammatory diseases. It has been found that MSCs can regulate the intracellular iron level by secreting iron regulatory proteins, and inhibit the occurrence of Ferroptosis. On the other hand, MSCs can also modulate inflammatory response by releasing extracellular vesicles and extracellular nucleic acids, further improving inflammatory diseases. Specifically, MSCs regulate intracellular iron levels by regulating the expression of genes related to iron metabolism, such as ferritin and iron transporters. MSCs can also inhibit the production of oxidative stress and inflammatory mediators, thereby reducing the inflammatory response. In addition, MSCs can regulate the function of immune cells, inhibit the activation of inflammatory cells and release of inflammatory factors. In summary, studies on the effects and mechanisms of Mesenchymal stem cell targeting Ferroptosis provide new ideas and approaches for the treatment of inflammatory diseases. Further research will help to reveal the mechanism of MSCs in inflammatory diseases and provide better guidance for clinical application. These results will provide theoretical basis for the development of new therapeutic strategies and drugs, and bring new hope for the treatment of inflammatory diseases.

【关键字】 Inflammatory disease, Mesenchymal stem cell, Ferroptosis, Inflammation, Iron Metabolism

脑小血管病的细胞治疗

于念叶

中国科学院动物研究所

【摘要】 脑小血管病(cerebral small vessel disease,CSVD)主要指脑内小血管病变导致的一大类神经系统疾病，累及的血管直径一般为 40-200 μm ，包括发生于小动脉、微动脉、毛细血管和小静脉的病变。其主要临床表现为认知障碍、精神情绪异常和步态异常等。因该病受累人群广泛，具年龄相关性，近年来备受重视。其中大脑常染色体显性遗传动脉病伴皮质下梗死和白质脑病(CADASIL)是由 NOTCH3 基因突变引起的常染色体显性疾病，是一种常见的显性遗传性脑小血管病，也是成人遗传性缺血性中风和血管性痴呆最常见的形式。本文对 CADASIL 转基因模型小鼠进行 N2 细胞治疗，行为学水迷宫结果表明，细胞治疗后，显著改善小鼠的认知能力。此外，细胞治疗组小鼠的肌纤维粗细和紧密程度也得到了显著改善。目前脑小血管病治疗暂无针对性的有效手段，因此本研究的开展，可能为遗传性脑小血管病治疗提供一种新的治疗途径。

【关键字】 脑小血管病；细胞治疗

Discovery and Application of Postnatal Nucleus Pulposus Progenitors Essential for Intervertebral Disc Homeostasis and Degeneration

高博

西京医院

【摘要】 Intervertebral disc degeneration (IDD) results from the dysfunction of nucleus pulposus (NP) cells and the exhaustion of NP progenitors (ProNPs). The cellular applications of NP cells during IDD are currently limited due to the lack of in vivo studies showing whether NP cells are heterogeneous and contain ProNPs throughout postnatal stages. In this study, single-cell RNA sequencing of purified NP cells is used to map four molecularly defined populations and uterine II receptor (UTS2R)-expressing postnatal ProNPs is identified, which are markedly exhausted during IDD, in mouse and human specimens. The lineage tracing shows that UTS2R+ ProNPs preferentially resides in the NP periphery with its niche factor tenascin-C and give rise to functional NP cells. It is also demonstrated that transplanting UTS2R+ ProNPs with tenascin-C into injured intervertebral discs attenuate the progression of IDD. The study provides a novel NP cell atlas, identified resident ProNPs with regenerative potential, and revealed promising diagnostic and therapeutic targets for IDD.

【关键字】 Sc-RNA seq; intervertebral disc; lineage tracing; nucleus pulposus cell atlas; stem cell therapy.

lncRNA CARMN 通过 Wnt 信号调控乳腺及乳腺癌干细胞功能

李明洋、王超尘、王腾、刘铭镐

浙江大学

【摘要】 乳腺的发育、泌乳及哺乳后组织重塑等过程依靠乳腺干细胞的增殖、分化和凋亡以实现，乳腺干细胞的调控异常可导致乳腺疾病和乳腺癌发生。近年来，长链非编码 RNA 被证实与广泛参与乳腺发育和乳腺癌发生发展。通过高通量测序与原位表达验证，我们发现 lncRNA CARMN 在乳腺干细胞中明显富集。在体外培养的乳腺干细胞中，CARMN 敲低导致正常乳腺类器官形成和增殖能力下降。体内移植实验结果表明 CARMN 的敲低导致乳腺干细胞再生重塑乳腺导管的能力降低。在分子机制上，CARMN 的敲低导致 Twist1 等关键转录因子下调。我们进一步发现 lncRNA CARMN 与 Wnt 通路中的 $\Delta 1$ Catenin (CTND1) 直接结合，并参与 Wnt 通路激活。在乳腺癌中，lncRNA CARMN 敲除能够显著降低 MMTV-Wnt1 自发成瘤鼠来源的肿瘤干细胞在体内及体外的成瘤能力。综上，lncRNA CARMN 表达于乳腺干细胞中，通过 Wnt--Twist1 分子轴调控乳腺干细胞干性维持，及 Wnt 激活型乳腺癌的发生发展。

【关键字】 乳腺干细胞，Wnt，lncRNA，CARMN

Human dopaminergic neuron organoids derived from pluripotent stem cells

王馨悦、孙高英、王传玥、胡宝洋

中国科学院动物研究所

【摘要】 Parkinson disease (PD) is the world second most common neurodegenerative disorder, characterized by progressive rigid hypokinetic syndrome and irreversible degeneration of dopaminergic neurons (DNs) in the midbrain's substantia nigra pars compacta. Despite numerous studies on PD neural disturbance, our understanding of PD pathophysiology and drug therapy remains insufficient. We introduce a protocol for differentiating human dopaminergic neuron organoids (hDNOs) in a 3D culture following the developmental trajectory of DNs. These hDNOs, viable in vitro for over 1 year, comprise mature DN-like neurons and various glial cell types. Mature hDNOs formed neural network, exhibit giant depolarizing potential (GDP)-like events, and respond to dopamine agonists and antagonists. This suggests that hDNOs effectively emulate DNs' physiological function in vitro. When compared to human DNs from monolayer methods, DNs in mature hDNOs better reflect the structural and functional attributes of their in vivo counterparts. Our research offers a 3D in vitro model that closely represents midbrain DNs, potentially aiding in further understanding and promoting therapeutic advancements.

【关键字】 Parkinson disease, human dopaminergic neurons organoid, neural network, 3D in vitro model

hUCMSCs improve autophagy and promote testosterone synthesis via AMPK-mTOR pathway in aging mice

杨鸿宇 1,2, 薛函 1,2, 余丽梅 1,2, 何志旭 1,2

1. 遵义医科大学附属医院贵州省细胞工程重点实验室, 贵州 遵义, 563000
2. 遵义医科大学组织损伤修复与再生医学省部共建协同创新中心, 贵州 遵义, 563000

【摘要】 Purpose : To investigate the effect of human umbilical cord mesenchymal stem cells (hUCMSCs)-mediated AMPK/mTOR signaling pathway on autophagic capacity and testosterone synthesis in testicular tissue of aging mice.

Methods : The aging model was established by subcutaneous injection of D-galactose (D-gal) into the neck, and P5 hUCMSCs 5×10^5 cells were injected into the tail vein at the 9th week. Testicular weight and testicular index were measured 4 weeks after transplantation. Testosterone level was detected by ELISA. HE staining was used to observe the morphology of testis. Immunohistochemical staining was used to detect the expression of Beclin-1 and StAR. RT-PCR and Western blot were used to evaluate the molecular mechanism.

Results : The testicular function of aging mice was significantly improved after transplantation of hUCMSCs. Compared with the model group, the testis tissue structure of the hUCMSCs group tended to be normal, and the testicular index was significantly increased. The gene expression of Star, Cyp11a1 and Hsd17b3, the key enzymes of testosterone synthesis, was significantly increased, and testosterone level was increased. In addition, the activation of AMPK/mTOR pathway increased the expression of p-AMPK and decreased the expression of p-mTOR, up-regulated the mRNA expression of autophagy-related proteins Beclin-1 and Ulk1, improved the autophagy defect, and restored the function of testosterone synthesis.

Conclusions : By activating AMPK/mTOR pathway, hUCMSCs not only improved the autophagy ability of testis tissue in aging mice induced by D-gal, but also increased the level of key enzymes in testosterone synthesis, and restored the testicular function of aging mice.

【关键字】 hUCMSCs; Autophagy; Aging; Testicular function; AMPK/mTOR

Umbilical Cord Mesenchymal Stem Cells Rescued Cardiac Function via Up-regulating Mitophagy in D-galactose induced Oxidative Damage

刘娟、吴雨瞳、徐尚福、刘滔滔、薛函、冉昕、于泓、何志旭、余丽梅

遵义医科大学附属医院

【摘要】 Abnormal mitochondrial autophagy is involved in the regulation of myocardial oxidative injury and dysfunction. Mesenchymal stem cells (MSCs) have shown protective effects on myocardial tissue injured by ischemia or ischemia reperfusion. We investigated the effect and mechanism of human umbilical cord mesenchymal stem cells (hUCMSCs) on D-galactose (D-gal)-induced oxidative damage, cardiac dysfunction and mitophagy dysregulation in mice. The cardiac hypofunction model of mice was produced by subcutaneous injection of D-gal (200 mg/kg) daily for 9 weeks. At the end of the 9th week, hUCMSCs (5×10^5 cells/mice) were injected into caudal vein, and 4 weeks later, the therapeutic effects were determined. Ultrasonic Doppler detection revealed the D-gal-induced decreases of cardiac ejection fractions, left ventricular fractional shortening, cardiac output and stroke volume were ameliorated after hUCMSCs transplantation, while the increased left ventricular anterior wall and hear index were decreased by hUCMSCs. D-gal induced myocardial tissue structure disorder, morphological change and loss of myocardial cells were obviously reversed by hUCMSCs. D-gal increased oxidative stress, evidenced by the content of malonaldehyde in serum, was reduced in hUCMSCs group. The D-gal decreased mitophagy protein expressions of LC3, LAMP1 and Mfn2 were increased in hUCMSCs group, while D-gal increased HSP60 and DRP1 were reduced towards the control group by hUCMSCs. Overall, hUCMSCs transplantation was effective in removing D-gal induced cardiac damage and dysfunction, and the mechanisms are related to reduced oxidative injury of myocardial tissue and preferably maintained myocardial mitochondrial autophagy.

【关键字】 umbilical cord mesenchymal stem cells; mitochondria autophagy; cardiac function; D-galactose; oxidative damage

Neural aging and regulation research

李达

中国科学院动物研究所

【摘要】 Biologically, aging means decline of organisms vitality. It's a inevitable degeneration process of organizational structures and physiological functions. In the perspective of physiology, aging is a developmental cycle starting with fertilization, ending with death. Although modern medicine has promoted human health and partly extended life expectancy, fundamental new theories breakthroughs about aging are eagerly expected.

Essentially, the real pressing threat is not aging itself, but are many diseases follow. Aging is the main risk factor for many diseases, such as neurodegenerative diseases, cardiovascular diseases and cancer. Aging acts in complex ways on a mosaic of molecular and cellular process that have yet to be fully identified and remain poorly understood. Similar or identical abnormal regulation occur in different aging organisms. Carlos and his colleagues have been committed to exploring identities of aging in decades. They firstly enumerated nine tentative hallmarks of different organisms in 2013, and made a update recently. In their theory, aging is driven by hallmarks fulfilling the following three premises: (1) their age-associated manifestation, (2) the acceleration of aging by experimentally accentuating them, (3) the opportunity to decelerate, stop, or reverse aging by therapeutic interventions on them. Based on the above requirements, twelve hallmarks of aging can be put forward: genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, disabled macroautophagy, deregulated nutrient-sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, altered intercellular communication, chronic inflammation, and dysbiosis. Aging changes many genes expression model by regulating DNA methylation, histone modification, chromatin remodeling, retrotransposon activity, non-coding RNA (ncRNA) regulation, and RNA modification, all of which participate in the regulation of the aging process. Aging is associated with extensive remodelling of epigenome. From yeast to humans, an shared epigenetic trend detected in aging cells is the general loss of histones, which linked to numerous cell activities such as cell cycle exit and autophagy. It was reported and believed that DNA methylation in specific regions or at specific sites in the genome decreased with aging. Intriguingly, some CpG sites where DNA methylation levels changed, have been used to build 'epigenetic clocks' capable of predicting the chronological age of a sample with high accuracy. However, specific CpG sites selected by different clocks often do not overlap and different epigenetic clocks capture different biological signals, the clock concept should not be confused with overall methylation signatures of an aging individuals. But in terms of sheer excellence, Trapp and colleagues introduce 'scAge', a novel computational method that allows the determination of DNA methylation age at single-cell resolution. This tool can be applied to study functional heterogeneity between cells characterized by differences in their scAge, and could allow researchers to better understand mechanisms that contribute to organismal aging.

Except of gene damage, accumulation of protein damages over time also accompany with senescence. Post-translational modifications of proteins plays key roles in cell metabolism and cellular communications, affecting lifespan and aging. Protein misfolding and abnormal aggregation occur more frequently in aging individuals. Lewy body in PD patients and amyloid in Alzheimer disease patients are current widely known aging-related abnormal proteins. Besides, more than 200 kinds of proteins were found relating with aging. Within which Insulin-like growth factor (IGF) signaling, mitogen-activated protein kinases (MAPK), hypoxia-inducible factor 1 (HIF1), cytokine signaling, Forkhead Box O (FOXO) metabolic pathways, folate metabolism, advance glycation end products (AGE), and receptor AGE (RAGE) metabolic pathway are most remarkably. It's certain that damaged proteins affecting various physiological functions of the body, Whether it's instincts or the ability to learn. With the current view, replacement or supplement strategy perhaps is the best choice. Besides, the mechanisms of aging, a worthy focus of concern, are deserved to dig deeper.

【关键字】 stem cells; aging; neurodegeneration

PGE2 驱动 hESC-RPE 线粒体低毒兴奋效应以增强视网膜退行性疾病移植治疗效果

程政航

第三军医大学附属西南医院

【摘要】 年龄相关黄斑变性 (AMD) 是中老年人视力损害的首要因素，目前还没有有效的治疗方法。视网膜色素上皮细胞 (RPE) 移植是 AMD 具有潜力的治疗方式，但是往往因为不利的移植微环境和免疫排斥而损失大量细胞，造成移植效果不理想。前期研究表明，外周血循环在 AMD 进展过程中发挥重要作用，同时对移植后的细胞存活产生重要影响。在这里，我们建立了 hESC-RPE 和 AMD 患者 PBMC 共培养体系以模拟移植后免疫微环境，与正常组对比发现环加氧酶 2 (COX-2) 上调而 15-羟基前列腺素脱氢酶 (15-PGDH) 下调，这意味着前列腺素 E2(PGE2) 的表达维持在高水平状态，这与我在 AMD 患者黄斑区 RPE 的检测结果一致。PGE2 具有剂量依赖性和免疫调节效应，在不同条件下可作为免疫抑制分子和促炎因子。我们使用 PGE2 预处理后与 PBMC 共培养的 RPE 细胞表现出线粒体形态和代谢改善，抗凋亡和增殖能力增强，在体移植表现出更高的存活率和整合率。这可能是 PGE2 通过 EP2/EP4 信号诱导线粒体应激从而触发线粒体低毒兴奋效应 (mitohormesis)，促进代谢重编程和稳定蛋白质折叠等提高细胞抗逆性来实现的。总之，我们提供了一种通过 PGE2 驯化 RPE 细胞以提高耐受从而提高移植后存活率的方法，这为 RPE 细胞移植的临床转化提供了有益参考。

【关键字】 视网膜色素上皮细胞；前列腺素 E2；年龄相关黄斑变性；线粒体；视网膜

缺血性脑卒中小鼠模型的单细胞转录组图谱揭示小胶质细胞介导的外周免疫细胞脑部浸润

管其标

中国科学院动物研究所

【摘要】脑卒中是由于脑血管梗阻或者破裂导致脑组织损伤，进而造成神经功能障碍的一组疾病，一般分为缺血性和出血性两大类，以前者为主。缺血性脑卒中后，其病理生理变化非常复杂，其中包括损伤引起继发级联免疫反应，病灶部位固有的小胶质细胞率先激活，释放多种细胞因子和炎性物质，募集和趋化中性粒细胞、单核/巨噬细胞及淋巴细胞等免疫细胞至损伤部位，重塑损伤局部免疫微环境，加重了病灶部位神经元的损伤，影响卒中后神经功能修复。因此，揭示缺血性脑卒中后外周和病灶局部的免疫变化特征及机制，从而通过多维度调节炎症反应与继发性免疫损伤，促进卒中后神经功能恢复成为当前神经免疫的研究热点之一。近年来的研究证实，不同类型的外周免疫细胞敲除或抑制可以明显改善卒中后微环境促进神经功能恢复。近期本项目团队通过单细胞转录组测序发现，卒中后急性期小胶质细胞趋化单核巨噬细胞、中性粒细胞等外周免疫细胞入脑，在此基础上，将进一步揭示通过抑制小胶质细胞过度趋化外周炎性细胞、调控免疫微环境改善神经功能的具体机制，并进一步优化卒中治疗方案。

【关键字】缺血性脑卒中，神经免疫

干细胞与再生医学发展概述

李子和

中国科学院动物研究所

【摘要】衰老与再生从古至今一直以来就是人们所关注的焦点。从古老的神话中想象神仙通过修炼达到羽化飞升的不朽，到始皇帝遍寻天下寻求不老不死的灵丹妙药；古代的哲人们常常羡慕长江无穷无尽，又会感慨时光飞逝，发出“一死生为虚诞，齐彭殇为妄作”的长叹。在生命科学飞速发展的今天，古人的这些愿望正在一步一步的变为现实。从细胞学说的建立将生命的衰老和再生推进到细胞的层面；到干细胞的发现让人类意识到细胞再生和多向分化的可能性；再到细胞重编程，将细胞的命运倒转重排；这一步又一步的发现仿佛在告诉我们，没有什么是不可能的，干细胞与再生医学研究的推进以及成果的转化将让我们一步一步的走进神仙修炼的青山，让人类的健康与寿命登上新的台阶。

【关键字】干细胞 再生 衰老

Precise Correction of Lhcgr Mutation in Stem Leydig Cells by Prime Editing Rescues Hereditary Primary Hypogonadism in Mice

夏凯、项鹏

中山大学中山医学院

【摘要】 Hereditary primary hypogonadism (HPH), caused by gene mutation related to testosterone synthesis in Leydig cells, usually impairs male sexual development and spermatogenesis. Genetically corrected stem Leydig cells (SLCs) transplantation may provide a new approach for treating HPH. Here, a novel nonsense-point-mutation mouse model (LhcgrW495X) is first generated based on a gene mutation relative to HPH patients. To verify the efficacy and feasibility of SLCs transplantation in treating HPH, wild-type SLCs are transplanted into LhcgrW495X mice, in which SLCs obviously rescue HPH phenotypes. Through comparing several editing strategies, PEmax system is identified as an efficient and precise approach to correct the pathogenic point mutation in Lhcgr. Furthermore, delivering intein-split PEmax system via lentivirus successfully corrects the mutation in SLCs from LhcgrW495X mice ex vivo. Gene-corrected SLCs from LhcgrW495X mice exert ability to differentiate into functional Leydig cells in vitro. Notably, the transplantation of gene-corrected SLCs effectively regenerates Leydig cells, recovers testosterone production, restarts sexual development, rescues spermatogenesis, and produces fertile offspring in LhcgrW495X mice. Altogether, these results suggest that PE-based gene editing in SLCs ex vivo is a promising strategy for HPH therapy and is potentially leveraged to address more hereditary diseases in reproductive system.

【关键字】 testis, testosterone, hypogonadism, spermatogenesis, stem Leydig cells, prime editing

Therapeutic Potential of Double-Negative T (DNT) Cell Infusion in Alleviating Alzheimer's Disease Symptoms

谢苑芷、刘京、侯宗仁、刘凯伦、李灿、张真豪、王强

中国科学院动物研究所

【摘要】 Alzheimer's disease (AD) is characterized by progressive neurodegeneration that contributes to cognitive decline. Among the immune cells implicated in modulating neuroinflammation, $\text{TCR}\alpha\beta+\text{NK1.1-CD4-CD8}$ -double-negative T (DNT) cells have shown efficacy in mitigating neural functional decline across several neurological disorders, suggesting their promise for AD intervention. To explore this, we infused expanded DNT cells into $5\times\text{FAD}$ mice, a recognized AD model. This treatment significantly attenuated neuroinflammation in the recipients, with mechanisms distinct from other therapeutic contexts, potentially mediated by the downregulation of H2-Aa and upregulation of Skap2. Crucially, the treatment notably reduced plaque accumulation and steered microglia toward a more homeostatic and neuroprotective phenotype. Additionally, AD mice receiving DNT cell infusion exhibited enhanced cognitive ability, heightened synaptic plasticity, improved oligodendrocyte health, and increased neuronal complexity. Collectively, our findings underscore DNT cell transplantation as a compelling therapeutic avenue for AD.

【关键字】 Alzheimer's disease, cell therapy, $\text{A}\beta$ plaques, $\text{TCR}\alpha\beta+\text{NK1.1-CD4-CD8}$ -double-negative T cells

下丘脑环路调控慢性应激中免疫红细胞的生成

刘伯男^{1,2,3,4}, 王琪^{1,2,3,4}, 张婷婷^{1,3,4}, 骆斯佳^{1,2,3,4}, 张璟祎^{1,2,3,4}, 卢盈妃^{1,2,3,4}, 王思远^{1,3,4}, 胡宝洋^{1,2,3,4}*

1. 中国科学院动物研究所
2. 中国科学院大学存济医学院
3. 中国科学院干细胞与再生医学创新研究院
4. 北京干细胞与再生医学创新研究院

【摘要】伴随着快节奏的生活和不断上升的生活成本，慢性压力成为现代社会人类面临的一个普遍挑战。以往的研究表明，压力导致的慢性应激状态会对系统免疫产生影响，使淋巴细胞的数量减少，导致外周免疫抑制和更高的感染风险，但很少有人将其与免疫红细胞联系起来。然而，越来越多的研究表明免疫红细胞参与免疫反应的调节，并通过细胞粘附和分泌细胞因子发挥积极作用。通过对公共数据库中重度抑郁症患者外周全血样本的测序数据分析，我们发现红细胞的相关基因与多种免疫细胞呈中度相关性，并参与调控外周免疫系统。因此，我们建立了9周的慢性不可预知应激模型来研究慢性应激中免疫红细胞的功能。实验结果表明，慢性应激导致小鼠股骨中的交感神经表达上升和免疫红细胞生成增多，而血液和骨髓中的免疫细胞则减少。手术消融交感神经或使用局部药物抑制交感神经可以抑制免疫红细胞数量的增多，进而改善由慢性应激导致的外周及骨髓中CD8⁺T细胞减少。逆行示踪实验表明，下丘脑视前核(PVN)是调控这一反应的主要脑区，激活PVN的促肾上腺皮质激素释放激素(CRH)神经元可以调控外周骨髓中红细胞的生成，进而调节免疫反应。我们的研究建立了慢性应激条件下中枢与外周神经系统的联系，为应激和免疫类疾病的治疗提供了新思路。

【关键字】慢性应激 免疫红细胞 交感神经 下丘脑 促肾上腺皮质激素释放激素

Regulation of human amniotic mesenchymal stem cells on follicular developmental and inflammatory cytokines for therapy of cis-platinum induced ovarian insufficiency mice

王圆圆、余丽梅、罗娇、刘璐、王钰莹、范振海、杨鸿宇

遵义医科大学附属医院

【关键字】 Abstract:Background:Premature ovarian insufficiency (POI) due to chemotherapy is associated with severe physical damage and psychological burden on women. In the present study, we investigated whether hAMSC can effectively restore ovarian function and structure following cisplatin (CDDP) injury.

Method:POI mice models were established through intraperitoneal injection of cisplatin. Subsequently, transplantation of hAMSC was conducted to administer POI mice. Ovaries and plasma of these mice models were harvested after seven-eighteen days of treatment.Ovarian morphology and follicle number were assessed by hematoxylin and eosin staining. ELISA was used to detect hormone levels, which are related to ovarian function in serum.To assess monitor the estrous cycle a vaginal exfoliated cell smear was used. To explore the underlying mechanisms of hAMSC treatment for ovarian function recovery, the Additionally, we conducted HAMSCs were labeled with PKH26, and cell implantation and distribution were observed. Immunohistochemical staining was used to detect protein expression.

Result:After transplantation of hAMSC, the ovarian function-related hormone levels, restore normal estrous cycleand and the number of ovarian follicles returned to nearly normal degrees, its therapeutic effect is better than DES replacement therapy.Meanwhile, there was a significant improvement in CDDP-induced POI may involve the increased expression of FSHR, IGF-1 and VEGF protein and the decreased expression of Tnf- α protein in ovarian tissue. Furthermore, the improvement of ovarian function and proliferation was associated with the up-regulation of GDF-9, OCT4, POI1B, FOXL2 mRNA expression and the down-regulation of SCF mRNS expression in ovarian tissues.

Conclusions:This study suggested that hAMSC promoted ovarian functions and proliferation by regulating cytokines expression. Therefore, hAMSC transplantation could be a promising and efficient clinical therapy for POI in the near future.

【关键字】 Human amniotic mesenchymal stem cells, Cisplatin, Mice, premature ovarian insufficiency

中枢神经系统的免疫应答通路的探究

李逸凡、胡宝洋

中国科学院动物研究所

【摘要】小胶质细胞在神经损伤期间释放的许多信号小分子可能会促进神经性炎症的许多行为状态。近年来的许多研究已经揭示了与炎症反应时的细胞内神经元途径的重要性。但是，关于小胶质细胞途径参与这种病理学的信息仍然很少。而 NF- κ B 信号通路可以调控多种参与炎症反应的细胞因子，以应答多种胞外细胞信号刺激，然后产生免疫、炎症反应，并影响细胞增值、分化。与此同时，许多研究表明蛋白激酶在神经元毒性和小胶质细胞激活中的重要作用。少数蛋白激酶已成为调节小胶质细胞活化的重要信号成分，例如促分裂原活化蛋白激酶（MAPK）就是其中之一。故而，作者的前期工作主要探究了，在细菌脂多糖刺激下，形成的炎症免疫应答小鼠模型中，MAPK 蛋白激酶与 NF- κ B 分子的作用机制与机理。为进一步探究中枢神经系统内的小胶质细胞的增殖分化，神经元细胞的再生的重大课题，指明了其中可能存在的分子调控机制与方向。

【关键字】 NF- κ B 通路，MAPK 通路，中枢神经系统的免疫

Comparison of chemicals-induced 2-cell like state in mouse embryonic stem cells

于永芹、刘林

南开大学

【摘要】 Mouse embryonic stem cells (mESCs) are heterogeneous in that about 1-5% of a given ESC population express Zscan4 (Zscan4+) which marks a transient 2C-state and expanded development potential. Thus far, various chemicals have been shown to promote 2C-state. We sought to directly compare the efficiency of various individual chemicals or in combination in promoting 2C-state using Zscan4+ -tomato-red as an indicator. These chemicals included sodium butyrate (NaB), retinoic acid (RA), Dot1l inhibitor (EPZ), splicing inhibitor pladienolide B (PlaB), and crotonic acid (CA). These individual chemicals can induce 2C-state to various degrees. However, the 2C state induced by CA, RA, NaB or NaB+RA can only maintain for limited passages (P2-3), followed by ESC differentiation in morphology. In contrast, 2C-state is maintained for more than 20 passages in PlaB or in PlaB+CA conditions. PlaB or PlaB+CA produced 2C-state shown by Zscan4+ tomato red at higher efficiency of approximately 13% by flow cytometry, and higher rates by immunofluorescence microscopy, compared with those of controls (1-2%). RNA-seq revealed that 2-cell genes are expressed at higher levels in PlaB, and highest in PlaB+CA cultures, compared to controls without adding chemicals. The PCA analysis revealed that ESCs may undergo distinct cellular trajectories in response to PlaB and that combination of PlaB+CA induces different states. Thus, our results show that PlaB together with CA further promote reprogramming to 2C-like state.

【关键字】 : Mouse embryonic stem cells (mESCs), 2-cell genes, PlaB, NaB, RA, EPZ, crotonic acid (CA)

AFG3L2 突变引起常染色体隐性遗传的脊髓小脑共济失调的致病机理研究

李虹雨、马晴雯、鲍莉雯、龚秀丽、曾凡一

上海市儿童医院

【摘要】：常染色体隐性遗传的脊髓小脑共济失调（autosomal recessive spinocerebellar ataxias, SCARs）是一类较常见的神经退行性疾病，致病机制复杂。我们收集到一例携带 AFG3L2 复合杂合突变的 SCAR 家系，父母分别携带一个 AFG3L2 突变，但无临床表型。利用 SCAR 家系特异的 hiPSCs (human induced pluripotent stem cells)，进行分子水平的致病机理研究。通过 RACE (rapid amplification of cDNA ends) 实验，发现家系 hiPSCs 中的 AFG3L2 野生型和突变型 mRNA 表达失衡。母亲和患者的 hiPSCs 的 AFG3L2 蛋白呈现单倍剂量，并存在不同程度的线粒体结构和功能异常。已知 AFG3L2 突变可以通过上调 MCU 复合物组成亚基 EMRE 的表达，介导 SCA28 (spinocerebellar ataxia 28) 患者 Purkinje cells 的 Ca^{2+} 过载，导致 Purkinje cells 死亡。我们只在患者的 hiPSCs 中，发现线粒体 Ca^{2+} 过载，MCU 复合物组成亚基 MICU1 表达的降低，EMRE 表达的升高。以上结果提示，利用患者特异性 hiPSCs 我们找到了 MICU1 介导的 Ca^{2+} 过载可能是导致 SCAR 患者发病的致病机制之一，为此类疾病未来进行干细胞或基因治疗提供了依据。

【关键字】 基因 AFG3L2，常染色体隐性遗传的脊髓小脑共济失调，线粒体损伤， Ca^{2+} 过载

Predictive Value of Pre-Treatment ctDNA Genomic Landscape in Relapsed or Refractory Multiple Myeloma Patients Undergoing anti-BCMA CAR-T Therapy: Insights from Tumor Cells and T Cells

陈蓉蓉

浙江大学医学院附属第一医院

【摘要】 Anti-B-cell maturation antigen (BCMA) chimeric antigen receptor T (CAR)-cell therapy has yielded remarkable safety and efficacy in refractory or relapsed multiple myeloma (RRMM). The circulating tumor-derived cell-free tumor DNA (ctDNA) exhibited distinct advantages over bone marrow (BM)-based genetic approaches in addressing the challenges posed by tumor heterogeneity in distribution and genetic variations in MM. Here, we profiled a total of 108 samples from MM patients before treatment of ctDNA for its predictive value in the relapse and primary resistance of the CAR-T cells therapy. The CAR-T cell proportion and the CD8/CD4 subset were monitored throughout the treatment process. We observed that high ctDNA level ($> 1430\text{ng/ml}$) was strongly associated with shorter progression-free survival (PFS) ($P=0.007$). Meanwhile, it also significantly related to higher percentages of bone plasma cells by FCM ($P=0.013$), lower percentages of CAR-T cells at peak ($P=0.037$) and higher percentages of CD8⁺ T cells ($P=0.034$), which enabled integration of tumor and T cell effector-mediated factors for assessing treatment failure. Alterations in several individual genes indicated poor outcomes, including IGLL5 ($P=0.004$) play a role in the immune response, IRF4 ($P=0.024$) involving in NF- κ B signaling pathway and CREBBP ($P=0.041$) participating in the epigenetic regulation of gene expression. Multivariate logistic regression analysis revealed ERBB4 was statistically referring to resistance to CAR-T cell therapy ($P=0.04$). Among patients with ERBB4 mutation, 4 patients failed to get complete response and all got early relapse. In addition, the patients with two multiple-site ctDNA mutation have terrible outcome with progression-free survival time less than 6 months, thorough information on the genomic instability ($P < 0.001$). Our research demonstrated the feasibility of detecting multiple myeloma (MM)-derived ctDNA using a 154-gene panel sequencing, serves as an adjunct non-invasive measure of substantial tumor burden and a prognostic genetic feature that can assist in predicting response to anti-BCMA CAR-T therapy.

【关键字】 anti-BCMA CAR-T therapy; circulating tumor DNA (ctDNA); multiple myeloma

一种有效筛选出能够制备出嵌合体小鼠的 iPSCs 的方法

杨冠恒 1,2,3, 郭歆冰 1,2,3, 龚秀丽 1,2,3, 桑晓 1,2,3, 陈雁雯 1,2,3, 郭传亮 1,2,3, 鲍莉雯 1,2,3, 张敬之 1,2,3, 曾凡一 1,2,3

1. 上海交通大学医学遗传研究所上海市儿童医院上海交通大学医学院附属儿童医院, 上海 200040
2. 上海交通大学基础医学院组织胚胎学与遗传发育学系, 上海 200025
3. 国家卫健委医学胚胎分子生物学重点实验室上海市胚胎与生殖工程重点实验室, 上海 200040

【摘要】目的：在体外诱导体细胞重编程成诱导性多能性干细胞（induced pluripotent stem cells, iPSCs）所形成的克隆中同时存在重编程完全和不完全的干细胞，对这两种细胞进行区分并筛选需要经过复杂的多能性验证实验，为此本研究开发一种可通过基因位点控制区（Locus Control Region, LCR）调控 GFP 表达，直接在体细胞重编程过程中筛选出重编程完全和不完全的多能性干细胞的方法。

方法：用本团队自主制备的具有红系特异性 GFP 表达的 β 珠蛋白基因的 HS23-GFP 转基因小鼠，取其尾尖皮肤，在体外制备成皮肤成纤维细胞（Tail tip fibroblasts, TTF）。用慢病毒载体转基因体系将重编程基因 Klf-4、Sox2、c-Myc、Oct4 转染进 TTF 进行体细胞重编程。形成克隆后进行挑克隆细胞建系，用碱性磷酸酶（alkaline phosphatase, ALP）初步验证干细胞的多能性，用 RT-PCR 方法对 Sox2、c-Myc、Oct4 多能性基因进行定量检测，并对不同克隆细胞系进行嵌合体小鼠制备。

结果：HS23-GFP 转基因小鼠的 TTF 在体外重编程过程中同时出现了绿色荧光蛋白（GFP+）表达和不表达（GFP-）的细胞克隆。在荧光显微镜下进行挑克隆建系，制备出 GFP+ iPS 细胞系和 GFP-iPS 细胞系。经多能性实验验证，GFP+ iPSCs 和 GFP-iPSCs 的 ALP 均为阳性结果，多能性基因 Sox2、c-Myc、Oct4 在 mRNA 水平均明显表达。嵌合体小鼠形成实验发现用 GFP+ iPSCs 能够制备出嵌合体小鼠，并有效稳定地嵌合进行受体小鼠，血细胞中可追踪到 GFP+ iPSCs 在受体体内开成的 GFP+红细胞。而用 GFP-iPSCs 不能形成嵌合体小鼠，受体体内追踪不到 GFP+细胞。因此，GFP+ iPSCs 是重编程完全的 iPS 细胞系，而 GFP-iPSCs 则是重编程不完全的细胞系。

结论：本研究开发出可通过 HS23-GFP 的表达直接筛选出在重编程过程中重编程完全的 iPSCs，这一筛选方法能够更为高效、快速、简单、直接地获取高质量的 iPS 细胞系。

【关键字】位点控制区，绿色荧光蛋白，重编程，诱导性多能干细胞，嵌合体

transient activation of PIEZO1 mechanosensitive channel facilitates ex vivo expansion of hematopoietic stem cells

王琪炜、李金鑫、姜玲俐、钱鹏旭

浙江大学

【摘要】 实现功能性造血干细胞 (HSCs) 的长期离体扩增对于开发基于 HSC 移植的临床应用至关重要。了解 HSCs 维持其功能的微环境是先决条件，其中机械感知是关键因素之一。研究已揭示机械敏感离子通道 (MSICs) 在造血系统中至关重要，但它们在离体培养的 HSCs 扩增和功能维持中的作用仍不清楚。在这里，我们展示 PIEZO1 是 HSCs 中显著表达的 MSIC。令人意外的是，PIEZO1 的缺失和持续化学激活对离体培养的 HSCs 有害，暗示维持离体培养的 HSCs 需要短暂的 PIEZO1 激活。为了寻找导致这种激活的条件，我们筛选了不同的微粒，并证明了直径为 500 纳米的硬质聚合物微粒通过膜张力短暂激活 PIEZO1。PS500 (直径为 500 纳米的聚苯乙烯微球) 显著促进了小鼠骨髓 (BM) 和人脐带血 (hUCB) 来源的 HSCs 的离体扩增，这些细胞具有长期体内再造能力。在机制上，短暂激活的 PIEZO1 通道引发了依赖钙离子的增殖细胞因子转录，最终导致 STAT3 的激活，以维持自我更新并促进细胞增殖和存活。总体而言，我们的结果表明，PS500 短暂激活 PIEZO1 机械感知通道，并且能够有效扩增功能性的 HSCs 而不产生毒性，为生产应用于临床的功能性 HSCs 提供了有希望的策略。

【关键字】 PIEZO1, hematopoietic stem cells, expansion, microspheres, HSC transplantation

IGFBP7 预防骨髓间充质干细胞衰老的作用和潜在机制研究

李晓钰、胡磊、王松灵

首都医科大学口腔健康北京实验室

【摘要】目的：

细胞衰老会导致干细胞功能的障碍，进而严重损害组织稳态及组织再生。如何有效调控间充质干细胞的衰老是维持组织功能稳定并提高组织再生效率的关键。胰岛素样生长因子（IGF）-胰岛素样生长因子结合蛋白（IGFBP）系统与间充质干细胞的维持和分化密切，并参与从线虫到哺乳动物等多种生物的年龄相关疾病和衰老进程，但其在干细胞衰老和组织再生中的作用和潜在机制还需进一步研究。

材料和方法：

1. 通过获得性和丧失性功能研究，在体内外明确 IGFBP7 对 DPSCs 衰老水平的调控作用
2. 通过 Seahores 及阻断/激活线粒体电子传递链等明确 IGFBP7 调控线粒体代谢在 DPSCs 功能稳态维持中的作用
3. 通过 CHIP/WB 等明确 IGFBP7 通过线粒体代谢调控细胞衰老的分子机制

结果：

首次发现 IGFBP7 可以预防 DPSCs 衰老并增强其成骨分化潜能。通过构建稳定敲低和过表达 IGFBP7 的 DPSCs, 发现 IGFBP 增强 DPSCs 的线粒体氧化磷酸化能力和糖酵解水平, 并促进 DPSCs 中线粒体生物发生相关基因和糖酵解途径关键酶的表达。进一步发现 IGFBP7 可显著上调 SIRT1, 通过诱导 H3K36ac 去乙酰化使 H3K36ac 与 p21 启动子的结合亲和力降低, 进而导致 p21 转录减少。随后, 利用 ROT 阻断或辅酶 Q10 激活 DPSCs 中的线粒体电子传递链, 证实 IGFBP7 通过调节线粒体代谢预防 DPSCs 衰老并促进组织再生的作用。

结论：

本研究为深入了解 IGFBP7 在细胞衰老过程中的作用和开发新的治疗策略以促进组织再生奠定基础。

【关键字】 IGFBP7; 骨髓间充质干细胞; 衰老; 线粒体功能及代谢; SIRT1; p21

Microplastics dampen the self-renewal of hematopoietic stem cells by disrupting the gut microbiota-hypoxanthine-Wnt axis

姜玲俐 1,2,3, 叶逸山 2,3,4, 韩颖丽 1,2,3, 王琪炜 1,2,3, 鲁欢 1,2,3, Jinxin Li 2,3,4, 钱文畅 1,2,3, 曾欣 1,2,3, 张召茹 1,2,3, 赵妍敏 2,3,4, 施继敏 2,3,4, 罗依 2,3,4, 黄河 2,3,4, 钱鹏旭 1,2,3

1. Center for Stem Cell and Regenerative Medicine and Bone Marrow Transplantation Center of the First Affiliated Hospital, Zhejiang University School of Medicine Hangzhou 310058, China.
2. Liangzhu Laboratory, Zhejiang University Medical Center, 1369 West Wenyi Road, Hangzhou 311121, China.
3. Institute of Hematology, Zhejiang University & Zhejiang Engineering Laboratory for Stem Cell and Immunotherapy, Hangzhou 310058, China.
4. Bone Marrow Transplantation Center, The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China.

【摘要】 Microplastics (MPs) are contaminants ubiquitously found in the global biosphere that can enter the human body through inhalation or ingestion, posing significant risks to human health. Recent studies emerge that MPs are present in the bone marrow and damage the hematopoietic system. However, it remains largely elusive about the specific mechanisms by which MPs affect hematopoietic stem cells (HSCs) and their clinical relevance in HSC transplantation (HSCT). Here, we established a long-term MPs intake mouse model and found that MPs induced alterations to the intestinal microbiota and metabolites, significantly reducing the level of Rikenellaceae and hypoxanthine, eventually dampening the self-renewal of HSCs by disrupting the gut microbiota-hypoxanthine-Wnt axis. Furthermore, we validated in a cohort of human patients receiving allogeneic HSCT from healthy donors, and revealed that the survival time of patients was negatively correlated with levels of MPs, while positively with abundance of Rikenellaceae, and hypoxanthine in the HSC donors' feces and blood. Overall, these findings shed light on the harmful effects and underlying mechanisms of microplastics on HSCs, which may provide potential strategies for preventing microplastic-induced damage to the hematopoietic system.

【关键字】 Microplastics; Hematopoietic Stem Cells; Intestinal Microbiota; Hematopoietic Stem Cell Transplantation

Sialin (SLC17A5) 通过调控线粒体代谢维持间充质干细胞功能稳态

李晓钰、王松灵

首都医科大学口腔健康北京实验室

【摘要】目的：

Sialin 可作为细胞膜硝酸盐等转运通道发挥多种生理作用。课题组前期研究发现，Sialin 可不依赖于细胞膜转运通道在调控间充质干细胞功能、疾病防控等稳态医学中发挥关键作用，但目前具体机制尚不清楚。因此，进一步阐明 Sialin 生物学功能对稳态医学研究具有重要科学意义。

材料和方法：

1. 构建 Slc17a5^{-/-}小鼠并通过获得性和丧失性功能研究，明确 Sialin 对 MSCs 功能稳态的调控作用
2. 对 Sialin 进行亚细胞器定位，通过 Seahores 等明确 Sialin 调控线粒体代谢在 MSCs 功能稳态维持中的作用
3. 构建靶向线粒体过表达 Sialin 并分离提取线粒体蛋白，通过 IP-MS 等明确线粒体 Sialin 调控线粒体代谢的分子机制

结果：

1. Slc17a5^{-/-}小鼠骨形成障碍，MSCs 成骨分化潜能降低，衰老水平增加
2. Sialin 增强 MSCs 成骨分化潜能并降低衰老水平
3. Sialin 定位于 MSCs 线粒体，靶向线粒体 Sialin 可提升 MSCs 线粒体功能及代谢活性，其中差异通路主要富集在 TCA 循环等代谢途径，阻断或激活 MSCs 线粒体电子传递链可直接反向调控敲低或过表达 SLC17A5 MSCs 成骨分化潜能及衰老水平的变化
4. Sialin 通过调控线粒体功能维持 MSCs 功能稳态

结论：

1. 首次发现 Sialin 通过胞内信号转导调控线粒体的新功能，拓展 Sialin 生物学功能
2. 首次揭示 Sialin 激活线粒体代谢的新机制，为进一步研究 Sialin 生物学功能奠定基础
3. 研究结果有助于开发靶向调控线粒体代谢、维持细胞及机体功能稳态的技术手段

【关键字】 Sialin；间充质干细胞；线粒体功能及代谢；细胞功能稳态；骨稳态

NAT10 regulates the stability of HSC-specific mRNAs to control hematopoiesis

李卫倩¹, 霍悦¹, 张召茹², 钱鹏旭², 王芳¹, 余佳¹

1. State Key Laboratory of Common Mechanism Research for Major Diseases, Institute of Basic Medical Sciences, Haihe Laboratory of Cell Ecosystem, The Key Laboratory of RNA and Hematopoietic Regulation, Chinese Academy of Medical Sciences, School of Basic Medicine Peking Union Medical College, Beijing, China.

2. Bone Marrow Transplantation Center, The First Affiliated Hospital, Liangzhu Laboratory, Institute of Hematology, Zhejiang Engineering Laboratory for Stem Cell and Immunotherapy, Center of Stem Cell and Regenerative Medicine, School of Medicine, Zhejiang University, Hangzhou, China.

【摘要】 The self-renewal capacity of multipotent hematopoietic stem cells (HSCs) supports blood system homeostasis throughout life. Thus, the maintenance of HSC homeostasis is a key issue in the field of hematology. RNA modification, especially RNA m6A modification and its related enzymes play important roles in hematopoietic development and blood diseases. However, the function of multifunctional RNA ac4C modification in hematopoiesis has not been reported. This project focuses on the function and mechanism of ac4C-modified enzyme NAT10 in the maintenance of HSC homeostasis.

【关键字】 HSC homeostasis, NAT10, RNA stability

mESCs 分化为 TEPs 及 Aire 敲低对胸腺 T 细胞发育与分化的影响

李远迪¹, 高杰¹, 胡蓉¹, 何志旭², 苏敏¹

1. 贵州医科大学

2. 遵义医科大学

【摘要】 自身免疫调节因子 (Aire) 主要在髓质胸腺上皮细胞 (mTECs) 中表达, 可通过调节组织特异性抗原 (TSA) 的转录来调节免疫耐受。本研究旨在通过诱导小鼠胚胎干细胞 (mESCs) 分化为胸腺上皮祖细胞 (TEPs), 确定敲低 Aire 基因的 mESCs 对体外诱导分化的 TEPs 转录组的影响, 并以 NOD/Ltj 小鼠作为自身免疫性疾病模型, 通过胸腺内注射 Aire shRNA 慢病毒, 分为未处理组、Control shRNA 组和 Aire shRNA 组, 探讨敲低小鼠胸腺 Aire 基因对 T 细胞发育和分化以及小鼠 1 型糖尿病 (T1D) 发生发展的影响。结果显示, 敲低 Aire 的 mESCs-TEPs 中, EpCAM1 阳性细胞中 K5、K8 双阳性 TEPs 比例降低, RNA-seq 结果显示, 细胞外基质 (ECM)-受体相互作用等途径发生改变, 其相关基因 SPP1 表达降低, Fn1 和 CD44 表达增高。敲低 NOD/Ltj 小鼠胸腺内 Aire 基因后, 小鼠血糖升高较快, 加速 T1D 发病进程。病理切片显示 Aire shRNA 组小鼠胰岛炎性浸润加重, 胸腺 Aire 表达降低。Aire shRNA 组胸腺内 T1D 相关 TSAs (INS2、GAD67) 和 mTECs 发育成熟相关分子 (Aire、CD80、MHC-II) 的 mRNA 表达水平降低, 同时, Aire shRNA 组中 ECM-受体相互作用途径中的相关基因 SPP1 表达降低, Fn1 和 CD44 表达增高, 与体外实验结果一致。Aire shRNA 组胸腺内 CD4⁺ CD8⁻ T 细胞比例增多, Tregs 减少; Insulin 刺激各组脾细胞后, Aire shRNA 组抗原特异性 T 细胞增殖和活化明显增加。以上结果提示, 敲低 mESCs 中的 Aire 基因会诱导 TEPs 的分化效率降低, ECM-受体相互作用等途径发生改变, 敲低胸腺中的 Aire 基因会损害 NOD/Ltj 小鼠的免疫耐受, 加速 NOD/Ltj 小鼠 T1D 疾病的进展。

【关键字】 自身免疫调节因子; 胚胎干细胞; 胸腺上皮细胞; 1 型糖尿病

基因编辑造血干细胞移植治疗 β 654 地中海贫血小鼠

鲁丹、龚秀丽、郭歆冰、陈燕雯、朱怡文、方彧聃、蔡勤、许淼、杨华、曾凡一

上海市儿童医院

【摘要】目的： β -地中海贫血（地贫）是一种遗传性血液病，由 β -珠蛋白基因突变导致 β -珠蛋白合成减少或缺乏引起。我们在以往的研究中通过 CRISPR-Cas9 删除额外外显子的策略制备了基因编辑的 β 654 小鼠（ β 654-ER 小鼠），并纠正了小鼠中异常 β -珠蛋白 mRNA 的剪接途径。在本研究中，我们通过连续移植 β 654-ER 小鼠的造血干细胞进一步探讨了删除额外外显子的基因编辑造血干细胞对 β -地贫的治疗作用。

方法：将来自 β 654-ER 小鼠的基因编辑造血干细胞和野生型小鼠的造血干细胞分别移植到受辐照的 β 654 小鼠中，系统地阐明移植后 β 654 小鼠血液学、遗传学、病理学和表型的变化。

结果：基因编辑造血干细胞移植可将致死剂量辐射后小鼠的存活率提高到 100%，并能够有效实现造血重建和长期造血。与未移植的 β 654 小鼠相比，基因编辑造血干细胞移植后的小鼠的血液学参数得到显著改善，红细胞形态恢复正常，脾脏体积和重量明显减少，肝脏和脾脏髓外造血情况得到显著改善。与野生型小鼠造血干细胞相比，基因编辑造血干细胞移植的治疗效果在血液学参数和组织病理学方面无显著差异。

结论：本实验数据表明 β 654-ER 小鼠的基因编辑造血干细胞移植可以完全纠正 β 654 地贫的表型。本研究进一步证明了删除额外外显子基因编辑策略的有效性，同时为该基因编辑策略制备的造血干细胞的临床应用提供了参考和基础实验数据。

【关键字】 β 654 地中海贫血，造血干细胞移植，基因编辑

RNA binding protein HuR regulated by OIP5-AS1 may be involved in maternal transcript degradation during the human maternal-to-zygotic transition

魏豪、刘艳娜、张月华、邱家俊、曾凡一、颜景斌

上海交通大学医学院附属儿童医院

【关键字】 The maternal-to-zygotic transition is an essential step in the early development of humans, wherein maternal gene transcripts undergo extensive degradation, and zygotic genes are activated. Dysregulation of maternal transcript degradation may be associated with various reproductive disorders. However, to the best of our knowledge, the exact mechanism of maternal transcript degradation during maternal-to-zygotic transition remains unclear. The present study identified an oocyte-specific module through weighted gene co-expression network analysis, and enrichment analysis of genes in this module revealed that the genes were associated with transcription factor binding, protein modification and the cell cycle. Within this module, the present study identified a maternal long non-coding RNA, OIP5 antisense RNA 1 (OIP5-AS1), which may bind to the RNA binding protein human antigen R (HuR), restricting its availability to other mRNAs, and potentially contributing to maternal transcript degradation during MZT. Further experiments validated the physical interaction between OIP5-AS1 and HuR in induced pluripotent stem cells. RNA immunoprecipitation sequencing identified mRNAs that bind to HuR protein, and their functions were revealed to be associated with transcriptional regulation and the cell cycle. These findings support the idea that the HuR protein, regulated by OIP5-AS1, may be involved in maternal transcript degradation and other critical biological processes during maternal-to-zygotic transition in early human embryonic development. Our study contributes to continued investigation of the mechanism of maternal transcript degradation.

【关键字】 Early embryonic development, Long non-coding RNAs, Maternal transcript degradation, RNA binding protein, Maternal-to-zygotic transition

Small extracellular vesicles derived from acute myeloid leukemia cells promote leukemogenesis by transferring miR-221-3p

Mengyu Li 1,2 , Guohuan Sun 2 , Jinlian Zhao 3 , Yajie Wang 3 , Shangda Yang 2 , Tao Cheng 2 , Hui Cheng 2

1. Tianjin Medical University

2. Institute of Hematology & Blood Diseases Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College

3. The First People's Hospital of Yunnan Province

【摘要】 Small extracellular vesicles (sEVs) transfer cargos between cells and participate in various physiological and pathological processes through their autocrine and paracrine effects. However, the pathological mechanisms employed by sEV-encapsulated microRNAs (miRNAs) in acute myeloid leukemia (AML) are still obscure. In this study, we aimed to investigate the effects of AML cells-derived sEVs (AML-sEVs) on AML cells and delineate the underlying mechanisms. We initially used high-throughput sequencing to identify miR-221-3p as the miRNA prominently enriched in AML-sEVs. Our findings revealed that miR-221-3p promoted AML cell proliferation and leukemogenesis by accelerating cell cycle entry and inhibiting apoptosis. Furthermore, Gbp2 was confirmed as a target gene of miR-221-3p by dual luciferase reporter assays and rescue experiments. Additionally, AML-sEVs impaired the clonogenicity, and particularly the erythroid differentiation ability, of hematopoietic stem and progenitor cells. Taken together, our findings reveal how sEVs-delivered miRNAs contribute to AML pathogenesis, which can be exploited as a potential therapeutic target to attenuate AML progression.

【关键字】 Acute myeloid leukemia; Small extracellular vesicles; miR-221-3p; Gbp2

成纤维细胞生长因子 4 抑制大鼠睾丸间质干细胞分化但刺激其增殖

王义炎、王梦云、乔薪颐、叶蕾、王洪、杨进、郑柯、崔榕、葛仁山

温州医科大学附属第二医院

【摘要】背景和目的：成纤维细胞生长因子 4（Fibroblast growth factor 4, FGF4）是一种肝素结合生长因子，属于成纤维细胞生长因子家族。该家族的蛋白在胎儿发育、出生后生长和多种组织再生中起着关键作用，可促进细胞增殖和分化。本研究旨在探究 FGF4 对大鼠睾丸间质干细胞增殖和分化的影响。方法：我们在成年雄性 SD 大鼠中建立了二甲磺酸乙烷（ethane-dimethane sulfonate, EDS）消除睾丸间质细胞再生模型，并在 EDS 后第 14 天至 27 天经睾丸内注射 FGF4（0、10 和 100 ng/睾丸/天）进行处理。在 EDS 后 28 天，收集血清及睾丸，测定血清睾酮水平，计数睾丸间质细胞数量，测定睾丸相关基因和蛋白表达。在体外利用 3D 曲细精管培养系统，用 FGF4 或 FGF 受体抑制剂处理探究对睾丸间质干细胞增殖和分化的影响，并用 FGF4 处理纯化的睾丸间质祖细胞和成熟细胞，进一步探究其对睾丸间质细胞类固醇合成的影响。结果：在 EDS 后第 28 天，FGF4 在 100 ng/睾丸内能增加血清睾酮水平，但不影响黄体生成素和卵泡刺激素水平。FGF4 以 10 和 100 ng/睾丸增加睾丸间质细胞数量，但不影响支持细胞数量，并下调单个睾丸间质细胞基因（Lhcgr、Star、Cyp11a1、Hsd3b1、Cyp17a1、Hsd17b3、Insl3 和 Nr5a1）及其蛋白的表达。在曲细精管 3D 培养系统中，FGF4 抑制培养基睾酮水平，下调睾丸间质细胞基因（Lhcgr、Scarb1、Star、Cyp11a1、Cyp17a1 和 Hsd17b3）的表达，但 10 或 100 ng/ml FGF4 增加 EdU 阳性睾丸间质干细胞。此外，高于 1 ng/ml 的 FGF4 抑制睾丸间质祖细胞和成熟细胞类固醇生成。结论：FGF4 抑制大鼠睾丸间质干细胞分化但刺激其增殖。

【关键字】成纤维细胞生长因子 4，睾丸间质干细胞，增殖，分化，睾酮

Mesenchymal Stromal Cells Alleviate Depressive and Anxiety-like Behaviors via a Lung Vagal-to-Brain Axis in Male Mice

张小然、黄晶、黄玮俊、项鹏

中山大学

【摘要】 Major depressive disorder (MDD) is one of the most common and disabling mental disorders. More than one-third of patients fail to respond to conventional antidepressants; hence, new approaches to antidepressant drug discovery are urgently needed. As a potential treatment for depression, peripheral delivery of mesenchymal stromal cells (MSCs) is attractive due to the pleiotropic properties and apparent efficacy of these cells, but the underlying mechanisms remain elusive. Here, we show that bone marrow-derived MSCs are capable of alleviating stress-induced depressive and anxiety-like behaviors in two murine depression models. Intriguingly, improvement of symptoms was not due to a reduction in proinflammatory cytokines, but rather activation of 5-hydroxytryptamine (5-HT) neurons in the dorsal raphe nucleus (DRN). Mechanistically, peripheral delivery of MSCs activated the pulmonary innervating vagal sensory neurons of nodose ganglia, which further projected to the nucleus of the solitary tract (NTS), thereby inducing the release of 5-HT from the DRN. We identified that MSC-secreted brain-derived neurotrophic factor (BDNF) plays an important antidepressant role through tropomyosin receptor kinase B (TrkB)-mediated activation of lung sensory neurons, and that nebulized inhalation of a TrkB agonist (7, 8-DHF) also achieved a significant therapeutic effect. This study reveals a previously unknown activity of peripheral MSCs in regulating central nervous system function and demonstrates a "lung vagal-to-brain axis" strategy for MDD therapy.

【关键字】 Mesenchymal stromal cells, Major depressive disorder, lung vagal-to-brain axis, 5-hydroxytryptamine neurons

The adipose-neural axis is involved in cardiac arrhythmias

范玉宝¹, 黄珊珊¹, 李苏华², 吴冰原², 黄里³, 赵琦¹, 郑振达², 谢旭晶², 刘佳⁴, 黄玮俊¹, 孙佳琦¹, 王茂生⁵, 朱秀龙⁵, 朱洁明², 项鹏^{1,6}, 李伟强^{1,6}

1. 中山大学干细胞与组织工程教育部重点实验室
2. 中山大学附属第三医院心血管内科
3. 高州市人民医院干细胞与再生医学中心
4. 中山大学附属第三医院 VIP 医疗服务中心
5. 高州市人民医院心血管中心
6. 中山大学细胞生物学与组织胚胎学系

【摘要】 Dysfunction of the sympathetic nervous system and increase of epicardial adipose tissue (EAT) have been independently associated with the occurrence of cardiac arrhythmia. However, their exact roles in triggering arrhythmia remain elusive due to a lack of appropriate human disease models. Here, using the in vitro co-culture system with sympathetic neurons, cardiomyocytes, and adipocytes, we show that adipocyte-derived leptin could activate sympathetic neurons and increase the release of neuropeptide Y (NPY), which in turn trigger arrhythmia of cardiomyocytes by interaction with Y1 receptor (Y1R) and subsequently enhancing the activity of Na⁺/Ca²⁺ exchanger (NCX) and calcium/calmodulin-dependent protein kinase II (CaMKII). The arrhythmic phenotype could be partially blocked by leptin neutralizing antibody, or an inhibitor of Y1R, NCX or CaMKII. More importantly, increased EAT thickness accompanied with higher leptin/NPY blood levels was detected in atrial fibrillation patients compared to control group. Our study provides the first evidence that adipose-neural axis would contribute to arrhythmogenesis and represent a potential therapeutic target for arrhythmia.

【关键字】 Arrhythmia; Epicardial adipose tissue; Sympathetic neurons; Adipose-neural axis; NPY

红系特异性启动子与 BCL11A 三代慢病毒干扰在 β 地中海贫血基因治疗中的研究

李燕 2、何志旭 1、张鹏 2

1. 遵义医科大学
2. 贵州医科大学

【摘要】 目的：重组的红系特异性启动子与 BCL11A 慢病毒干扰质粒在体外细胞中 γ 珠蛋白的表达分析。

方法：1.构建含红系特异性启动子 GYP A 与 BCL11A 三代慢病毒干扰质粒

将筛选的红系特异性启动子 GYP A 与 BCL11A 三代慢病毒质粒构建及优化

2. GYP A-BCL11A shRNA 三代慢病毒质粒转导红白血病 HEL 细胞表达情况

分组：实验组：转染 GYP A-BCL11A sh1RNA 组、GYP A-BCL11A sh2 RNA 组

实验对照组：只转染慢病毒骨架质粒组（NC 组）

空白对照组：未经处理的 HEL 细胞（MOCK 组）

在 RNA 水平、蛋白水平了解 BCL11A 下调情况及 γ 珠蛋白的表达情况。

3. GYP A-BCL11A shRNA 三代慢病毒质粒转导造血干/祖细胞（HSPCs）表达情况，

人脐带血分选单个核细胞后经 CD34+ 磁珠分选筛选 CD34+ 的 HSPCs 进行 CC110 干细胞扩增、转导三代慢病毒干扰质粒及包装质粒，经红系诱导分化培养、流式细胞分选，在 RNA 水平、蛋白水平了解 BCL11A 和 γ 珠蛋白的表达情况。

结果：1.构建红系特异性启动子 GYP A 与 BCL11A 干扰三代慢病毒质粒，与包装质粒 pLP1、pLP2、p-VSVG 包装后筛选出最优转导比例；

2.GYP A-BCL11A RNA 干扰三代慢病毒质粒转导 HEL 细胞和人 HSPCs 中，在蛋白水平和 mRNA 水平均提示实验组（GYP A-BCL11A sh1RNA 组、GYP A-BCL11A sh2 RNA 组）较对照组（Mock 组、NC 组）BCL11A 表达下调和 γ 珠蛋白表达增加。

结论：红系特异性启动子 GYP A 和 BCL11A RNA 干扰序列的三代慢病毒质粒在体外（HEL 细胞和人 HSPCs）转导后均提示 BCL11A 下调、 γ 珠蛋白的表达量升高。

【关键字】 BCL11A， γ 珠蛋白，造血干/祖细胞， β 地中海贫血

Nuclear pore interactome reveals domain mediated mRNA export fate by FXR1 in human embryonic stem cells

杨嘉宾、陈仲扬、赫佳音、马艳妮、余佳

中国医学科学院基础医学研究所

【摘要】 mRNA export is a crucial step for gene expression, facilitated by the interaction between mRNA transporters and the nuclear pore complex (NPC). However, only a few mRNA transport factors associated with NPC were identified. Here, we comprehensively depicted the composition of nuclear pore interactome in human embryonic stem cells (hESCs), from which we identified a series of novel RNA-binding proteins participated in mRNA export. Among them, FXR1 functioned as a cytoplasmic mRNA transport acceptor through interacting with cytoplasmic fibers of nuclear pore, promoted the release of G-quadruplex containing mRNA from nuclear pore, simultaneously mediated the localization of nucleoporins mRNA on nuclear pore, further facilitating their local translation. The two distinct functions of FXR1 in mRNA export depended on the different RNA-protein interaction module and binding kinetics of the two RNA-binding domains of FXR1. More importantly, the decline of FXR1 and nuclear pore activity helped hESCs to achieve fate transition by impeding the nuclear export of transcribed RNAs, which was required for hESC differentiation.

【关键字】 Keywords: nuclear pore complex (NPC), mRNA export, FXR1, hESC differentiation

高度可重复性类器官平台的建立及其应用

张晓姗、刘雅文、汪阳明

北京大学

【摘要】类器官作为一种由干细胞分化而来的三维复杂模型，因其具有与体内器官相似的结构与功能，而被广泛应用于疾病建模、药物测试和人类发育研究等方面。然而，当前类器官技术仍存在许多限制其发展的问題：1) 培养成本高；2) 操作步骤繁琐；3) 样品间均一性和批次间可重复性低。这些问題阻碍了类器官的标准化培养，难以实现自动化和高通量研究。因此，本研究通过对目前的类器官培养方法进行改进，开发了一个相对标准化的人类胚胎干细胞来源类器官构建流程。其中最关键的发现是第一步仅添加低浓度 Pluronic F-127 (PF-127) 即可使细胞聚集成尺寸高度均一的球体 (0.0125%，甚至低至 0.0005%，而处理微流控器件的浓度则高达 1-4%)。24 小时成球后，在培养基中添加促进干细胞向相应组织类型分化的小分子和蛋白，即可在体外较为简易地构建高均一性、高可重复性、高存活率的多种类器官模型，且具有培养体系小、培养成本低和人为干预少等优点。进一步证明该平台可以应用于抗生素毒性测试。该研究为类器官培养提供了一个新的普适性平台，为高通量筛选、疾病建模及人类器官发育研究提供了新的技术平台。

【关键字】类器官，人类胚胎干细胞，药物筛选

基于 MH 序列多态性的新型细胞交叉污染检测方法的建立

伍义行、张彤彤、朱羽婕、周彦铸、庄安琪、陈艳、陈善梅

中国计量大学

【摘要】目的：细胞交叉污染是指细胞在分离、培养和使用过程中，混入了来源于种属内或种属外的非目标细胞而造成的污染。若交叉污染的细胞系被用于研究或生产，则会导致研究结论错误、细胞治疗面临安全隐患等严重后果。目前尚无单一方法可确保细胞交叉污染检测无误，因此建立一套特异、灵敏的细胞交叉污染检测体系具有重要意义。方法：微单倍型（MH）作为在一定 DNA 片段范围内由两个或多个紧密连锁的单核苷酸多态性位点组合而成的多等位基因分子标记，具有高度多态性和极低的突变频率，在个体识别与混合 DNA 分析中具有独特优势。本研究基于 MH 原理建立细胞系交叉污染检测方法，经模拟交叉污染检测和 STR 分型验证，并联合染色体核型分析与同工酶谱分析进行了适用性验证。结果：由筛选的 131 个位点组成的 MH 检测体系具有灵敏、特异、稳定等优点，目前能检测到 1% 的细胞交叉污染，其检测结果与 STR 方法一致，且灵敏度高于 STR 方法。当出现 10% 以下的污染情况时，STR 方法便无法区分 stutter 峰与细胞交叉污染；而 MH 法检测无 stutter 伪峰，且至少可检测到 1% 的交叉污染（经完善后预期可检测 1% 以下的交叉污染）。适用性验证结果表明：该方法能用于细胞遗传稳定性与不同种属来源细胞系交叉污染的检测。结论：本研究首次将 MH 遗传标记用于细胞交叉污染鉴定，成功建立了一种新的细胞交叉污染检测方法，弥补了 STR 鉴定的不足，为细胞系鉴定、细胞治疗产品质量控制以及细胞库对储存细胞系的质量监测提供了新的选择。该研究成果已获中国发明专利授权。

【关键字】细胞交叉污染；微单倍型；短串联重复序列；检测方法

Ang-(1-7)/MasR 与 Ang- II /AT1R 平衡在 hUMSCs 抗人源化 ACE2 小鼠肺纤维化的作用研究

莫楠 1,2, 范振海 1,2, 李博涵 1,2, 王艳阳 1,2, 何志旭 1,2

1. 遵义医科大学附属医院贵州省细胞工程重点实验室
2. 遵义医科大学组织损伤修复与再生医学省部共建协同创新中心

【摘要】目的：观察人脐带间充质干细胞（hUMSCs）对博来霉素（BLM）诱导肺纤维化（PF）模型小鼠的疗效并探讨其机制。

方法：小鼠随机分组：空白组（Control）、抗人源化 ACE2 空白组（ACE2）、模型组（BLM）、ACE2 模型组（ACE2/BLM）、治疗组（UC）和 ACE2 治疗组（ACE2/BLM+UC）、建立改良法小鼠 PF 模型，建模后第 8 天尾静脉注射 5×10^6 cells/mL hUMSCs 0.2 mL；第 21 天处死小鼠，计算肺脏指数；HE、Masson 染色及透射电镜观察组织病理学及超微结构改变；免疫组织化学、Western Blot 及 ELISA 法检测肺组织中蛋白表达水平；流式细胞术检测炎症细胞因子表达水平。体外建立 A549 细胞与 hUMSCs 共培养体系，CCK8 和流式细胞术观察细胞增殖凋亡情况。

结果：BLM 及 ACE2/BLM 组小鼠肺组织结构破坏明显，可见胶原纤维沉积，肺指数、Ashcroft 评分、HYP 含量均明显升高（ $P < 0.001$ ），经 hUMSCs 治疗后上述指标均显著下降（ $P < 0.001$ ）；超微结构发现 BLM 和 ACE2/BLM 组局部可见胶原纤维沉积，巨噬细胞浸润，基底膜增厚，肺泡 II 型上皮细胞减少，而 UC、ACE2/BLM+UC 组较 BLM 组明显好转。与 Control 组相比，BLM 及 ACE2/BLM 组肺组织中 Collagen- I、 α -SMA、Vimentin 表达量明显升高，E-cad 降低，而 UC、ACE2/BLM+UC 组 α -SMA、Vimentin 表达量较 BLM 组明显下降（ $P < 0.05$ ），E-cad 上升（ $P < 0.01$ ）；BLM 及 ACE2/BLM 组小鼠肺组织中 ACE2、Ang-(1-7)、MasR 表达较 Control 组下降，而 UC 和 ACE2/BLM 组较 BLM 组表达明显升高；与 Control 组相比，BLM 和 ACE2/BLM 组小鼠肺组织中 TGF- β 、TNF- α 、IL-4、IL-6 表达量明显升高（ $P < 0.01$ ），而 UC 和 ACE2/BLM+UC 组较 BLM 和 ACE2/BLM 组明显下降（ $P < 0.01$ ）。

结论：hUMSCs 可减轻小鼠 PF，其机制可能是通过降低肺组织中促炎促纤维化因子的表达，EMT 形成以及 Ang-(1-7)/MasR 与 Ang- II /AT1R 平衡有关。

【关键字】肺纤维化;人脐带间充质干细胞

Development of a humanized mouse model with functional human maternal–fetal interface immunity

董帅、付聪、舒畅、谢敏、李艳、邹俊、孟一姊、徐鹏、单延红、田慧敏、何津、杨永广、胡正

吉林大学第一医院

【摘要】 Maternal–fetal immunity possesses specialized characteristics to ensure pathogen clearance while maintaining tolerance to the semi-allogeneic fetus. Most of our understanding on human maternal–fetal immunity is based on conventional rodent models that may not precisely represent human immunological processes owing to the huge evolutionary divergence. Herein, we developed a pregnant HIS mouse model through busulfan preconditioning, which hosts multilineage human immune subset reconstitution at the maternal–fetal interface. Human maternal–fetal immunity exhibits a tolerogenic feature at the mid gestation stage (embryo day [E] 14.5) and human immune regulatory subsets were detected in the decidua, including regulatory T (Treg) cells, M2 macrophages, and cytokine producing natural killer (NK) cells. However, the immune system switches to an inflammatory profile at the late gestation stage (E19) when M2 macrophages disappear and the immunosuppressive potency of Treg cells is lost. Cell–cell interaction network contributing to the alternations in human maternal–fetal immune atmosphere was revealed based on scRNA-Seq analysis, wherein human macrophages play crucial roles by secreting several immune regulatory mediators. Furthermore, depletion of Treg cells at E2.5 and E5.5 resulted in severe inflammation and fetus rejection. Collectively, these results demonstrate that the pregnant HIS mouse model permits the development of functional human maternal–fetal immunity and offers a unique tool for human maternal–fetal immunity investigation to facilitate drug discovery for reproductive disorders.

【关键字】 Humanized mice, maternal–fetal interface, human immune system, regulatory T cell

间充质干细胞来源 IGF2 分泌缺失诱导肝脏枯否细胞 M1 型极化

周彩平、桂薇薇、林细华

浙江大学医学院附属邵逸夫医院

【摘要】目的：胰岛素样生长因子 2 (IGF2) 分泌缺失与肝脏枯否细胞代谢重编程过程密切相关，并参与代谢相关脂肪性肝病 (MAFLD) 的发生和进展。本研究通过间充质干细胞 Igf2 特异性敲除小鼠探讨 IGF2 缺失在肝脏枯否细胞极化中的作用和相关分子机制，为生长激素补充预防、缓解以及治疗 MAFLD 提供理论依据和新的理念。

方法：从 NCBI 基因表达数据库 (GEO) 中下载人源和鼠源 MAFLD 患者及其正常对照肝脏转录组测序数据集，利用生物信息学分析差异表达基因，并分析血清 IGF2 表达量与肝功能指标的相关性。利用 Tabula Muris 小鼠单细胞开源数据库 (<https://tabula-muris.ds.czbiohub.org/>) 和 Human Protein Atlas 人类蛋白质图谱数据库 (<https://www.proteinatlas.org/>) 挖掘 IGF2/Igf2 及 IGF2R/Igf2r 的组织表达分布情况。采用特异性重组酶 Cre/LoxP 系统和间充质干细胞特异性 Prx1-Cre 工具鼠构建间充质干细胞特异性 Igf2 敲除小鼠模型 (Prx1-Cre+Igf2^{flox/flox})，葡萄糖耐量实验、胰岛素耐量实验检测两组小鼠糖代谢，肝脏灌流提取出枯否细胞并进行流式细胞检测两组小鼠中 M1、M2 指标。

结果：MAFLD 患者相比正常对照血清中 IGF2 表达量显著降低。Human Protein Atlas 人类蛋白质图谱数据库和 Tabula Muris 小鼠单细胞开源数据库发现 IGF2/Igf2 在间充质干细胞细胞中表达丰富，而 IGF2R/Igf2r 则高表达在肝脏组织，尤其是枯否细胞中。我们成功构建并鉴定了间充质干细胞特异性 Igf2 敲除小鼠模型 (Prx1-Cre+Igf2^{flox/flox})，且 Igf2 敲除组小鼠糖耐量、胰岛素耐量受损。流式细胞分析显示 Igf2 敲除组小鼠 M1 型巨噬细胞比例增高。

结论：MAFLD 患者体内 IGF2 表达显著降低。公共数据库分析显示 IGF2/Igf2 在间充质干细胞细胞中表达丰富，而 IGF2R/Igf2r 则高表达在肝脏组织，尤其是枯否细胞中。间充质干细胞特异性 Igf2 敲除小鼠通过促进肝脏枯否细胞 M1 极化诱发脂肪肝相关特性。

【关键字】 IGF2；间充质干细胞；MAFLD；肝脏枯否细胞；巨噬细胞极化

Multi-Gene Engineered iPSC-Derived CAR-NK cells Display Robust Anti-Tumor Effects in Acute Myeloid Leukemia

王艺芸¹, 王林钦¹, 邵谧¹, 何向军², 岳亚男², 周怡璇², 王东睿¹,
胡永仙¹, 杨璐菡², 黄河¹

1. 浙江大学医学院附属第一医院
2. 杭州启函生物科技有限公司

【摘要】 The demand for novel therapies targeting acute myeloid leukemia (AML) remains pressing. Cellular immunotherapy, such as CAR-T cell therapy, has exhibited promising initial clinical outcomes in AML patients. However, the manufacture of autologous cellular products has proven intricate, and clinical responses are hindered by the intrinsic heterogeneity of AML blasts. In this study, our objective was to genetically engineer iPSC-derived NK cells for use as readily available therapy, addressing the challenges in AML treatment. We engineered QN-023a iPSCs with five key genetic modifications: an IL-15 receptor and IL-15 fusion (IL-15 RF) molecule to augment their long-term functionality, a CD33-targeted CAR to identify and eliminate AML cells, a CD33 knockout to prevent fratricide among CD33 CAR-iNK cells, a high-affinity, non-cleavable CD16 to enhance ADCC, and a CD38 knockout to prevent fratricide when combined with the anti-CD38 monoclonal antibody (daratumumab). The engineered QN-023a cells were effectively differentiated into NK cells on a large scale and demonstrated robust efficacy in eliminating heterogeneous AML cells through synergistic recognition of NK intrinsic receptors activation, CD33 and CD38. Our study showcases a novel approach for addressing the challenges posed by heterogeneous malignancies using NK cells, highlighting their potential as an off-the-shelf medical solution.

【关键字】 Acute myeloid leukemia (AML), Induced pluripotent stem cells (iPSC), iPSC-derived natural killer cell (iNK), Chimeric antigen receptor (CAR).

PDCD4 缺失的间充质干细胞促进皮肤损伤修复的作用及机制研究

刘丽媛、姜杨、郑成云

山东大学第二医院

【摘要】背景：皮肤损伤是组织缺损性疾病较为常见的症状，面临着难以愈合、组织来源缺乏、手术难度大、免疫排斥等难题。间充质干细胞（mesenchymal stem cells, MSCs）作为种子细胞在促进皮肤损伤修复方面的研究越来越受到人们的重视。程序性细胞死亡 4（programmed cell death 4, PDCD4）是经典的抑癌基因，在多种肿瘤中发挥一定的抑癌作用。近年来，发现 PDCD4 还参与免疫反应的调控，参与自身免疫性或炎症反应性疾病。

方法：慢病毒感染构建 PDCD4 敲减的 MSC 细胞系（shPDCD4-MSCs），Transwell 实验检测 MSCs 上清对成纤维细胞迁移的影响。构建小鼠皮损模型（1cm×1cm），随机分为三组（阴性对照组、MSCs-水凝胶组、shPDCD4-MSCs-水凝胶组），定期更换敷料且计算皮损面积。并于不同的时间点处死小鼠，取皮损边缘处组织进行 Masson、CD31、Col-I、Col-III 等免疫组化染色。

结果：体外细胞实验发现 shPDCD4-MSCs 可明显促进成纤维细胞的迁移。将 MSCs 与 VitroGel 水凝胶混合（MSCs-水凝胶复合物）作用于小鼠的皮损处，发现 MSCs 能够促进小鼠皮肤愈合，且 shPDCD4-MSCs 组对小鼠皮肤的愈合促进作用更加明显。免疫组化发现，与对照组相比 shPDCD4-MSCs 组中 Masson、CD31、Col-I、Col-III 明显升高。

结论：我们新的发现将 shPDCD4-MSCs 与水凝胶结合，促进了皮肤创面的愈合，有望成为治疗皮损的新策略。

【关键字】 PDCD4，间充质干细胞，皮肤损伤修复

过表达白介素 1 受体拮抗剂的间充质干细胞治疗出血性膀胱炎的疗效及机制研究

宋佳霖、姜杨、郑成云

山东大学第二医院

【摘要】背景：出血性膀胱炎是异基因造血干细胞移植术后常见的并发症之一，一般认为早发性膀胱炎与预处理方案中使用的毒性药物环磷酰胺等有关，目前对其治疗手段没有明确的共识，临床常用药物美司钠虽可预防其发生，但效果甚微，疾病影响患者生活质量，严重时可导致患者死亡。

方法：构建稳定过表达白介素 1 受体拮抗剂（IL-1RA）的间充质干细胞（MSCs），流式检测其表面标记的表达；EDU 增殖实验、划痕实验等检测细胞增殖、迁移能力；mRNA 测序比较过表达后靶基因的改变。腹腔注射环磷酰胺制备大鼠出血性膀胱炎模型，使用 IL-1RA-MSCs 治疗，观察疗效并检测治疗后膀胱组织的改变。

结果：细胞模型制备成功，流式分析证实过表达 IL-1RA 不改变 MSCs 表面分子标志的表达，IL-1RA-MSCs 能明显促进血管内皮细胞的增殖及迁移；动物实验发现大鼠血尿明显减轻，组织病理学发现 IL-1RA-MSCs 治疗组大鼠膀胱组织出血、水肿明显减轻、炎性细胞浸润明显减少；mRNA 测序发现 IL-1RA-MSCs 血管生成相关通路明显活化。另外，IL-1RA-MSCs 培养上清中提取的外泌体在体外实验中也发现与细胞有相似的优势。

结论：IL-1RA-MSCs 能够明显减轻炎症促进血管形成，可能为临床工作中治疗出血性膀胱炎提供有效的治疗方法。

【关键字】出血性膀胱炎、白介素 1 受体拮抗剂、间充质干细胞

The ATF4-RPS19BP1 axis modulates ribosome biogenesis to promote erythropoiesis

Zheng Zhaofeng 1 , Yang Shangda 1 , Gou Fanglin 1 , Tang Chao 1 , Zhang Zhaoru 2 , Jiang Penglei 2 , Qian Pengxu 2 , Zhu Ping 1 , Cheng Hui 1 , Cheng Tao 1 , 郑昭烽

1. State Key Laboratory of Experimental Hematology, National Clinical Research Center for Blood Diseases, Haihe Laboratory of Cell Ecosystem, Institute of Hematology & Blood Diseases Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College

2. Center for Stem Cell and Regenerative Medicine and Bone Marrow Transplantation Center of the First Affiliated Hospital, Zhejiang University School of Medicine; Liangzhu Laboratory, Zhejiang University Medical Center; Institute of Hematology, Zhejiang University

【摘要】 Hematopoietic differentiation is controlled by intrinsic regulators and the extrinsic hematopoietic niche. ATF4 plays a crucial role in the function of fetal and adult hematopoietic stem cell maintenance; however, the precise function of ATF4 in the bone marrow niche and how ATF4 regulates adult hematopoiesis remain largely unknown. Here, we employ four cell-type-specific mouse Cre lines to conditionally knock out Atf4 in Cdh5⁺ endothelial cells, Prx1⁺ bone marrow stromal cells, Osx⁺ osteo-progenitor cells, and Mx1⁺ hematopoietic cells, and uncover the role of Atf4 in niche cells and hematopoiesis. Intriguingly, depletion of Atf4 in niche cells does not affect hematopoiesis; however, Atf4-deficient hematopoietic cells exhibit erythroid differentiation defects, which lead to hypoplastic anemia. Mechanistically, ATF4 directly regulates the transcription of Rps19bp1 which is in turn involved in 40S ribosomal subunit assembly to coordinate ribosome biogenesis and promote erythropoiesis. Finally, we demonstrate that under conditions of 5-fluorouracil-induced stress, Atf4 depletion impedes the recovery of hematopoietic lineages, which requires efficient ribosome biogenesis. Taken together, our findings highlight the indispensable role of the ATF4-RPS19BP1 axis in the regulation of erythropoiesis.

【关键字】 ATF4; hematopoietic stem cell; niche; erythropoiesis

A programmed intracellular fabrication of high-functioning mitochondria supplies energy for osteoarthritis therapy

陈旭日¹, 欧阳宏伟^{1,2}

1. Dr. Li Dak Sum & Yip Yio Chin Center for Stem Cells and Regenerative Medicine, and Department of Orthopedic Surgery of the Second Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou 310058, China.
2. Liangzhu Laboratory, Zhejiang University, Hangzhou 310058, China.

【摘要】 Osteoarthritis (OA) is a common degenerative joint disease characterized by the breakdown of joint cartilage. Mitochondrial dysfunction of the chondrocyte is a risk factor for OA progression. Mitotherapy enhances ATP synthesis, oxygen consumption, and cell viability, thereby improving systemic function. However, the acquisition of active mitochondria remains a major challenge for tissue regeneration. Mesenchymal stem cells (MSCs) were a rich source of mitochondria. mc-MSCs were efficient for mitochondria expansion under a customized medium. Mitochondria could be easily prepared because of the exhibited strong proliferative and self-renewal abilities of mc-MSCs. mc-MSCs exhibited higher mitochondrial bioenergetics and its mitochondria showed higher activities. Transcriptome revealed that enhanced cell proliferation and mitochondrial biogenesis of mc-MSCs were through the upregulated AMPK pathway. At last, mc-Mito corrected energy imbalance and restored cellular metabolism to improve cartilage homeostasis and protect against the pathological progression of OA. We constructed a robust and efficient intracellular mitochondrial expansion system in need of tissue engineering and regenerative medicine. This engineering strategy was universal and could be applied to a variety of mitochondrial disorders. In this study, we showed the great potential of mitochondrial therapy in the treatment of OA.

【关键字】 Mesenchymal Stem Cell; Mitochondria; Osteoarthritis.

Converging bioprinting and organoid towards advanced tumor microenvironment (Review)

王晓宇、罗依雪、马源锴、王鹏逾、姚睿

清华大学

【摘要】 3D bioprinting has demonstrated promising potential for preclinical tumor modeling with significant advantages over 2D cell cultures in replicating tumor microenvironment (TME). Recently, the utilization of tumor organoids instead of monodispersed tumor cells in 3D printing tumor models is emerging as a groundbreaking approach to simulate the volumetric tumor tissues, which combines the advantages of assembling heterogeneous TME components and maintaining aggregated cell behaviors. Herein, we discuss how combining 3D bioprinting and tumor organoids provides multiple guidance to recapitulate TME hallmarks and highlight their future incorporation with organ-on-a-chip technology towards integrative organotypic tumor models, aiming to improve the biomimicry and predictability of therapeutic performance. Finally, we look ahead to the remaining challenges for achieving personalized medicine and predictive clinical integration.

Introduction: reconstructing tumor microenvironment for faithful in vitro tumor modeling

Cancer is a major global health challenge, accounting for approximately one in six deaths worldwide in 2020. Cures are still inadequate for most types of cancers despite substantial efforts and progress made in pathological mechanism exploration and anti-cancer therapy development. There is an urgent need for high-fidelity and reproducible preclinical tumor models to facilitate the development of efficient and patient-specific therapy. Even though still in its infancy, incorporating tumor organoids in 3D printing tumor models opens new avenues for a more accurate TME recapitulation. By further integrating organ-on-a-chip technique, fluidic dynamics and immune components can be introduced, thereby enhancing TME recapitulation and improving the drug test accuracy

3D bioprinting hierarchical tumor models using tumor organoids as building blocks

Tumor organoids are among the most widely used in vitro tumor models since the self-organized 3D assembly of neoplastic cells can accurately reproduce the crucial solid tumor hallmarks, including the tumor-like 3D cell-cell physical contacts, heterogeneous cell populations, (epi-)genetic landscape and growth kinetics. Utilizing tumor organoids as basic building blocks for 3D bioprinting would provide new possibilities by introducing the miniaturized aggregates into a heterogeneous 3D niche with supporting hydrogels and stromal cells. This converging strategy allows the self-organization of tumor-sized anatomy with hierarchical function modules, enabling a better simulation of the intrinsic TME characteristics of in vivo tumor tissues. Several spheroid bioprinting strategies have been developed to enable the precise deposition of cell spheroids, including material-free approaches (kenzan method and fluidic-based singularization) and hydrogel-based bioprinting methods (extrusion-based spheroid bioprinting and drop-on-demand bioprinting).

Integrating organ-on-a-chip technology towards a level-up TME simulation and more accurate therapy response

While recent progress has been made in depositing heterogeneous TME components through the organoid-based 3D bioprinting strategy, there is still a long way to go to mimic the intrinsic tumor progression process and the in vivo pharmacokinetics and pharmacodynamics. These physiological processes highly depend on the tumor-immune interaction and crosstalk between different functional organs, which are always simplified in tumor models under static culturing due to the lack of a functional hierarchical circulation system. Organ-on-a-chip technology is being explored as an advancement in creating more realistic tumor models by replicating the natural vascular perfusion and microcirculation system. Recent progress has been made in developing and applying 3D printing tumor-on-chip models.

Concluding remarks

Our timely review highlighted the significant progress made in the synergetic fabrication of in vitro tumor models, which may eventually outperform animal models and pave the way for more rapid and cost-effective drug development, precision medicine, and pathological investigation. Though still in its infancy, this field holds tremendous potential for addressing the challenges faced in deriving patient-specific tumor models and regulating post-printing processes. Interdisciplinary efforts from clinicians, biologists, and engineers are also required to standardize the bioengineering process of tumor models and fully realize the application from the bench to the bedside.

【关键字】 tumor organoid, 3D bioprinting, organ-on-a-chip, in vitro tumor models

成纤维细胞对人毛囊干细胞来源毛囊类器官结构的影响及其作用机制

连尉伶、曾炫皓、臧青、张琦、林尽染、吴文育、徐金华

复旦大学附属华山医院

【关键字】 目的：雄激素性脱发（androgenetic alopecia, AGA）是临床最常见的病理性脱发，患者治疗意愿强烈，但疗效有限。毛囊类器官的构建有助于进一步开展 AGA 相关的新药研发、基因疗法和组织工程技术，然而目前这项技术仍面临培养周期长、个体异质性反馈差的困境。因此本研究基于 AGA 患者枕部毛囊中毛囊干细胞（Hair follicle stem cells, HFSC）和成纤维细胞（Hair follicle fibroblasts, HFFB）的分离、培养、鉴定，探究成纤维细胞对人毛囊干细胞来源毛囊类器官结构的影响及其作用机制。

方法：首先，本研究通过空间转录组技术探究 HFSC 和 HFFB 的空间位置信息，为构建毛囊类器官的“种子细胞”提供数据支持。其次，我们从人枕部毛囊中原代提取并培养了 HFSC 和 HFFB，并进行基因水平和蛋白水平的鉴定；之后，在特定培养条件下成功诱导毛囊类器官，并通过对毛囊标志物进行形态学鉴定，对比不同培养方式下毛囊类器官的差异；最后，基于转录组测序，我们对相关富集通路进行研究，以探讨 HFFB 影响毛囊类器官形成的作用机制。

结果：通过空间转录组测序技术定义了皮肤组织中 HFSC 和 HFFB 基因表达的空间分布图谱，空间差异表达分析表明 HFFB 较毛囊间成纤维细胞更能促进上皮谱系分化和组织再生。同时，人枕部毛囊来源的 HFSC 和 HFFB 状态良好，可进行稳定培养、传代，相应细胞标志物表达阳性且表征稳定，并成功利用人 HFSC 作为“种子细胞”诱导毛囊类器官，且扩增倍数较大，1 个毛囊单位约可诱导出 300 个毛囊类器官。另一方面，HFFB 可提高毛囊类器官的诱导率和存活率，有助于人毛囊干细胞来源的毛囊类器官的结构成熟。进一步的机制探讨发现，HFFB 能显著促进多种表皮生长因子的生成，并通过上调 IGF-1R、Wnt/ β -catenin、MAPK/p38 通路参与 HFSC 向毛囊类器官的诱导。

结论：本研究成功利用人 HFSC 和 HFFB 作为“种子细胞”，共同分化诱导出表征稳定、结构成熟毛囊类器官。同时，该研究证实了 HFFB 影响 HFSC 向类器官分化成熟的有利作用，并进一步揭示潜在的相关通路。综上所述，本研究的发现可为毛发再生医学研究、毛发生长发育研究和脱发药物新药筛选提供一定的理论依据。

【关键字】 毛囊干细胞，成纤维细胞，毛囊类器官，Wnt 信号通路，IGF-1R 信号通路，MAPK 信号通路

Development of a pig bioreactor supporting robust human hematopoiesis for large-scale production of functional human immune cells

胡正 1, 邹俊 1, 汪正铸 1, 许凯 2, 海棠 2, 李子义 1, 李伟 2, 周琪 2, 杨永广 1

1. 吉林大学
2. 中国科学院动物所

【摘要】 There is an urgent need for large animal models to study human hematopoiesis and regenerate functional human immune cells in vivo. Herein, we generated gene-edited immunodeficient pigs that lack T, B and NK cells (RG pig) and have attenuated macrophage xenoreactivity (RGD pig) and tested their potential to support human hematopoietic engraftment and differentiation. In RG pigs, human CD34⁺ cell transplantation achieved human hematopoietic engraftment in bone marrow, but poor chimerism in blood and spleen. However, human CD34⁺ cell-transplanted RGD pigs showed high levels of human hematopoietic chimerism composed of T, B, NK, and myeloid cells. These RGD pigs had robust human hematopoiesis in bone marrow and ongoing thymopoiesis in thymus. Furthermore, human T and B cells developing in RGD pigs were functional and expressed broad receptor repertoires. Thus, the RGD pig offers a useful preclinical model for investigating human normal or diseased hematopoiesis and therapies, and a powerful bioreactor for large-scale production of human immune cells.

【关键字】 Bioreactor; Immunodeficient pig; Hematopoietic stem cell; Human immune reconstitution; Immunotherapy

利用诱导多能干细胞构建 bardet-biedl 综合征肾脏模型探索 BBS7 复合杂合突变影响肾脏发育的机制研究

肖蓉¹, 闵婕²

1. 中国医学科学院基础医学研究所
2. 首都医科大学附属儿童医院

【摘要】背景: Bardet-Biedl 综合征 (BBS) 是一种具有肾脏发育异常等临床表现的罕见病, 肾功能衰竭是 BBS 患者首位致死原因。目前已知 BBS 致病基因有 26 个, BBS7 突变在我国高发, 并与肾脏异常高度相关。BBSome 功能缺陷与 BBS 疾病密切相关, 其中 BBS7 是 BBSome 关键核心组分之一, 解析 BBS7 在 BBS 这一类肾纤毛病中的致病机制, 利用腺病毒载体递送碱基编辑器对突变位点进行修复, 具有重要临床意义。方法: 本研究拟通过 BBS 患者 (BBSmut/mut) 及健康对照的外周血单核细胞重编程为诱导多能干细胞, 并通过基因编辑技术对患者的突变位点进行修复。首先通过建立体外长期培养肾脏祖细胞 (NPC) 的培养体系, 随后分别进行 2D 分化形成 TEC 和 3D 分化形成肾脏类器官。蛋白质组学等检测 BBSmut/mut 与对照细胞之间的 BBSome 核心蛋白复合物组分的蛋白表达水平及蛋白间相互作用水平, 研究 BBSome 组装及其功能是否存在差异。随后利用腺病毒载体递送碱基编辑器对突变位点进行修复, 检测疾病表型是否回复。结果: BBSmut/mut 存在 NPC 分化及 TEC 和肾脏类器官形成的缺陷; BBS2-7-9 复合物的表达在诱导多能干细胞中与对照相似, 在分化细胞中显著下调甚至不表达, BBSome 小体组装存在缺陷, 并且泛素化水平明显上升。结论: BBS7 突变在分化后蛋白表达异常, 进一步影响 BBSome 组装和功能发挥, 是导致 BBS 肾脏异常的重要原因之一。

【关键字】 BBS7, BBSome, 肾脏类器官, 点突变修复

Modeling human anti-pig xenoimmune responses in a pig artery tissue grafted humanized mouse model

方铭慧，邹俊，徐飞，王雪，杨永广，胡正

吉林大学第一医院

【摘要】 Abstract Content:

Background: Blood vessels that contain endothelial cells (ECs) on the surface are in direct contact with host blood and are the first target of xenograft rejection. Currently, our understanding of human anti-pig vessel immune responses is primarily based on in vitro assays using pig ECs. Therefore, it is necessary to develop an animal model that permits in vivo study of human immunological rejection of pig vessels.

Methods: Pig artery tissues (PAT) were transplanted into human immune system (HIS) mice or immunodeficient NSG mice (as controls). Intra-graft human immune cell infiltration and antibody deposition were quantified using histology and immunohistochemistry. Donor antigen-specific immune responses were quantified using a mixed lymphocyte reaction and a complement-dependent killing assay.

Results: Pig CD31⁺ ECs were detected and increased 2-fold from weeks 3 to 5 in PAT xenografts from immunodeficient NSG mice. However, compared with NSG mice, PAT xenografts in HIS mice had significantly lower numbers of porcine CD31⁺ ECs and showed a marked reduction from week 3 to week 5. PAT xenograft rejection in HIS mice is associated with intensive infiltration of human immune cells, deposition of human IgM and IgG antibodies, and the formation of a tertiary lymphoid structure. Robust donor pig antigen-specific human T cells and antibody responses were detected in PAT-transplanted HIS mice.

Conclusion: We have developed a humanized mouse model to evaluate human anti-pig xenoimmune responses by PAT transplantation in vivo. This model is expected to facilitate the refinement of pig gene-editing strategies (the expression on EC surface) and the testing of local immunosuppressive strategies for clinical pig organ xenotransplantation.

【关键字】 Key Words: endothelial cells, xenotransplantation, humanized mice, rejection, artery

CD19 CAR-T 细胞治疗 R/R NHL 后中枢神经系统复发

赵梦雨，杨婷婷，董叶恬，周凌辉，孔德麟，黄河，胡永仙

浙江大学医学院附属第一医院骨髓移植中心

【摘要】CD19 靶向嵌合抗原受体 T (CAR-T) 细胞疗法对复发/难治性(R/R)非霍奇金淋巴瘤(NHL)显示出显著的抗肿瘤疗效。然而，中枢神经系统(CNS)复发的 NHL 病人预后较差，死亡率高。我们报道了一项对 80 例接受 CAR-T 细胞治疗的 NHL 患者的研究，描述了中枢神经系统复发的特征和预后。本研究中 8 例(10%)患者在 CAR-T 细胞治疗后出现孤立性中枢神经系统复发，1 例患者中枢神经系统合并系统性复发。中枢神经系统复发患者的 1 年 OS 和 1 年 PFS 显著低于未复发组(OS, 31.7% [95%CI 10.5-96.4] vs 90.7% [95%CI 81.2-100], $P < 0.001$; PFS, 11.11% [95%CI 1.75-70.51] vs 90.7% [93.94%CI 81.2-100], $P < 0.001$), 但与仅全身复发组相比无差异(OS: 48.12% [95%CI 33.94-68.23], $P=0.4$; PFS: 13.89% [95%CI 6.16-31.33], $p = 0.99$)。总体来看，本研究中 CNS 复发患者 1 年的预后显著差于未复发组的患者，提示了预防 CNS 复发的重要性。(本研究相关临床试验包括：ChiCTR1800015575; NCT03118180; NCT04532281; NCT04532268; NCT04213469)。

【关键字】 CAR-T; 非霍奇金淋巴瘤; 中枢神经系统复发; 预后特征

Spatial transcriptome analysis explores human fetal vaginal epithelial stem cell

赵光锋、叶紫英、胡娅莉

南京大学医学院附属鼓楼医院

【摘要】 Objective To observe and analyze the localization of different molecular markers for the vagina in fetuses of various gestational ages and to explore the latent vaginal epithelial precursor cells.

Methods In order to establish comprehensive spatial gene expression patterns in vagina, especially for its epithelia, we collected two distinct sections of the vagina from two typically developing human fetuses that were ethically aborted at the Obstetrics Department of Nanjing Drum Tower Hospital at 23 post-conceptual weeks (PCW). These specimens were carefully obtained with full adherence to ethical guidelines and necessary approvals. Both sections collected for this study were specifically cross-sections of the fetal vagina near the vaginal orifice at 23 post-conceptual weeks (PCW). The sequencing results were verified and analyzed by multiple complementary approaches, including cross-referencing with existing literature, immunohistochemistry, and immunofluorescence techniques.

Results To establish a comprehensive profile of cell populations in the vagina, we conducted an initial UMAP clustering analysis on cell-covered spots derived from the two tissue sections. This identified nine distinct clusters, including five regions consisting of epithelial cells, one region representing the vaginal mucosa lamina propria, and three regions corresponding to vaginal muscle cells.

The epithelial cell regions were categorized into distinct subregions, including the basal cell layer, suprabasal cell layer, intermediate cell layer, superficial epithelial region, and desquamation region. During the analysis of epithelial cells, we observed a significant degree of heterogeneity within the vaginal epithelial cell population. We also identified several regional-epithelial-characteristic markers for different subregions of vaginal epithelia. Through our analysis, we discovered that different subregions of the vaginal epithelial cells exhibited distinct enrichments for various functions. Each subregion displayed a unique expression profile, with many molecules specifically associated with the function's characteristic of that particular subregion.

We find that both of COL17A1 and SOX2 effectively designate the basal vaginal epithelium and hence may serve as markers for human vaginal epithelial stem cells. We also discovered that AXIN2, a mouse vaginal epithelial stem cell marker, is expressed in a relatively wide range of locations in the human fetal vagina, not limited to the basal epithelial layer, and may not be a suitable marker for human vaginal epithelial stem cells.

Conclusion In this study, we conducted an analysis of the transcriptome expression profile of human vaginal epithelial cells as they undergo differentiation from the basal to superficial layers. Our study highlighting heterogeneity in human vaginal epithelial cells and offering insights into the physiology of the vaginal mucosa. These findings contribute to our understanding of vaginal epithelium and have implications for future research and applications in the field of vaginal reconstruction.

【关键字】 Spatial transcriptomics, vaginal epithelium, vaginal stem cell

表观遗传编辑调控 B2M 超级增强子构建通用型干细胞

徐婧怡、王飞、柳华

浙江大学

【摘要】 同种异体干细胞是当前再生医学应用潜力最大的干细胞源。人类白细胞抗原（HLA）不匹配引起的免疫排斥反应是同种异体干细胞治疗发展的最大阻碍。现有构建低免疫原性通用型细胞的策略主要通过 B2M 基因敲除同时敲入 NK 细胞抑制分子实现，这类策略存在影响基因组稳定性、造成细胞毒性等安全隐患。本研究中，我们发现了一段炎症因子 IFN γ 刺激响应性的 B2M 超级增强子（B2M-SE），在同种异体的环境中对 HLA-I 分子的表达起着关键的调控作用。针对 B2M-SE 的单次表观遗传学编辑，能够使人间充质干细胞（MSCs）表面的 HLA-I 分子水平低于激活同种异体 T 细胞反应的阈值，同时也能够使 MSCs 逃避 NK 细胞的杀伤，我们将这种 MSCs 命名为“Goldilocks-Level Of B2M Expression MSCs（GLOBES）”。体外实验及人免疫系统重建小鼠模型中的体内实验均证明 GLOBES 不引起免疫系统活化、杀伤和记忆，同时能在体内存活更长时间。在人免疫系统重建小鼠的脂多糖（LPS）致急性肺炎模型中，GLOBES 也能发挥优异的治疗作用。因此，表观遗传学编辑 B2M-SE 在构建用于同种异体细胞治疗的通用型供体细胞方面具有巨大潜力。

【关键字】 干细胞，IFN γ ，HLA-I，超级增强子，表观遗传编辑，免疫原性，细胞治疗，同种异体移植

The culture system of porcine embryonic-derived pluripotent stem cells was screened according to the transcriptome characteristics of porcine E7-8 epiblast

余卓然、王红兴、颜廷胜、刘忠华

东北农业大学

【摘要】 Embryonic Stem Cell (ESC) can maintain self-renewal and proliferate indefinitely during culture, while retaining multi-directional differentiation potential. ESCs have two pluripotency states, Naïve states, represented by mouse ESCs (mESCs), and Primed states, represented by human ESCs (hESCs). Naïve pluripotency has comprehensive differentiation capacity and germline chimeric potential, while Primed pluripotency has limited differentiation capacity and chimeric contribution potential. So far, species other than mice and rats have not successfully established Naïve state ESCs with the ability of germline chimerism. Pig is a large animal model whose physiological structure and immune characteristics are very similar to human, the establishment of porcine ESC is of great significance for the establishment of human genetic disease model and human xenotransplantation donor. Since 1990, the research of porcine ESCs has made great progress. However, there is no porcine pluripotent stem cell (pPSC) that can realize germ-line chimerism. In addition, in the study of pESC also face several key problems: the early embryonic development period corresponding to Naïve status is unclear, the pluripotency regulation mechanism is unclear, the pluripotency marker genes are uncertain, and the evaluation criteria are unclear. The pluripotency of ESC is derived from the embryo, but after in vitro culture, the maintenance and regulation network of pluripotency of ESCs has changed. For example, mESC more closely resembles the pre-epiblast (Pre-EPI) than the Inner Cell Mass (ICM). It is of great significance for the identification of pig pluripotent cell lines and the understanding of pluripotent state.

The study showed the greatest similarity between mouse embryonic Pre-EPI cells and Naïve mESC. Therefore, this study first compared the transcriptome data of mouse, human Naïve and Primed ESC and their embryonic cells at each early stage to verify the similarity between Naïve cells and pre-EPI cells. Then, the single-cell transcriptome data of early porcine embryos at different developmental stages were analyzed, and the specific developmental stage in which Pre-EPI appeared in early pig embryos was preliminarily determined by comparison with the transcriptome data analysis results of early mouse and human embryos. On this basis, the signal pathways enriched in porcine Pre-EPI were analyzed, and the expression patterns of key genes of pluripotency related signal pathways in different developmental stages of porcine embryos were compared and analyzed to further clarify the regulatory characteristics of porcine Pre-EPI signal pathways. We further screened porcine embryo-derived pluripotent stem cell culture system. In summary, we draw the following conclusions: (1) Porcine E7-8 EPI corresponds to Naïve Pre-EPI; (2) The expression patterns of porcine E7-8 EPI and mouse E4.5 EPI homologous genes were similar; (3) Both X chromosomes of porcine E7-8 EPI are active; (4) The culture system based on the transcriptome characteristics of porcine E7-8 EPI signaling pathway can significantly improve the pluripotency of porcine embryo-derived pluripotent stem cells.

【关键字】 pig, epiblast, pluripotent stem cell

Low-intensity pulsed ultrasound improves osteogenesis under oxidative stress in periodontal ligament stem cells via Akt-FOXO1

唐丽¹, 杨珂²

1. 重庆医科大学附属第一医院
2. 重庆医科大学附属儿童医院

【摘要】 Background: Periodontitis comprises a series of inflammatory responses resulting in alveolar bone loss. The inhibition of osteogenesis in periodontal ligament stem cells (PDLSCs) due to inflammation is a contributing factor to impaired alveolar bone regeneration. This issue continues to pose a significant challenge in the field of periodontitis therapy. The oxidative stress environment caused by inflammatory responses significantly impacts the osteogenic differentiation capacity of PDLSCs. This study aimed to assess the effects of low-intensity pulsed ultrasound (LIPUS) on PDLSCs subjected to oxidative stress, investigating whether LIPUS could rescue the impaired osteogenic differentiation of these stem cells.

Methods: Oxidative stress induced by H₂O₂ was studied in PDLSCs. The siRNA-FOXO1 was utilized to investigate the significant role of LIPUS on osteogenic effects under oxidative stress conditions. Cell proliferation was assessed using the Cell Counting Kit-8. Intracellular levels of reactive oxygen species (ROS), malondialdehyde (MDA) activity, and the expression levels of 3-NT and 4-HNE were measured to determine the extent of oxidative stress. Alkaline phosphatase (ALP) staining, Alizarin red S staining, and protein expression levels of RUNX2, ALP, and OPN were applied to evaluate the osteogenic potential of PDLSCs. Western blot analysis was performed to detect the protein expression levels of total FOXO1, phospho-FOXO1, total Akt, and phospho-Akt.

Results: The study revealed that exposure to 300 μ M H₂O₂ for 6 hours caused increased oxidative injury and decreased osteogenic differentiation capacity in PDLSCs. However, pretreatment with LIPUS resulted in a reduction of H₂O₂-induced intracellular ROS and MDA production. Additionally, LIPUS pretreatment inhibited the expressions of 3-NT and 4-HNE. Furthermore, LIPUS pretreatment increased the levels of RUNX2, OPN, and ALP proteins, promoting positive ALP staining and Alizarin red S staining. Notably, LIPUS pretreatment decreased the phosphorylation of FOXO1 and Akt, while the total levels of FOXO1 and Akt remained unaffected. Further experimentation involving FOXO1 knockdown demonstrated that reducing the levels of this protein resulted in a decrease in the antioxidant and osteogenesis effects of LIPUS.

Conclusions: These results suggest that LIPUS attenuates oxidative stress by modulating the Akt-FOXO1 signaling pathway, thereby rescuing the osteogenic differentiation capacity of PDLSCs under oxidative stress. Thus, FOXO1 plays a key role in the protective effect of LIPUS on oxidatively injured PDLSCs.

【关键字】 Periodontitis, Periodontal stem cells, Low-intensity pulsed ultrasound, Oxidative damage, Osteogenic differentiation, Forkhead box protein O1

BRD4 通过募集 EHMT1/2 抑制终末红细胞生成

张蒙、陈谊金、黄朦朦、孟夜、张杰、罗黔、霍大伟、郑海琼、徐玉林、钱鹏旭、黄河

浙江大学医学院附属第一医院

【摘要】由诱导多能干细胞 (iPSCs) 生产红细胞是有望缓解临床“血荒”的重要研究方向，但是 iPSCs 来源红细胞脱核效率低，难以满足临床需求。解析红细胞终末分化的分子机制能帮助提高 iPSCs 来源红细胞的成熟度和脱核效率，为人工血液的应用提供理论依据和解决方案。红细胞终末分化涉及复杂精密的表观和转录调控。在这项研究中，我们利用靶向表观和转录调控因子的小分子文库筛选红系终末分化过程中的关键调控因子，发现抑制溴域蛋白 BRD4 可以加速红细胞成熟，从而提高脱核效率。有趣的是，抑制 CDK9 并没有发现类似 BRD4 的表型，进一步的实验证明 BRD4 的长异构体和短异构体均为红细胞分化的强效抑制因子。RNA-seq、ATAC-seq 和 Cut&Tag 联合分析的结果显示 BRD4 抑制染色质浓缩相关基因的表达。通过 CO-IP 及功能研究，我们发现 BRD4 通过与 EHMT1/2 相互作用来抑制靶基因转录。综上所述，我们发现在红细胞终末分化过程中，BRD4 的功能不依赖于经典的 CDK9 通路，而是通过 EHMT1/2 抑制靶基因转录从而负调控红系终末分化。我们的研究为提高红细胞脱核效率提供了新方法，并为治疗红细胞分化障碍导致的相关疾病提供了潜在的治疗靶点。

【关键字】 BRD4;终末红细胞生成;脱核;EHMT1/2

Nrf2 regulates immunosuppressive ability of umbilical cord mesenchymal stromal cells on the therapeutic effect of experimental bronchopulmonary dysplasia

章杰、杨珂

重庆医科大学附属儿童医院

【摘要】 Background Human umbilical cord Mesenchymal stem cells(UC-MSCs) -based therapy has emerged as a promising approach for the treatment of bronchopulmonary dysplasia (BPD). However, the donor-to-donor heterogeneity is partially responsible for the incongruence of the MSCs-based clinical data. Our previous research found that the expression level of Nrf2 protein modulated the immunosuppressive ability of UC-MSCs. In this study, we aimed to investigate the variations in Nrf2 expression in UC-MSCs from different donor sources and determine the role of Nrf2 in the treatment of hyperoxia-induced BPD.

Methods The immunological phenotype, the expression of Nrf2, and the immunosuppressive ability were detected in UC-MSCs from three different donors in vitro. Nrf2 was knocked down in UC-MSCs through siRNA transfection. Subsequently, peripheral blood mononuclear cells (PBMCs) labeled with carboxyfluorescein diacetate succinimidyl ester(CFSE) were cocultured with UC-MSCs followed by detection the proliferative capacity. The IDO-1 expression induced by IFN γ was detected to evaluate immunosuppressive ability in vitro. Neonatal rats with BPD were established through hyperoxia treatment. UC-MSCs, UC-MSCs transfected with siRNA-Nrf2 or UC-MSCs transfected with siRNA-Nrf2 preteated with IFN γ were intratracheal administrated to BPD rats. The tissue sections of the lung was analyzed morphometrically. Pulmonary inflammatory cytokines of the bronchoalveolar lavage fluid (BALF) were measured via enzyme-linked immunosorbent assay. BALF cell count were measured. The mechanism of Nrf2 regulating IDO-1 expression was detected by chromatin immunoprecipitation assay(ChIP) and western-blot.

Results In three distinct sources of UC-MSCs, over 95% of these cells exhibited expression for CD90, CD105, and CD73, while less than 1% expressed CD45, CD34, and HLA-DR. However, there were differences in the expression of Nrf2. UC-MSCs with low level of Nrf2 expression demonstrated reduced ability to inhibit PBMC proliferation in co-culture, as well as lower levels of IDO-1 expression induced by IFN- γ . The downregulation of Nrf2 impaired the immunosuppressive ability of UC-MSCs. Transplantation of UC-MSCs improved pulmonary alveolarization ($P < 0.01$, for mean linear intercept). Meanwhile, treatment with hUC-MSCs ameliorated lung inflammation. The hUC-MSCs groups exhibited a significant attenuation in the expression of pro-inflammatory cytokines interleukin (IL)-1 β and IL-6, as well as a decrease in BALF protein levels ($P < 0.01$, $P < 0.001$, and $P < 0.05$ respectively). However, the downregulation of Nrf2 in UC-MSCs weakened the therapeutic effect. In lung tissues, the expression of IDO-1 was found to be significantly increased following UC-MSCs treatment, while this effect was attenuated in the treatment of UC-MSCs with NRF2 knockdown. ChIP assay revealed that Nrf2 regulated the phosphorylation level of Stat3, and it was found that phosphorylated Stat3, rather than Nrf2, bound to the promoter region of IDO-1.

Conclusions The expression of Nrf2 in UC-MSCs could serve as an indicator of their immunosuppressive ability and potentially play a crucial role in the treatment of BPD.

【关键字】 Nrf2, bronchopulmonary dysplasia, IDO-1, UC-MSCs, immunosuppressive ability

Bifunctional nanoparticles regulate directional differentiation of neural stem cells and polarization of microglia

王树萍、张朔、刘琦、孙春辉、任娜、王金刚、刘宏

济南大学

【摘要】 Object:

The pathological mechanisms of neurodegenerative diseases not only include functional damage of neurons but also involve dysregulation of the neuroimmune microenvironment. Neural stem cells (NSCs) as a type of self-renewing and multipotential stem cell are the most promising candidates in the regeneration of functional neurons. Pathological neuroinflammation related to neurodegeneration is mainly mediated by microglia, which are the resident immune cells of central nervous system. It is necessary to find a strategy that can regulate both the directional differentiation of NSCs and microglia in the damaged microenvironment for treatment of neurodegenerative diseases. In this study, we innovatively synthesized a composite nano regulator based on small molecule retinoic acid (RA) and metal ion Ca^{2+} to simultaneously regulate neuronal differentiation of NSCs and M2 polarization of microglia.

Methods:

Calcium retinoate (RA-Ca) nanoparticles with particle sizes around 200-300nm were prepared by complexation reaction, which can be uptake by cells into the lysosome and slowly release RA and Ca^{2+} under the low pH microenvironment. For differentiation of NSCs and microglia , related proteins and genes were analyzed by Western Blot and RT-qPCR.

Results:

The results of protein and gene expression indicated that RA-Ca nano-regulators not only enhanced the differentiation of NSCs into neurons but also promoted M2 polarization of microglia. In addition, co-culture of NSCs and microglia confirmed that RA-Ca nano-regulators could further enhance neuronal differentiation of NSCs by mediating the polarization of microglia towards M2.

Conclusions:

The finding of this study demonstrated that the RA-Ca nano-regulators combined of RA and Ca^{2+} would be a promising therapeutic strategy to regulate both the differentiation of NSCs and neuroinflammation for neurodegenerative diseases treatment .

【关键字】 neural stem cell, microglia, differentiation, retinoic acid, calcium ion

Effect of 1 μ M BPA on human neural stem cells via ERR α and TGF- β 1 signaling

孙吉坤、贾紫璇、张婧、潘慧心、王清路

山东体育学院

【摘要】 Objectives:

Bisphenol A (BPA) is a chemical commonly used in the production of plastics, producing 2,700 tons of plastics containing BPA each year worldwide. However, BPA damages neural stem cells, leading to neurodevelopmental disorders. Previous studies have shown that large doses of BPA are toxic, but the effect of low-dose BPA exposure on NSCs is unclear.

Methods:

The Cells were cultured and processed, with a model of NSCs poisoned by 1 μ M BPA, as well as immunoblotting, immunostaining, RNA-sequencing and data analysis, Chip-PCR chromatin immunoprecipitation, etc. The effects of low concentrations of BPA on the proliferation and apoptosis of human neural stem cells were investigated.

Results:

We found that low concentrations of BPA had no significant effect on cell morphology, but altered cell proliferation and apoptosis. The results of GO functional analysis indicated that 1 μ M BPA promotes cell cycle and may inhibit NSC differentiation. TGF- β pathway, and p53 signaling pathway were closely related to cell differentiation fate by KEGG pathway analysis. BPA activates the expression of the TGF- β 1 gene by binding to the ERR α receptor and the TGF- β 1 promoter. Chip-PCR results also showed that ERR α could bind to the promoter of TGF- β 1 at 1 μ M BPA exposure. Therefore, 1 μ M BPA, can initiate TGF- β 1 signaling pathway through ERR α , promote the proliferation of human NSC and reduce cell apoptosis.

Conclusions

In this paper, we found the effect of low concentration of BPA on NSCs by initiating the TGF- β 1 signaling pathway by combining ERR α , providing new insights into the prevention and treatment of neurogenic diseases.

【关键字】 Human neural stem cell; Bisphenol A; TGF- β 1 signaling; ERR signaling

基于 H3K4me3/H3K9me3 参与成纤维细胞生长因子 9 (FGF9) 刺激 Leydig 干细胞自我更新和分化的机制研究

全荷花、鲍肃好、何佳怡、王义炎、葛仁山、李晓珩

温州医科大学附属第二医院

【摘要】研究目的：成纤维细胞生长因子 9 (FGF9) 是成纤维生长因子家族成员之一，其受体 FGFR 在睾丸中有表达，对睾丸的形成与功能起着关键作用。已有研究表明，FGF9 在 Sry 的作用下与 Sox9 共同关闭卵巢的形成，将性腺向睾丸分化；FGF9 可以促进小鼠精原干细胞的分化；组蛋白修饰在调控精子发生时也起到了重要作用。但是 FGF9 对睾丸间质干细胞自我更新与分化过程的调控以及组蛋白修饰的作用还未有研究。

方法：体内实验：选取 56 日龄雄性 SD 大鼠，一次性腹腔注射 75 mg/kg 的二甲磺酸乙烷 (EDS)，14 天后，每日在大鼠睾丸内注射不同浓度的 FGF9 (0, 10 和 100 ng/睾丸)，持续 14 天。给药结束后，将大鼠进行安乐死处死，取血测定睾酮 (T)、促黄体生成素 (LH) 以及促卵泡生长激素 (FSH) 等激素水平；取双侧睾丸，一侧睾丸冻入 -80℃ 行 qPCR 及 WB 检测雄激素生成通路上相关基因及蛋白 (LHCGR、STAR、SCARB1、CYP11A1、CYP17A1、HSD11B1 和 HSD17B3 等) 的表达，WB 检测 H3K4me3/H3K9me3 修饰的动态蛋白变化，ChIP-Seq 检测 H3K4me3/H3K9me3 修饰调控的基因表达与睾丸间质干细胞发育及雄激素生成相关基因的互作关系；对侧睾丸用 Bouin's 液固定后行免疫组化和免疫荧光，计数 CYP11A1+ 和 SOX9+ 的睾丸间质细胞和支持细胞，计数 PCNA+ 与 CYP11A1+ 增殖的睾丸间质细胞；结合转录组学和组蛋白组学数据，确定 FGF9 与 H3K4me3/H3K9me3 修饰调控的基因，与睾丸间质干细胞发育的关系。

体外实验：选取 56 日龄 SD 大鼠，安乐死之后取睾丸分离曲细精管，采用 3D 悬浮培养，给予不同浓度的 FGF9 (0, 10 和 100 ng/mL)，培养 1 周/3 周后，取培养基检测睾酮含量，取曲细精管检测睾丸间质干细胞增殖的情况，qPCR 及 WB 检测雄激素生成通路上相关基因及蛋白的表达，WB 检测 H3K4me3/H3K9me3 修饰的动态蛋白变化，确定 H3K4me3/H3K9me3 修饰调控的基因以及修饰酶表达和活性，分析这些基因与睾丸间质干细胞发育的关联。

结果：FGF9 刺激睾丸间质干细胞的增殖与分化，刺激睾酮的合成，刺激睾酮合成通路上关键基因与蛋白的表达，诱导 H3K4me3/H3K9me3 甲基化修饰的发生，与睾酮合成通路上关键基因产生互作，对睾酮合成起正反馈作用。

结论：FGF9 可以促进睾丸间质干细胞的自我更新与分化，诱导了睾丸间质细胞的组蛋白 H3K4me3 和 H3K9me3 的甲基化修饰，与睾酮生成通路互作而刺激睾酮的生成，提示了 FGF9 对睾丸间质干细胞发育新的调控机制。

基金资助：浙江省自然科学基金探索项目，LY22H040010，葛仁山；国家自然科学基金项目，81730042 (重点项目)，82371610 (面上项目)，葛仁山

【关键字】成纤维细胞生长因子 9/FGF9，睾丸间质干细胞，自我更新，分化，睾酮，H3K4me3/H3K9me3 修饰

RNA 结合蛋白 YBX1 调控胚胎干细胞多能性退出的研究

郭传亮 1,2, 洪磊 1,2, 杨冠恒 1,2, 蔡勤 1,2, 张少清 1,2, 龚秀丽 1,2, 李文秀 1,2, 郭昕冰 1,2, 薛燕 1,2,3, 曾凡一 1,2,3

1. 上海市儿童医院, 上海交通大学医学遗传研究所

2. 上海市胚胎与生殖工程重点实验室暨国家卫健委医学胚胎分子生物学重点实验室

3. 上海交通大学基础医学院组织胚胎学与遗传发育学系

【摘要】 目的: 胚胎干细胞 (Embryonic stem cells-ESCs) 具有自我更新和分化两大特性, 前者调控机制相关研究较为充分, 但关于 ES 细胞如何开启分化相关机制研究则相对缺乏。RNA 结合蛋白 (RBPs) 在 RNA 介导的基因调控和细胞命运决定中具有重要的作用, 我们前期工作发现 YBX1 是 Nanog 的 RNA 结合蛋白之一, 本研究旨在探索 YBX1 对 ES 细胞多能性退出的调控作用, 为 ES 细胞命运决定机制研究提供新的切入点。

方法: 通过 RNA 结合蛋白免疫共沉淀测序 (RIP-seq) 鉴定 ES 细胞中与 YBX1 结合的转录本。建立 YBX1-KD (Knock down) ES 细胞系并通过 RNA-seq 分析全基因组表达谱, 同时对差异表达基因进行功能分析和筛选。用 Realtime PCR, Western Blot, ICC 等方法验证候选基因表达。

结果: RIP-seq 结果显示与 YBX1 结合的 RNA 主要参与 ES 细胞多能性调控, 除了 ES 细胞多能性因子 Nanog 外, 还发现多个参与 ES 细胞多能性退出相关因子, 例如 Wnt3a。YBX1-KD ES 细胞克隆明显变小, 凋亡细胞增多, 多个多能性退出相关基因表达下调, 也包括 Wnt3a。另外, YBX1-KD ES 细胞中分化基因尤其是肾小球上皮细胞分化和单核细胞分化相关基因则表达上调。

结论: 通过鉴定与 YBX1 的转录本以及分析 YBX1-KD ES 细胞差异表达基因, 我们发现 YBX1 与多个多能性退出相关基因转录本结合并调控其表达, 敲低 YBX1 会导致 ES 细胞自我更新能力下降, 分化基因上调。预示 YBX1 可能对 ES 细胞多能性退出的调控有一定作用。

【关键字】 RNA 结合蛋白, 多能性, 胚胎干细胞

ALKBH5 Modulates Hematopoietic Stem and Progenitor Cell Energy Metabolism through m6A Modification-Mediated RNA Stability Control

高义萌^{1,2 *}, Joshua T. Zimmer², Radovan Vasic², 刘诚扬², Rana Gbyli², 郑书剑², Amisha Patel², 刘伟², 齐志红², 李亚萍², Raman Nelakanti², 宋远斌³, Andrew Z. Xiao², Sarah Slavoff², Richard Kibbey², Richard A. Flavell², Matthew D. Simon², Toma Tebaldi², 李华兵⁴, Stephanie Halene²

1. 同济大学
2. Yale University
3. 中山大学肿瘤防治中心
4. 上海交通大学医学院

【摘要】 N6-methyladenosine (m6A) RNA modification controls numerous cellular processes. To what extent these post-transcriptional regulatory mechanisms play a role in hematopoiesis has not been fully elucidated. We here show that the m6A demethylase ALKBH5 controls mitochondrial ATP production and modulates hematopoietic stem and progenitor cell (HSPC) fitness in an m6A-dependent manner. Loss of ALKBH5 results in increased RNA methylation and instability of oxoglutarate-dehydrogenase (Ogdh) messenger RNA and reduction of OGDH protein levels. Limited OGDH availability slows the tricarboxylic acid (TCA) cycle with accumulation of alpha-ketoglutarate (a-KG) and conversion of a-KG into L-2-hydroxyglutarate (L-2-HG). L-2-HG inhibits energy production in both murine and human hematopoietic cells in vitro. Impaired mitochondrial energy production confers competitive disadvantage to HSPCs and limits clonogenicity of Mll-AF9-induced leukemia. Our study uncovers a mechanism whereby the RNA m6A demethylase ALKBH5 regulates the stability of metabolic enzyme transcripts thereby controlling energy metabolism in hematopoiesis and leukemia.

【关键字】 m6A modification; RNA stability; ALKBH5; hematopoietic stem and progenitor cells; ATP production; energy metabolism; oxidative phosphorylation (OXPHOS); stress hematopoiesis; metabolic switch

The inhibition of ULK1 promotes human erythroid progenitor proliferation and inhibits differentiation by upregulating AHR signaling

陈谊金、郑海琼、罗黔、张朦朦、张杰、张蒙、钱鹏旭、黄河

浙江大学医学院附属第一医院

【摘要】 Unc-51 like autophagy activating kinase 1 (ULK1) drives organelle clearance during erythroid maturation. However, it is unclear whether ULK1 impacts erythroid differentiation. In this study, we found that inhibition of ULK1 by inhibitor SBI-0206965 (SBI) or ULK1 shRNA promoted erythroid progenitors' proliferation while inhibiting differentiation. Meanwhile, the number of mitochondria, cell cycle, and apoptosis were not impacted. The proteomics and RNA-sequencing data showed that the expression of AHR signaling-related genes like CYP1B1, CYP1A1, and AHRR were upregulating by SBI suggesting the upregulation of AHR signaling. Moreover, both AHR antagonist StemRegenin 1 and AHR shRNA rescued the effects of ULK1 repressed in erythroid progenitors. The total expression of AHR was not impacted by a ULK1 inhibitor, while the expression of AHR in the nucleus was increased, indicating that ULK1 plays a role in regulating AHR activation. In conclusion, ULK1 regulated the proliferation and differentiation of erythroid progenitors by AHR signaling. This study will provide a theoretical foundation to generate mature red blood cells and a new approach toward the large-scale production of human erythrocytes in vitro.

【关键字】 ULK1; AHR; Erythroid progenitors; Erythroid differentiation.

Naringenin promotes exosomes of immature dendritic cells derived from induced pluripotent stem cells to alleviate the rejection of transplantation

黄晓燕¹, 靳占奎¹, 李研¹, 赵向绒¹, 冯杨萌¹, 封青¹, 李亚萍¹, 徐翠香^{1*}, 田普训²

1. 陕西省人民医院

2. 西安交通大学医学部第一附属医院

【摘要】 Background: Low induction rate and the characteristic of proning to maturation after stimulation in vivo limit the application of immature dendritic cells (imDCs) to induce donor-specific immunotolerance. We aimed to obtain the imDCs from induced pluripotent stem cells (iPSCs-imDCs), and used Naringenin (Nar) to increase the induction rate and inhibit the maturation of imDCs (Nar-iPSCs-imDCs) for inducing transplantation immune hyporesponsiveness. Methods: iPSCs were differentiated into imDCs in culture medium with or without Nar (iPSCs-imDCs and Nar-iPSCs-imDCs). The iPSCs-imDCs and Nar-iPSCs-imDCs were stimulated by Lipopolysaccharides for 48h, respectively. Then the DC-related surface markers, endocytotic ability and apoptosis of the two group cells were analyzed by flow cytometry. The effects of the two group cells on T-cell and regulatory T (Treg) cell proliferative function in vitro were analyzed by mixed lymphocyte reaction (MLR). Cytokine expression was detected by ELISA. Skin grafts were assessed for rejection degree using slit-lamp biomicroscopy and statistical evaluation of graft survival was performed using Kaplan-Meier curves. Results: Compared with iPSCs-imDCs, Nar-iPSCs-imDCs expressed higher CD11c levels and lower CD80, CD86 and MHC II levels and possessed higher Treg cell proliferative function. The levels of interleukin (IL)-2, interferon- γ in Nar-iPSCs-imDCs were lower than those in iPSCs-imDCs, whereas IL-4, IL-10 and TGF- β levels were higher. The endocytotic capacity and apoptosis rate of Nar-iPSCs-imDCs was significantly higher after treatment with lipopolysaccharides. In Balb/c mice recipients immunized with iPSCs-imDCs or Nar-iPSCs-imDCs 7 d before skin grafting, the Nar-iPSCs-imDCs group showed higher ability to inhibit donor-specific CD4+ T-cell proliferation and induce CD4+CD25+FoxP3+ Treg cell proliferation in the spleen, and Nar-iPSCs-imDCs group prolong skin graft survival span with a donor-specific pattern. Conclusion: This study demonstrates for the first time that Nar-iPSCs-imDCs could have a markedly improved therapeutic effect of chronic organ allograft rejection, presenting a new potential strategy for the clinical implementation of stem cell biotechnology combined with traditional Chinese medicine.

【关键字】 Immature dendritic cells; induced pluripotent stem cells; Naringenin; immunotolerance; transplantation

诱导人多能干细胞定向分化为视网膜祖细胞及其机制研究

刘逸凡、徐国彤、金彩霞

同济大学医学院

【摘要】前言：视网膜变性疾病（RD）是一类严重影响人类视力的致盲性眼科疾病，其中感光细胞的丧失是视网膜变性的主要原因。视网膜祖细胞（RPC）是一类神经类成体干细胞，具有定向分化为视网膜感光细胞的能力，并且可以分泌支持视网膜神经细胞存活和发育的神经营养因子的能力，因此将视网膜祖细胞移植到视网膜下腔，通过其分化为感光细胞可以定向弥补感光细胞的缺失，可有望起到改善视网膜变性的治疗效果。

结果：尽管 RPC 在视网膜变性疾病的细胞治疗中具有显著的优势，然而与胚胎干细胞以及诱导多能干细胞不同，作为神经类的成体干细胞，RPC 在体外分离后的扩增培养较为困难，体外扩增能力有限。因此，我们将人诱导多能干细胞（hiPSCs）在 12-18 天内分化成高表达 RPC 特异性标记物的视网膜祖细胞（hiPSC-RPC），并在体外稳定传代培养。我们的前期研究发现 MSX1 会影响 RPC 的增殖，抑制 MSX1 后引起细胞形态的变化，引起细胞骨架系统、细胞连接等系统及钙离子的变化，其中涉及小 G 蛋白家族、钙离子调控等通路。此外，将该 hiPSC-RPC 移植到 MNU 诱导的视网膜变性大鼠的视网膜下腔后，细胞可以存活至少 8 周，并能有效的保护因 MNU 诱导的感光细胞损伤凋亡造成的视功能下降以及视网膜结构的破坏。

结论：总之，我们构建获得的 hiPSC-RPCs 诱导方案不仅周期短且高效，同时在视网膜变性疾病模型中显示良好的视功能恢复和保护视网膜结构的作用，为干细胞移植治疗视网膜变性疾病提供了有利的科学依据。

【关键字】视网膜祖细胞；诱导人多能干细胞；视网膜变性疾病

人脐带间充质干细胞通过调节 T 细胞反应治疗实验性过敏性结膜炎

李东丽、徐国彤、海滨

同济大学医学院

【摘要】目的：探讨不同途径注射的人脐带间充质干细胞对实验性过敏性结膜炎的治疗效果及作用机制。

方法：通过小鼠足垫内注射短豚草(SRW)花粉建立小鼠实验性过敏性结膜炎(EAC)模型。SRW花粉滴眼刺激后，小鼠单次结膜下或尾静脉注射 2×10^6 个人脐带来源的间充质干细胞(hUCMSCs)，或结膜下注射 hUCMSCs 条件培养基(hUCMSCs-CM)，以地塞米松滴眼液处理为阳性对照，评估随后的抓痕行为和临床症状。免疫染色和流式细胞术显示结膜和颈部淋巴结(CLN)的过敏反应和 CD4⁺ T 细胞亚群的活化。通过 RNA-seq 检测正常和 EAC 模型小鼠血清刺激下的 hUCMSCs 基因表达变化，qRT-PCR 和 Western blot 验证差异基因表达。通过体外直接共培养模式探讨 hUCMSCs 对 CD4⁺ T 细胞向 Th2 分化的调节作用。

结果：在这项研究中，成功培养和鉴定了人脐带来源的间充质干细胞；与尾静脉注射、hUCMSCs-CM 结膜下注射和对照组相比，结膜下注射 hUCMSCs 导致 EAC 小鼠抓伤次数减少，炎症评分降低。结膜下给药 hUCMSCs 可减少结膜中活化肥大细胞和浸润嗜酸性粒细胞的数量，并减少 CLN 中 Th2 细胞的数量。在体外用 EAC 小鼠血清预处理以模拟体内环境后，hUCMSCs 能够抑制幼稚 T 细胞(Th0)向 Th2 细胞的分化。进一步的证据表明，hUCMSCs 对 Th2 细胞分化的抑制是由 CRISPLD2 通过下调 STAT6 磷酸化介导的。

结论：结膜下注射 hUCMSCs 可抑制 Th2 过敏反应，减轻临床症状。这项研究不仅为治疗 AC 提供了潜在的治疗靶点，也为其他 T 细胞介导的疾病提供了潜在的治疗靶点。

【关键字】 过敏性结膜炎;人脐带间充质干细胞;免疫调节;结膜下注射; Th2 细胞

骨髓巨噬细胞参与骨髓增生异常肿瘤的无效造血

李陈元、邢通、姚伟丽、赵红艳、王婧、张圆圆、吕萌、许兰平、张晓辉、黄晓军、孔圆

北京大学人民医院

【摘要】 研究目的：越来越多的证据表明骨髓微环境在骨髓增生异常肿瘤（myelodysplastic neoplasms, MDS）中的重要作用(JTM2022)。骨髓巨噬细胞（macrophage, MΦ）作为骨髓微环境中的重要组分，对正常造血的调控作用已有报道(STTT2022, BJH2018)，但骨髓 MΦ在 MDS 中对正常造血和恶性造血的支持能力尚不清楚。本研究旨在探讨骨髓 MΦ在 MDS 不同临床阶段对正常造血和恶性造血的调控作用，为 MDS 的发病机制和治疗提供新的思路。

研究方法：本研究纳入较低危组 MDS 患者（N=15），较高危组 MDS 患者（N=15），初诊急性髓系白血病(acute myeloid leukemia, AML)患者（N=15），以及健康供者（N=15）作为对照。通过流式细胞术分析标准单核细胞亚群及 MΦ亚群数量。通过细胞吞噬和迁移实验、S100A8/S100A9 表达水平评估骨髓 MΦ的功能。采用体外共培养策略评估骨髓 MΦ与供者造血干细胞体外共培养实验和肿瘤细胞的支持能力。通过转录组测序对 MDS 患者骨髓 MΦ中的关键分子通路进行分析。

研究结果：我们的结果表明在较高危组 MDS 患者的骨髓中，促炎单核细胞亚群增加，骨髓 MΦ向 M2 方向分化。较高危组 MDS 患者骨髓 MΦ中 S100A8/A9 水平升高，吞噬能力降低，迁移能力增加。更重要的是，较高危组 MDS 患者骨髓 MΦ对正常造血干细胞的支持能力下降，而对 MDS 和 AML 肿瘤细胞的支持能力增加。与体外实验结果一致，转录组测序分析显示，较高危组 MDS 患者的 M2 型巨噬细胞的比例升高。此外，和较低危组 MDS 相比，较高危组 MDS 患者骨髓 MΦ中造血和免疫相关通路富集，提示骨髓 MΦ对造血的调节作用在不同临床类型的 MDS 患者中存在差异。

讨论与结论：我们的研究结果提示骨髓 MΦs 参与了 MDS 患者无效造血，修复异常骨髓 MΦs 可能是治疗 MDS 患者的潜在新策略。

【关键字】 骨髓增生异常肿瘤，骨髓微环境，巨噬细胞，造血调控

Correction of a ADPKD point mutation using adenine base editors in hiPSCs and kidney organoids

王菁文^{1,2}, 邱燕玲^{1,2}, 张磊³, 周欣瑶^{1,2}, 胡思慧^{1,2}, 刘倩宜^{1,2}, 刘思邈^{1,2}, 武学清³, 黄军就^{1,2}

1. MOE Key Laboratory of Gene Function and Regulation, State Key Laboratory of Biocontrol, School of Life Sciences, Sun Yat-sen University, Guangzhou
2. Key Laboratory of Reproductive Medicine of Guangdong Province, School of Life Sciences and the First Affiliated Hospital, Sun Yat-sen University, Guangzhou
3. Center of Reproductive Medicine, Children's Hospital of Shanxi and Women Health Center of Shanxi, Taiyuan, Shanxi

【摘要】 Autosomal dominant polycystic kidney disease (ADPKD) is a dominant genetic disease primarily caused by mutations in the PKD1 gene, resulting in the formation of numerous cysts and eventual kidney function impairment. However, there are no gene therapy studies aimed at correcting PKD1 gene mutations currently. In this study, we identified two ADPKD mutation sites on the PKD1 gene, c.1198 (C>T) and c.8311 (G>A) in patients. The correction efficiencies of different adenine base editors (ABEs) were tested using the HEK293T-PKD1 c.1198 (C>T) and HEK293T-PKD1 c.8311 (G>A) reporter cell lines. The results showed that the ABE system can effectively repair the c.8311 (G>A) point mutation but not c.1198 (C>T) site, and ABE_{max} has higher efficiency and minimal predicted off-target effects. Then we generated induced pluripotent stem cells (iPSC_{mut}/WT) from the peripheral blood mononuclear cells (PBMCs) of the heterozygous patient to develop a disease cell model. Since the iPSC_{mut}/WT did not show typical disease phenotype in stem cell status, we subsequently differentiated iPSCs into kidney organoids in vitro, which expressed renal organ specific marker proteins, such as CDH1 and LTL. Adding Forskolin could stimulate cAMP signaling and lead to cystic expansion of renal epithelial tissue in iPSC_{mut}/WT differentiated kidney organoids, which is similar to the vesicle phenotype in ADPKD patient's kidney. While the kidney organoids differentiated from ABE-corrected iPSC did not show the cystic phenotype. Herein we tried to use this organoid to test the possibility of AAV-mediated ABE editing therapeutic strategy. The dual AAV split-ABE_{max} system was applied to deliver ABE_{max} into the kidney organoids and the average editing efficiency was about 6.46%. In general, this study lays the groundwork for gene therapy aimed at ADPKD using ABE single-base editing tool.

【关键字】 Gene editing, ABE, hiPSC, kidney organoid, ADPKD

人脐带血造血干细胞诱导分化的表观遗传调控机制研究进展

贾炳豪、刘春亚、唐琴、任立成

海南医学院

【摘要】造血干细胞(hematopoietic stem cells, HSCs)是血液系统中的一类多能干细胞,具有自我更新和多谱系分化两种基本特征。造血干细胞主要存在于骨髓中。其能自我更新和多向分化为各种功能的血细胞,维持血液系统的建立和动态平衡。造血干细胞的这些重要特性以及造血干细胞移植在临床上的广泛应用,结合现代基因治疗和基因编辑技术的快速发展,使得基于造血干细胞治疗多种血液疾病和免疫疾病的基因治疗研究在近年来取得了很大的进展。然而我们对于造血干细胞向多谱系分化过程中的表观调控机制及相关分子机制尚不完全清楚。在机体的生命周期中,造血干细胞位于血液系统最顶端,通过自我更新和多向分化维持着整个血液系统的稳态,这一过程受到严密而精细的调控。血液生态失衡则会导致各种血液疾病,如白血病等,也与机体各种重大疾病息息相关。本文将主要针对于造血干细胞生物学特征、体外扩增、分化表观遗传调控机制研究进展等方面做一综述。

【关键字】脐带血; 造血干细胞; 体外扩增; 表观遗传调控; 细胞因子

人脐带间充质干细胞外泌体联合 ATRA 应用于脐带血造血干细胞体外扩增研究

贾炳豪、刘春亚、唐琴、任立成

海南医学院

【摘要】 体内正常造血是造血干细胞(hematopoietic stem cells, HSCs)和骨髓间充质干细胞相互作用的结果, 骨髓间充质干细胞通过直接接触和分泌大量的可溶性细胞因子维持体内正常造血。全反式维甲酸 (all-trans retinoic acid, ATRA) 在调节造血干细胞的自我更新和多能造血干细胞的分化中起着重要作用。本研究将人脐带来源间充质干细胞外泌体联合 ATRA 对 HSCs 体外扩增进行一个方案的优化, 从而提高 HSCs 体外扩增效率。本研究通过免疫磁珠分选法将从人脐带血中分选获得 CD34+HSCs;组织块贴壁法将从人脐带的华通氏胶中获得脐带间充质干细胞(umbilical cord mesenchymal stem cells, UCMSCs), 传代扩增后使用更换为无血清培养基 48h 后进行收集其含有大量间充质干细胞外泌体的培养基上清, 将 ATRA 与 UCMSCs 培养外泌体联合应用于 HSCs 扩增培养, 通过细胞计数、流式检测及集落分析来判定扩增效应。联合培养方案的造血干细胞在数量、CD34+ HSCs 的比例及集落形成的数量等方面均明显多于现广泛使用的单独细胞因子的培养方案。UCMSCs 培养上清中含有大量的细胞分泌出胞外的外泌体成分及其诸多有利于造血干细胞扩增的生长因子, 这些外泌体成分因子和 ATRA 联合应用能显著提高 HSCs 扩增效率。

【关键字】 全反式维甲酸, 间充质干细胞, 造血干细胞, 外泌体, 细胞因子

Deciphering biophysical cues in cell fate conversion

王鹏元

瓯江实验室/温州医科大学

【摘要】 Cell fate manipulation is a critical process in cell therapies and regenerative medicine. Efficient strategies in maintaining the stemness of stem cells or differentiating stem cells into specific cell types are still limited. To date, a number of studies have reported that biophysical cues in the form of nanotopographies can influence stem cell attachment, proliferation, and differentiation. Specific surface nanotopographies can enhance the efficiency of cell reprogramming or maintain the stemness of stem cells. While biochemical cues are generally efficient, biophysical cues have other advantages, such as scalability, cost-effectiveness, longer lifetime, and ease of being defined. In our group, several biomimetic structures, including nanogrooves, nanopillars, nanopores, and colloidal crystals, have been fabricated using various nanotechnologies. Our findings show that through surface physicochemical cues, we can direct cell fate and phenotype, which reveals the fundamental questions in cell biology and benefits cell-based therapies. We believe that combining optimal biophysical cues with current biological approaches has great potential to improve efficiency and generate functional cells.

【关键字】 cell plasticity; biophysical cues; epigenetic, cell reprogramming; transdifferentiation

左归丸促进人脐带间充质干细胞迁移和归巢的分子机制研究

焦存 1,2, 芦现杰 1

1. 聊城市人民医院

2. 山东大学附属聊城人民医院

【摘要】 背景：课题组前期研究发现，合适浓度的左归丸能促进人脐带间充质干细胞（hUC-MSCs）的体外迁移，并促进 hUC-MSCs 归巢至损伤的卵巢组织。但是，左归丸调控 hUC-MSCs 迁移和归巢的多靶点作用机制尚不明确。目的：探讨左归丸调控 hUC-MSCs 迁移和归巢的具体分子机制。方法：提取对照组和左归丸组 hUC-MSCs 的总 RNA，通过 Illumina NovaSeq 6000 平台进行转录组测序（RNA-seq）分析。比较两组迁移和归巢相关基因（趋化因子及其受体 CXCR4、CXCR3 等，MMP（基质金属蛋白酶）家族）的表达情况，利用 Real-time PCR 对 hUC-MSCs 中相关差异表达基因（DEGs）进行验证。结果：RNA-seq 结果显示，左归丸组与对照组 DEGs 115 个，其中 51 个基因表达上调，64 个基因表达下调。筛选两组趋化因子及其受体 CXCR4、CXCR3 和 MMP 家族关键基因的表达变化。Real-time PCR 结果证实，与对照组比较，左归丸组 CXCR4、MMP2、MMP9、MMP10 和 MMP12 表达水平明显升高（ $P < 0.05$ ）。结论：左归丸可能通过上调 CXCR4、MMP2、MMP9、MMP10 和 MMP12 表达促进 hUC-MSCs 的迁移和归巢，从而改善干细胞治疗效果。基金项目：国家自然科学基金青年项目（82004402）；山东省中医药科技发展计划项目（2019-0893）。

【关键字】 人脐带间充质干细胞；左归丸；迁移；归巢；RNA-seq；趋化因子；基质金属蛋白酶

功能化干细胞源性凋亡小体纳米囊泡通过“找-吃”策略 靶向内皮细胞

钱姝桐¹, 毛佳怡², 赵秋羽², 卢博伦², 赵彬帆², 张柳成², 毛曦媛², 张余光²,
王丹茹², 孙晓明², 崔文国³

1. 浙江大学医学院附属第一医院
2. 上海交通大学医学院附属第九人民医院
3. 上海交通大学医学院附属瑞金医院

【摘要】目的：新生血管形成是驱动缺血组织修复的关键过程，慢性创面长期的缺氧微环境导致血管化不足，伤口延迟愈合。内皮细胞是组成新生血管的关键细胞，而脂肪干细胞（ADSCs）表面存在多种受体，这些受体允许 ADSCs 靶向受损组织。因此本文旨在构建工程化脂肪干细胞源性凋亡小体（ADSCs-ABs）靶向内皮细胞实现促血管化，为无细胞治疗提供新的策略。

方法：首先通过化学诱导 ADSCs 凋亡获得 ABs，然后通过优化的低渗处理-温和超声-药物混合-挤压处理的一系列步骤，获得载有去铁胺（DFO）的功能化 ADSCs-ABs。通过体内外实验分别验证其靶向内皮细胞促进血管化、伤口愈合的能力。

结果：体外实验显示 ADSCs-ABs 生物相容性良好，可以通过 CX3CL1/ CX3CR1 诱导缺氧微环境中的内皮细胞实现对其的“找-吃”，进而促进内皮细胞的增殖、迁移、成管能力。体内实验中，ADSCs-ABs 可以促进伤口快速闭合，同时可以通过释放“找-吃”信号靶向内皮细胞的同时实现促血管药物的缓释，促进糖尿病大鼠创面的新生血管形成。

结论：这些受体功能化的 ADSCs-ABs 可以通过释放“找-吃”的双重信号靶向内皮细胞并实现促血管生成药物的持续释放，为慢性糖尿病伤口愈合提供了一种新的策略。

【关键字】脂肪干细胞；内皮细胞；凋亡小体；纳米囊泡

肝脏干细胞的衰老与逆转

王敏君、陈费、刘清桂、胡以平

海军军医大学

【摘要】随着年龄的增加，肝脏稳态维持及再生能力明显下降并促进衰老相关疾病的发生。我们前期识别鉴定了表达 CD63 的肝脏干细胞以及其参与组织修复的能力，然而 CD63 阳性的肝干细胞是否发生衰老及其调控衰老的机制仍未报道。我们进一步研究发现肝干细胞会随着年龄的增加而发生衰老，表现为肝干细胞的数量减少、干细胞过度活化以及表达衰老和 DNA 损伤相关基因。而且衰老肝干细胞形成类器官的能力也明显减弱，体内分化为肝细胞参与损伤修复的能力降低。通过对年轻和衰老肝干细胞进行转录组测序分析，发现衰老肝干细胞中 JAK-STAT 信号通过被过度激活。利用 JAK 磷酸化抑制剂和 JAK 蛋白降解剂可有效抑制 JAK-STAT 信号的活化并逆转了衰老肝干细胞。衰老逆转的肝干细胞重新恢复类器官形成能力，体内可重新获得肝向分化能力，完成损伤肝脏的修复。因此，我们的研究不仅表明了肝干细胞会随着年龄的增加而发生衰老，还揭示了肝干细胞衰老的主要调控机制，并能成功逆转肝脏干细胞恢复其自我更新和分化能力，为临床上衰老相关肝脏疾病的防治提供有效的干预策略。

【关键字】 liver stem cell; rejuvenation; organoids culture; liver regeneration; aged-related liver diseases

联合疗法诱导产生肠道胰岛素的细胞并降低糖尿病小鼠的血糖

杜雯

广州医科大学

【摘要】作为一个高度再生的器官，肠道是细胞重编程的有前途的来源，可用于替代糖尿病中丢失的胰岛β细胞。之前的研究表明在肠内分泌前体细胞中敲除 FoxO1 基因能肠嗜铬细胞转化为胰岛素生成细胞，但其的数量极为有限。在该研究中，我们报告了人类胎儿肠道中存在具有潘氏/杯状细胞特征的胰岛素免疫反应细胞。谱系追踪实验表明，通过遗传或药理学 FoxO1 敲除，Paneth/goblet 谱系也可以转化为胰岛素谱系。此外，我们在肠道类器官中设计了一个筛选平台，通过准确定量 β 样细胞重编程并微调联合治疗，以提高小鼠和人类成年肠道类器官转化过程的效率。最后，我们发现了 FOXO1、Notch 和 TGF-β 的三重抑制剂的组合能够在肠道原位产生胰岛素分泌细胞，降低 STZ 注射诱导或 NOD 小鼠这两种 1 型糖尿病模型小鼠的血糖。这些发现说明了我们找到一种用肠道细胞替代胰岛素分泌的β细胞用于治疗糖尿病的新方法。

【关键字】胰岛素, Beta 细胞, 糖尿病

转录组分析 hESC-MSCs 治疗早期矽肺小鼠中的关键信号通路

胡文锋、杨佳丽、刘晓明

宁夏大学

【摘要】目的：通过转录组测序分析人胚胎干细胞来源间充质干细胞（hESC-MSCs）参与调控矽肺小鼠早期修复的关键信号通路。

方法：选取 6-8 周的 C57BL/6 小鼠共 10 只，随机分成两组：SiO₂ 组和 SiO₂+hESC-MSCs 组，分别在第 0 天和第 7 天进行 SiO₂ 气管滴注，在第 14 天给 SiO₂+hESC-MSCs 组进行尾静脉注射 100 mL 3×10⁶ 个 hESC-MSCs，并于注射后的第 3 天收集小鼠肺组织用于转录组测序分析。

结果：差异表达分析显示，两组共发现 1069 个差异表达基因，其中在 hESC-MSCs 治疗组中 511 个基因上调，558 个基因下调；差异基因的 GO 和 KEGG 功能富集分析表明，hESC-MSCs 治疗组能够通过调节 T 细胞功能，激活 NK 细胞以调节淋巴细胞激活等免疫调节作用参与小鼠矽肺的治疗。同时，在 hESC-MSCs 治疗组中平滑肌细胞增殖，胶原合成，调节内皮细胞和上皮细胞迁移，细胞黏附等参与上皮间质转化过程显著下调。在 hESC-MSCs 治疗组中，下调基因主要富集在炎症信号通路，如 TNF、NOD 样受体、IL-17 信号通路以及参与调控上皮间质转化发生的相关信号，如 PI3K-Akt、MAPK、JAK-STAT 等信号通路。

结论：hESC-MSCs 治疗早期矽肺小鼠主要是通过免疫调节，抑制炎症反应和上皮间质转化，改善肺脏微环境，激活肺脏干细胞的增殖，进而缓解矽肺小鼠的肺纤维化。

【关键字】 hESC-MSCs，矽肺，转录组测序，功能富集分析

MSCs-sEV 通过激活 DPCs 中 AKT 通路促进毛囊再生的作用与机制

田瑞云、李富荣

深圳市人民医院

【摘要】中国受脱发问题困扰的人群超过 2.5 亿且脱发年轻化趋势逐渐加剧，严重影响患者的心理健康和生活质量。传统的脱发治疗方法包括药物治疗和手术治疗，均具有一定的局限性而达不到理想的治疗效果。间充质干细胞（MSCs）的小细胞外囊泡（sEV）能够激活真皮乳头细胞（DPCs）并促进毛囊从休止期转变为生长期，具有潜在的治疗作用。课题组前期研究发现，MSCs 来源的 sEV 中可触发 DPCs 中 PI3K/AKT 信号通路，促使处于休止期的毛囊向生长期进行转换实现毛囊再生，但 sEV 激活 PI3K/AKT 通路的具体分子机制尚不清楚。本研究采用休止期小鼠脱发模型和雄秃小鼠模型对 sEV 促进毛囊再生的安全性和有效性进行了验证，结果显示与对照组和米诺地尔组相比，sEV 组小鼠休止期毛囊提前进入生长期，且背部毛囊覆盖率显著高于对照组证明了 sEV 促进毛囊再生的有效性。通过对炎症细胞浸润和脏器病理切片的分析发现 sEV 注射不引起严重的炎症反应，脏器未发生病变和 sEV 的滞留，表明了 sEV 促进毛囊再生的安全性。采用转录组和蛋白组技术分析 MSC-sEV 中 miRNA 表达和 DPCs 转录组表达水平并进一步进行体内实验，结果表明 MSC-sEV 中的 miR-125b 可以通过激活 DPCs 中的 AKT 信号通路参与毛囊从休止期向生长期转变的调控。上述临床前实验结果和分子机制的阐释，为 sEV 治疗脱发提供了坚实的临床前数据支持和理论基础。

【关键字】间充质干细胞；小细胞外囊泡；DPCs；AKT；毛囊再生

小鼠滋养层类器官的构建及功能筛选

林照博、毛倩

上海科技大学

【摘要】 The placenta has become one of the most diversified organs during the placental mammal radiation. Here, for the first time, we established culture conditions for establishment, maintenance, and differentiation of murine trophoblast organoids. Using mouse trophoblast organoids derived from a single stem cell, we performed an efficient CRISPR/Cas9 screening using a focused sgRNA library. Together, our results established a novel organoid model to investigate mouse trophoblast development and a practicable approach to perform forward screening in trophoblast lineages.

【关键字】 Mouse trophoblast organoid; CRISPR-Cas9

人多能干细胞的巨噬细胞分化与细菌感染模型

孙仕成^{1,2,3}, Elizabeth S Ng^{2,3}, Andrew G Elefanty^{2,3}, Sohinee Sarkar², Edouard G Stanley^{2,3}

1. 昌平实验室

2. 澳大利亚默多克儿童研究中心

3. 墨尔本诺和诺德干细胞医学中心

【摘要】人巨噬细胞多种分枝杆菌属的天然宿主，包括脓肿分枝杆菌（*M. abscessus*）。该细菌是一种影响免疫功能低下和囊性纤维化患者的新兴病原体，几乎没有可用的治疗方法。由于缺乏可处理的体外细胞内感染模型，阻碍了对有效治疗方法的开发。

本研究中，我们使用人多能干细胞衍生的巨噬细胞（hPSC-巨噬细胞）建立了脓肿分枝杆菌感染的可靠模型。为此，我们首先建立了高效的多能干细胞定向诱导分化体系，CD45+CD14+髓系细胞比例高达90%，表达HLA-DR，CD11b，TLRs，CD86和CD40等功能蛋白，具备抗原吞噬和T细胞抗原呈递的功能。hPSC-巨噬细胞高度易感染脓肿分枝杆菌感染，电子显微镜检查显示脓肿支原体存在于hPSC-巨噬细胞液泡中。RNA测序分析揭示了感染后具有不同基因和蛋白质表达模式的时间依赖性宿主细胞反应。表达tdTOMATO的hPSC巨噬细胞与表达GFP的分枝杆菌工程化，能够对细胞内感染进行基于图像的快速高通量分析和抗生素疗效的定量评估。综上，本研究报告了第一个基于hPSC的脓肿分枝杆菌感染模型，为研究病原体宿主相互作用和感染药物研发提供了一个简单、操作性强的高通量系统。

【关键字】多能干细胞 巨噬细胞 病原感染 微生物 抗生素 筛药

人多能干细胞的血液与淋巴免疫分化

孙仕成^{1,2,3}, Ali Motazedian¹, Jacky Li¹, Kevin Wijanarko¹, Jacqueline V Schiesser¹, Yi Yu¹,
Elizabeth S Ng¹, Andrew Elefanty^{1,2}, Edouard Stanley^{1,2}

1. 默多克儿童研究所
2. 墨尔本诺和诺德干细胞医学中心
3. 昌平实验室

【摘要】 血液和免疫发育在胚胎内和胚胎外组织的多个发育阶段发生。动脉内皮细胞（AEC）是胚胎造血的起始细胞，通过内皮到造血细胞转化过程产生造血祖细胞。此前，我们和其他研究团队建立了研究来自人类多能干细胞的 AEC 和血细胞的方法 (Sugimura 等 Nature 2017; Ng 等 Nat Biotechnol. 2016; Motazedian 等 Nat Cel Biol. 2021)。然而，在谱系特化、功能、稳健性和可重复性上，人多能干细胞的血液分化方法仍然存在挑战。

在此，我们报告一种新的高效且重复性高的分化方法，该方法可以模拟人动脉内皮细胞的发育、血细胞产生和免疫谱系特化的过程。发育时间轴单细胞 RNA 测序揭示了造血和淋巴细胞生成的动态进化，产生了与早期人类胚胎中存在的对应物的细胞类型 (Calvanese 等, Nature 2022)。我们的 AEC 还表达 NOTCH 配体 DLL4，该配体有力地支持淋巴分化，而无需外源性 NOTCH 配体。我们发现 IL7 是决定 T 细胞和先天淋巴谱系（ILC）之间命运选择的形态发生因素。这些发现传达了我们的多能干细胞的模型在研究人类胚胎造血和不同免疫细胞谱系之间的发育分化方面的优势，为研究血液和免疫疾病提供了新方法，更为开发新的免疫细胞治疗提供了“基础设施”平台。

【关键字】 多能干细胞 血液 免疫 发育 单细胞

脂肪干细胞来源的类神经干细胞球通过调节免疫微环境修复大鼠骶神经损伤

李君洋^{1,3}, 王玉², 尚爱加^{1,3}

1. 中国人民解放军总医院第一医学中心

2. 中国人民解放军总医院第四医学中心

3. 南开大学

【摘要】背景：骶神经损伤是周围神经损伤的重要形式之一，但对该疾病的治疗策略仍知之甚少。既往研究证实神经干细胞可以促进周围神经损伤后再生，但神经干细胞存在性质不稳定，获取困难等制约因素。脂肪干细胞经诱导后可以获取类神经干细胞球，但尚未有研究探究经脂肪干细胞诱导的类神经干细胞球在骶神经损伤后的修复作用。

方法：在本实验中，我们探究了脂肪干细胞诱导的类神经干细胞球对骶神经修复效果，并深入探究了相关的分子生物学机制。

结果：体外经诱导后成功制备类神经干细胞球，体内和体外实验均证实神经干细胞球通过调节局部免疫微环境促进骶神经损伤后再生过程。

结论：研究结果证实经脂肪干细胞诱导成地类神经干细胞球通过调节损伤微环境内巨噬细胞极化状态促进大鼠骶神经损伤后再生过程。

【关键字】诱导神经干细胞球；骶神经损伤；动物模型；巨噬细胞；神经炎症

DHH 通路在小鼠睾丸间质干细胞发育中的机制研究

李慧涛、苏铭、林杭、王义炎、李晓珩、朱琦琦、朱阳、葛仁山

温州医科大学附属第二医院、育英儿童医院

【摘要】 目的：建立体外小鼠睾丸间质干细胞（SLC）定向分化到成年睾丸间质细胞（LC）谱系的类器官培养系统，探索 DHH 通路如何调控 SLC 定向分化为成年 LC 谱系。

方法：采用表面含有 SLC 的生精小管，在基础培养基（MDF）中培养 7 天，然后转入含胰岛素-转铁蛋白-亚硒酸钠补充剂和 LH 的 MDF（LM）中培养 7 天，刺激 SLC 分化成祖细胞。随后，继续在 LM 中培养 14 天，刺激祖细胞发育成成年 LC，并产生大量睾酮。为了评估 SLC 的增殖能力，将小管在 M199 培养基中连续培养 28 天，并在第 4、7、14、21 和 28 天分别加入 EdU 染色剂，检测各时间点 EdU 掺入情况。同时，为了研究 DHH 在 SLC 定向分化过程中的作用，在小管培养中使用含 DHH 通路激动剂（SAG）的 LM 培养小管 7 天，然后继续在 LM 中培养 14 天，收集样本并检测睾酮的分泌水平。通过 qPCR 技术测量 LC 基因（Scarb1、Star、Cyp11a1、Hsd3b6 等）的表达水平。

结果：体外类器官培养系统中，SLC 定向分化为成年 LC，并分泌睾酮。DHH 通路的激活显著增加了 SLC 的增殖能力，并且显著增加培养基中睾酮的含量。此外，DHH 通路的激活显著上调了成年 LC 相关基因 Scarb1、Star、Cyp11a1 和 Hsd3b6 的表达水平。

结论：DHH 通路在 SLC 定向分化到成年 LC 谱系的发育过程中起着关键的调控作用。这些发现对于进一步理解 LC 发育机制以及开发相关疾病的治疗方法具有重要意义。

【关键字】 睾丸间质细胞；定向分化；生精小管；睾酮；增殖