南京大学 NANJING UNIVERSITY

MARC 模式动物研究所 Model Animal Research Center

2024 ANNUAL REPORT

Model Animal Research Center of Nanjing University
MOE key laboratory of model animal for disease study
National resource center for mutant mice

Director's Words

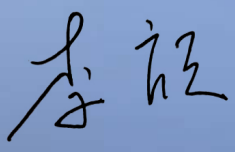
In 2024, the Model Animal Research Center (MARC) at Nanjing University celebrated a year of remarkable achievements and initiatives, reinforcing its position as a leader in biomedical research.

The year was distinguished by high-impact publications in prestigious journals such as *Cell, Nature Cancer, Nature Metabolism, Cell Discovery, Science Translational Medicine, Nature Communications, and Proceedings of the National Academy of Sciences*. These studies, built on genetic modified and humanized mouse models developed at MARC, contributed significantly to understanding disease mechanisms and advancing therapeutic innovation.

MARC fostered a vibrant academic exchange, hosting esteemed scholars like Professor Peng Liu from INSERM and Dr. Qingfeng Chen from A*STAR. International collaborations were further strengthened through faculty visits to France, the United States, and Germany. Notably, Dr. Liang Chi (NIH) and Dr. Yongzhen Liu (Princeton University) joined MARC's team, earning the prestigious Outstanding Overseas Young Scientist Fund from NSFC.

Engaging the broader community, MARC organized "The 3rd Youth Forum on Advanced Technologies of Neurodevelopment and Regeneration" and hosted the CSCB Laboratory Open Day, which showcased our cutting-edge facilities and fostered public enthusiasm for science. In its commitment to nurturing future talents, MARC also conducted a summer camp aimed at mentoring aspiring researchers.

Looking ahead, MARC reflects on its accomplishments while remaining committed to innovation, collaboration, and educational outreach. With a steadfast focus on advancing biomedical research and fostering international partnerships, MARC continues to pave the way as a premier institution in the model animal research community.



Yan Li
Director

IN FOCUS

IN DEPTH

IN ADDITION

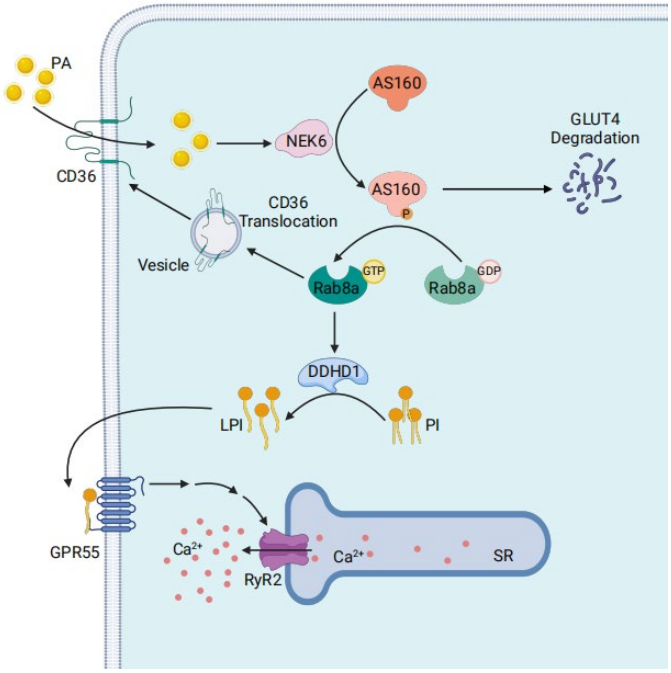
Research Highlight in 2024

Group Shuai Chen

AS160 is a lipid-responsive regulator of cardiac Ca2+ homeostasis by controlling lysophosphatidylinositol metabolism and signaling

Shu Su, Chao Quan, Qiaoli Chen, Ruizhen Wang, Qian Du, Sangsang Zhu, Min Li, Xinyu Yang, Ping Rong, Jiang Chen, Yingyu Bai, Wen Zheng, Weikuan Feng, Minjun Liu, Bingxian Xie, Kunfu Ouyang, Yun Stone Shi, Feng Lan, Xiuqin Zhang, Ruiping Xiao, Xiongwen Chen, Hong-Yu Wang* and Shuai Chen*

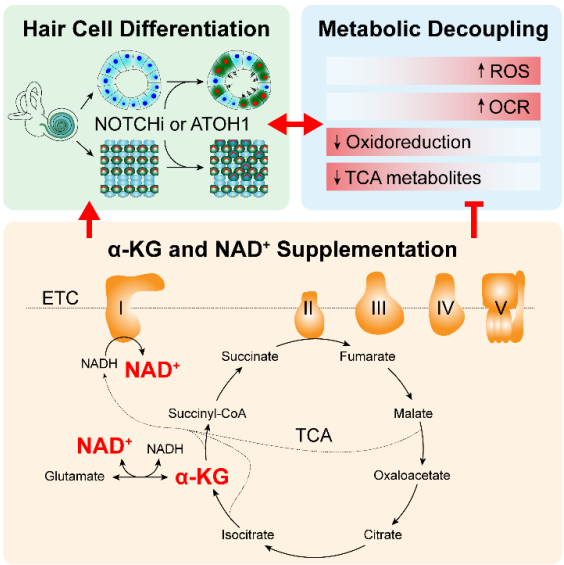
Obesity cardiomyopathy has been increasingly recognized as an obesity complication that develops myocardial dysfunction, independent of hypertension and coronary heart disease. Complex mechanisms are involved in the pathogenesis of obesity cardiomyopathy involving in structural, biochemical, molecular and functional alterations. The heart undergoes the contraction/relaxation cycle that is an energy-demanding process and controlled by shuttling of calcium (Ca^{2+}) between the cytosol and sarcoplasmic reticulum. The obese heart undergoes metabolic remodeling and exhibits impaired Ca^{2+} homeostasis, which are two critical assaults leading to cardiac dysfunction. The molecular mechanisms underlying these alterations in obese heart are not well understood. Here, we show that the Rab-GTPase activating protein AS160 is a lipid-responsive regulator of Ca^{2+} homeostasis through governing lysophosphatidylinositol (LPI) metabolism and signaling. Palmitic acid/high fat diet inhibits AS160 activity through phosphorylation by NIMA-related kinase 6 (NEK6), which consequently activates its downstream target Rab8a. Inactivation of AS160 in cardiomyocytes elevates cytosolic Ca^{2+} that subsequently impairs cardiac contractility. Mechanistically, Rab8a downstream of AS160 interacts with DDHD1 to increase LPI metabolism and signaling that leads to Ca^{2+} release from sarcoplasmic reticulum. Inactivation of NEK6 prevents inhibition of AS160 by palmitic acid/high fat diet, and alleviates cardiac dysfunction in high fat diet-fed mice. Together, our findings reveal a regulatory mechanism governing metabolic remodeling and Ca^{2+} homeostasis in obese heart, and have therapeutic implications to combat obesity cardiomyopathy.



Group Guoqiang Wan

Metabolic profiling of cochlear organoids identifies α-ketoglutarate and NAD+ as limiting factors for hair cell reprogramming (published in Advanced Science)

Cochlear hair cells are the sensory cells responsible for transduction of acoustic signals. In mammals, damaged hair cells do not regenerate, resulting in permanent hearing loss. Reprogramming of the surrounding supporting cells to functional hair cells represent a novel strategy to hearing restoration. However, cellular processes governing the efficient and functional hair cell reprogramming are not completely understood. Employing the mouse cochlear organoid system, Wan group performed detailed metabolomic characterizations of the expanding and differentiating organoids. They found that hair cell differentiation is associated with increased mitochondrial electron transport chain (ETC) activity and reactive oxidative species generation. Transcriptome and metabolome analyses indicate reduced expression of oxidoreductases and tricyclic acid (TCA) cycle metabolites. The metabolic decoupling between ETC and TCA cycle limits the availability of the key metabolic cofactors, α-ketoglutarate and NAD+. Supplementation of α-ketoglutarate and NAD+ promotes hair cell reprogramming both in vitro and in vivo. This study reveals metabolic rewiring as a central cellular process during hair cell differentiation, and highlights the insufficiency of key metabolites as a metabolic barrier for efficient hair cell reprogramming.



Group Yan Li

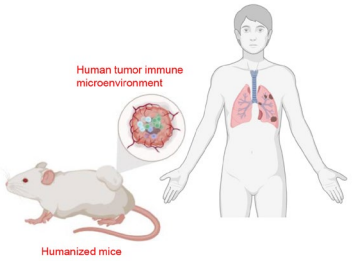
Humanized Mouse Models: Preclinical Models Bridging Immunotherapy Innovation and Clinical Treatment

Immunotherapy has emerged as a promising treatment for numerous cancers, transforming drug development. Despite clinical success, patient responses vary widely, and our understanding of its mechanisms and specific biomarkers is incomplete. Preclinical models that can accurately replicate human immune-tumor interactions are scarce, limiting in vivo evaluation of human-specific immunotherapies. Humanized mice represent a class of models characterized by the reconstruction of the human immune system through the transplantation of human peripheral blood mononuclear cells (PBMCs) or hematopoietic stem cells (HSCs) into immunodeficient mice. By further engrafting human tumor cells into humanized mice, it is possible to mimic the complex immune microenvironment of human tumor tissues. These models offer invaluable insights and support for research in tumor immunotherapy, as they allow for the investigation of human-specific immune responses and the efficacy of immunotherapeutic agents in a physiologically relevant context.

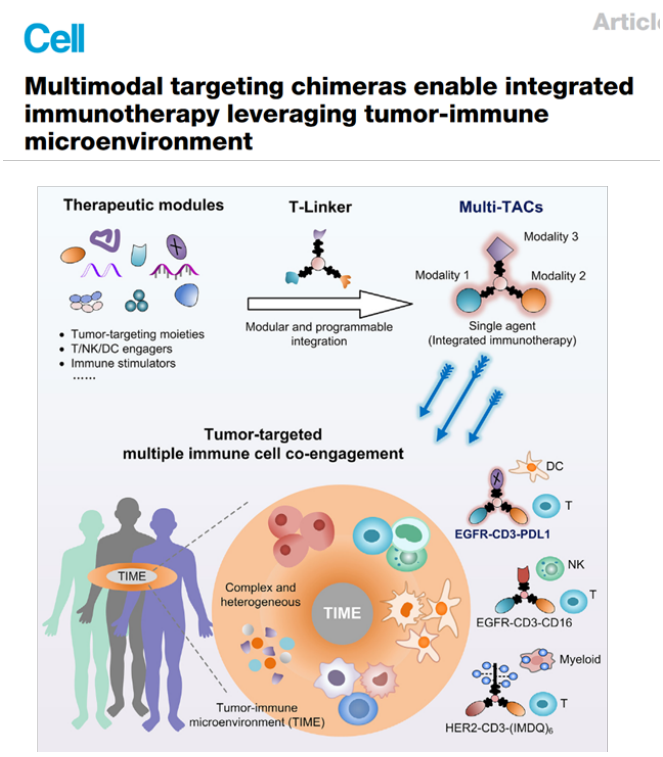
In the past year, our group evaluated three promising anti-tumor therapies or device using humanized mouse models. We elucidated their unique anti-tumor mechanisms, offering fresh perspectives for clinical management.

Real-time imaging of cytokines is crucial for assessing immune checkpoint blockade efficacy and optimizing treatment. We introduced a nanodevice for in situ photoactivated imaging of IFN-γ secretion from T cells, enabling quantitative imaging of endogenous IFN-γ dynamics in PBMC humanized mice responding to anti-PD-1 therapy.

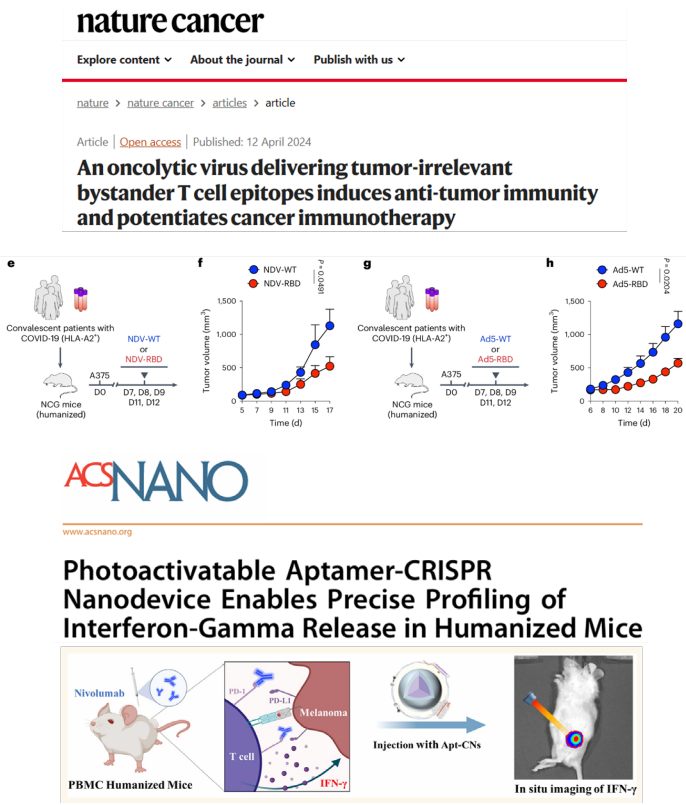
Tumor-specific T cells are vital in anti-tumor immunity but are scarce and functionally exhausted in the tumor microenvironment, limiting immunotherapy effectiveness. Conversely, tumor-irrelevant bystander T (TBYS) cells are abundant and functional in the tumor microenvironment. Our collaborators engineered oncolytic viruses encoding TBYS epitopes (OV-BYTE) to redirect tumor antigen specificity to TBYS cells, effectively inhibiting tumors in humanized mice. These results provide important insights into the improvement of cancer immunotherapies in a large population with a history of SARS-CoV-2 infection or coronavirus disease 2019 (COVID-19) vaccination.



Although immunotherapy has revolutionized cancer treatment, its efficacy is affected by the complexity and heterogeneity of the tumor-immune microenvironment. Strategies engaging multiple immune cells in TIME are desirable but challenging. Our collaborators developed triple orthogonal linker (T-Linker) technology to create multimodal targeting chimeras (Multi-TACs). To investigate the efficacy of Multi-TACs in human solid tumors, huHSC-NCG-hIL15 humanized mouse models with full reconstitutions of human immune cells were used. Our findings show that EGFR-CD3-PDL1 Multi-TAC promotes T and dendritic cell co-engagement, effectively targeting solid tumors.


Cell

Multimodal targeting chimeras enable integrated immunotherapy leveraging tumor-immune microenvironment


nature cancer

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Article | Open access | Published: 12 April 2024

An oncolytic virus delivering tumor-irrelevant bystander T cell epitopes induces anti-tumor immunity and potentiates cancer immunotherapy

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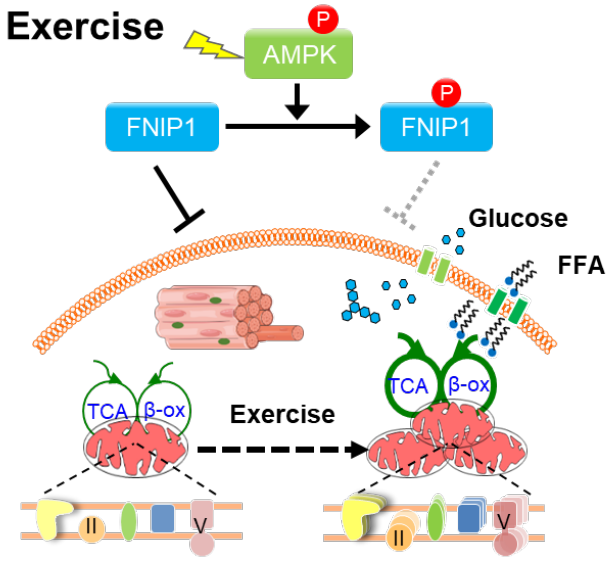
Photoactivatable Aptamer-CRISPR Nanodevice Enables Precise Profiling of Interferon-Gamma Release in Humanized Mice

Group Zhenji Gan

AMPK phosphorylation of FNIP1 (S220) controls mitochondrial function

Liwei Xiao, Yujing Yin, Zongchao Sun, Jing Liu, Yuhuan Jia, Likun Yang , Yan Mao, Shujun Peng, Zhifu Xie, Lei Fang, Jingya Li , Xiaoduo Xie , and Zhenji Gan

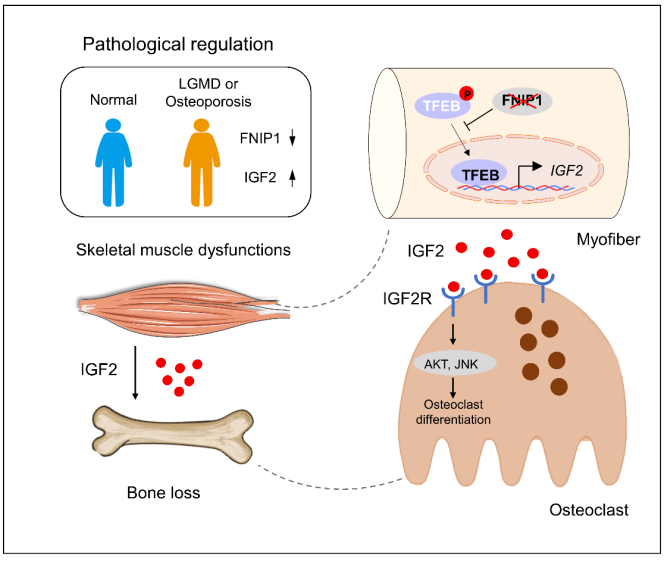
Exercise-induced activation of adenosine monophosphate–activated protein kinase (AMPK) and substrate phosphorylation modulate the metabolic capacity of mitochondria in skeletal muscle. However, the key effector(s) of AMPK and the regulatory mechanisms remain unclear. Here, we showed that AMPK phosphorylation of the folliculin interacting protein 1 (FNIP1) serine-220 (S220) controls mitochondrial function and muscle fuel utilization during exercise. Loss of FNIP1 in skeletal muscle resulted in increased mitochondrial content and augmented metabolic capacity, leading to enhanced exercise endurance in mice. Using skeletal muscle–specific nonphosphorylatable FNIP1 (S220A) and phosphomimic (S220D) transgenic mouse models as well as biochemical analysis in primary skeletal muscle cells, we demonstrated that exercise-induced FNIP1 (S220) phosphorylation by AMPK in muscle regulates mitochondrial electron transfer chain complex assembly, fuel utilization, and exercise performance without affecting mechanistic target of rapamycin complex 1–transcription factor EB signaling. Therefore, FNIP1 is a multifunctional AMPK effector for mitochondrial adaptation to exercise, implicating a mechanism for exercise tolerance in health and disease.



Muscle-bone cross-talk through the FNIP1-TFEB-IGF2 axis

Yan Mao, Zhen Jin, Jing Yang, Dengqiu Xu, Lei Zhao, Abdukahar Kiram, Yujing Yin, Danxia Zhou, Zongchao Sun, Liwei Xiao, Zheng Zhou, Likun Yang, Tingting Fu, Zhisheng Xu, Yuhuan Jia, Xinyi Chen, Feng-Nan Niu, Xihua Li, Zezhang Zhu, and Zhenji Gan

Clinical evidence indicates a close association between muscle dysfunction and bone loss; however, the underlying mechanisms remain unclear. Here, we report that muscle dysfunction-related bone loss in humans with limb-girdle muscular dystrophy is associated with decreased expression of folliculin-interacting protein 1 (FNIP1) in muscle tissue. Supporting this finding, murine gain- and loss-of-function genetic models demonstrated that muscle-specific ablation of FNIP1 caused decreased bone mass, increased osteoclastic activity, and mechanical impairment that could be rescued by myofiber-specific expression of FNIP1. Myofiber-specific FNIP1 deficiency stimulated expression of nuclear translocation of transcription factor EB, thereby activating transcription of insulin-like growth factor 2 (Igf2) at a conserved promoter-binding site and subsequent IGF2 secretion. Muscle-derived IGF2 stimulated osteoclastogenesis through IGF2 receptor signaling. AAV9-mediated overexpression of IGF2 was sufficient to decrease bone volume and impair bone mechanical properties in mice. Further, we found that serum IGF2 concentration was negatively correlated with bone health in humans in the context of osteoporosis. Our findings elucidate a muscle-bone cross-talk mechanism bridging the gap between muscle dysfunction and bone loss. This cross-talk represents a potential target to treat musculoskeletal diseases and osteoporosis.

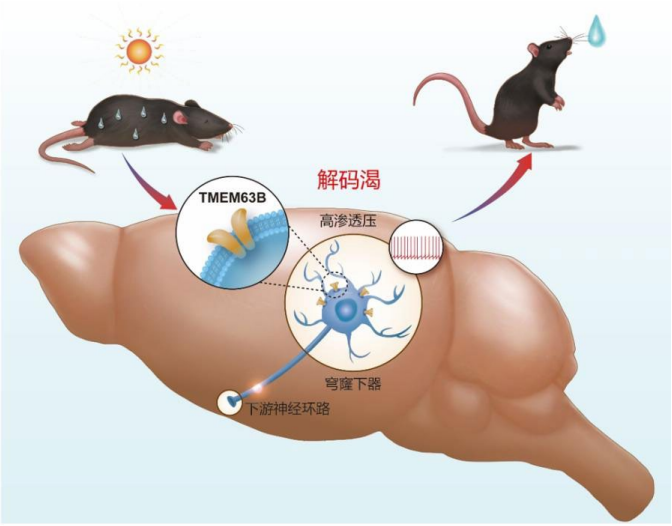


Group Yun Shi

TMEM63B channel is the osmosensor required for thirst drive of interoceptive neurons

Yang GL, Jia M, Li GZ, Zang YY, Chen YY, Wang YY, Zhan SY, Peng SX, Wan GQ, Li W*, Yang JJ*, Shi YS* (2024).

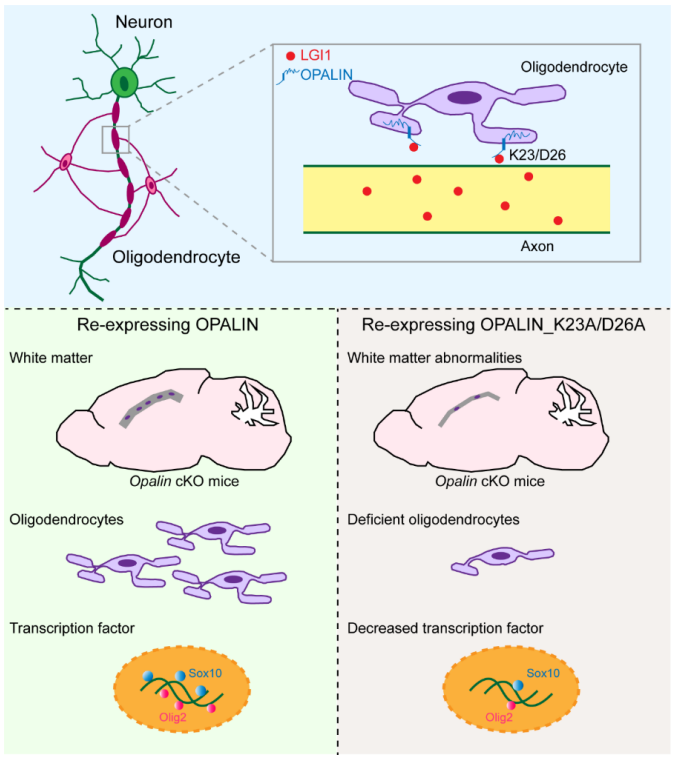
Thirst plays a vital role in the regulation of body fluid homeostasis and if deregulated can be life-threatening.Interoceptive neurons in the subfornical organ (SFO) are intrinsically osmosensitive and their activation by hyperosmolarity is necessary and sufficient for generating thirst. However, the primary molecules sensing systemic osmolarity in these neurons remain elusive. Here we show that the mechanosensitive TMEM63B cation channel is the osmosensor required for the interoceptive neurons to drive thirst. TMEM63B channel is highly expressed in the excitatory SFO thirst neurons. TMEM63B deletion in these neurons impaired hyperosmolarity-induced drinking behavior, while re-expressing TMEM63B in SFO restored water appetite in TMEM63B-deficient mice. Remarkably, hyperosmolarity activates TMEM63B channels, leading to depolarization and increased firing rate of the interoceptive neurons, which drives drinking behavior. Furthermore, TMEM63B deletion did not affect sensitivities of the SFO neurons to angiotensin II or hypoosmolarity, suggesting that TMEM63B plays a specialized role in detecting hyperosmolarity in SFO neurons. Thus, our results reveal a critical osmosensor molecule for the generation of thirst perception.



OPALIN is an LGI1 receptor promoting oligodendrocyte differentiation.

Teng XY, Hu P*, Zhang CM, Zhang QX, Yang G, Zang YY, Liu ZX, Chen G*, Shi YS*. (2024)

Leucine-rich glioma-inactivated protein 1 (LGI1), a secretory protein in the brain, plays a critical role in myelination; dysfunction of this protein leads to hypomyelination and white matter abnormalities (WMAs). Here, we hypothesized that LGI1 may regulate myelination through binding to an unidentified receptor on the membrane of oligodendrocytes (OLs). To search for this hypothetic receptor, we analyzed LGI1 binding proteins through LGI1-3×FLAG affinity chromatography with mouse brain lysates followed by mass spectrometry. An OL-specific membrane protein, the oligodendrocytic myelin paranodal and inner loop protein (OPALIN), was identified. Conditional knockout (cKO) of OPALIN in the OL lineage caused hypomyelination and WMAs, phenocopying LGI1 deficiency in mice. Biochemical analysis revealed the downregulation of Sox10 and Olig2, transcription factors critical for OL differentiation, further confirming the impaired OL maturation in Opalin cKO mice. Moreover, virus-mediated re-expression of OPALIN successfully restored myelination in Opalin cKO mice. In contrast, re-expression of LGI1-unbound OPALIN_K23A/D26A failed to reverse the hypomyelination phenotype. In conclusion, our study demonstrated that OPALIN on the OL membrane serves as an LGI1 receptor, highlighting the importance of the LGI1/OPALIN complex in orchestrating OL differentiation and myelination.



Student of the Year

Shuang Liu

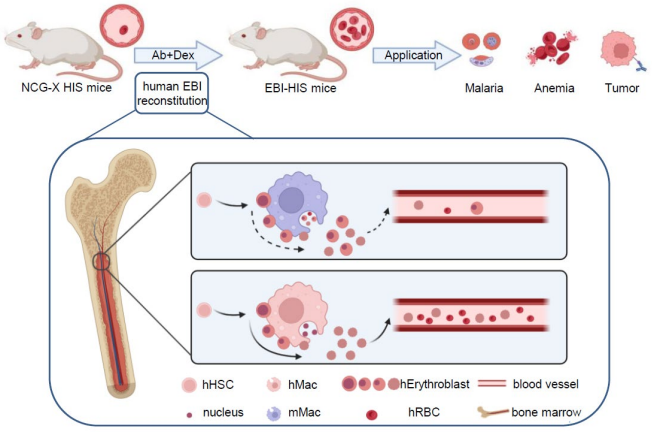
Shuang Liu received his Bachelor's degree of agriculture from Yantai University in 2019. He joined Dr. Yan Li's lab at the year of 2019 to study the human immune system mice. He won the 2nd Life Sciences Gempharmatech Cup Outstanding Award in 2023.

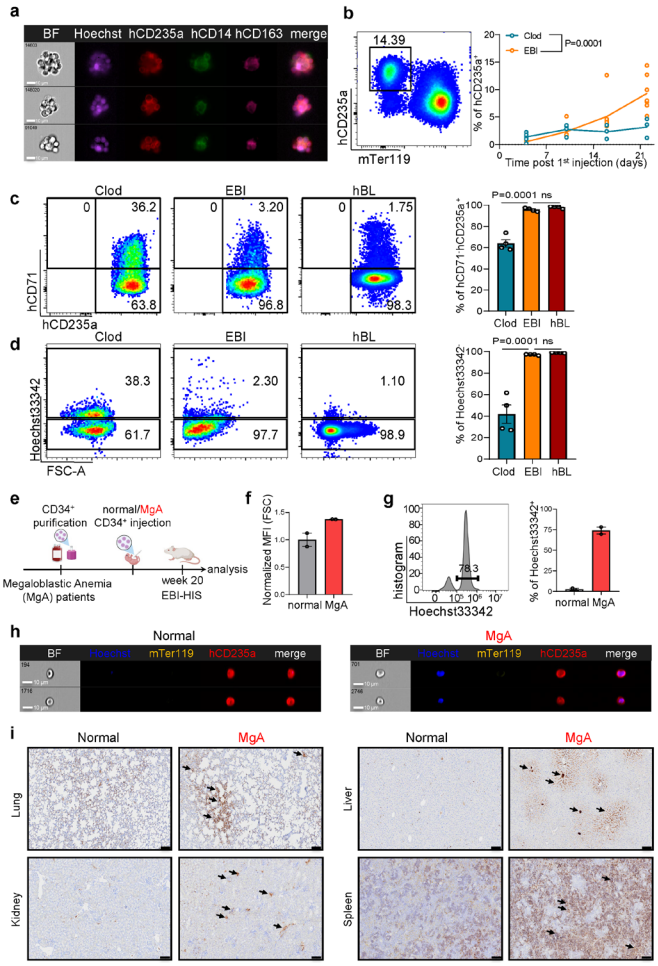
For the past five years, his research has focused on repopulating human erythrocytes in human immune system mice. He developed a novel erythroblastic island humanized mouse model, which successfully produces fully mature circulating human erythrocytes. This breakthrough addresses the long-standing challenge of abnormal maturation and poor reconstitution of human erythrocytes in humanized mouse models.

Conference

66th ASH annual meeting & exposition, Oral presentation. San Diego, USA

16th CSI meeting, Oral presentation. Hangzhou, China





Selected publications

1. Shuang Liu, Tong Zhou, Zijian Zhang, Tongxiao Cui, Shuhua Yu, Jin Zhang, Zhongyang Lv, Shuai Ding,Dongquan Shi, Deshan Ren, Ran Xie, Peipei Xu, Harvey F. Lodish, Yan Li*. (2024) Reconstruction of Megaloblastic Anemia in a Novel Erythroblastic Island Humanized Mouse Model with Mature Circulating Human Red Blood Cells, Blood. Doi:10.1182/blood-2024-193785. Oral Abstract.
2. Deshan Ren, Zijian Zhang, Xiangkuan Zheng, Chun Lu, Yuxian Song, Shuang Liu, Shuai Ding, Wei Zhang*, Yayi Hou*, Yan Li*.(2024) TLR5 expression marks brain boarder associated macrophages and protects neonatal mice frombacterial meningitis.hLife.doi:10.1016/j.hlife.2024.04.007
3. Xiufei Chen, Wenjie Zhou, Ren-Hua Song, Shuang Liu, Shu Wang, Yujia Chen, Chao Gao, Chenxi He, Jianxiong Xiao, Lei Zhang, Tianxiang Wang, Peng Liu, Kunlong Duan, Chen Zhang, Jinye Zhang, Yiping Sun, Felix Jackson, Fei Lan, Yun Liu, Yanhui Xu, Justin Jong-Leong Wong, Pu Wang, Hui Yang, Yue Xiong, Tong Chen*, Yan Li*, Dan Ye*.(2022) Tumor suppressor CEBPA interacts with and inhibits DNMT3A activity, Science Advances, doi: 10.1126/sciadv.abl5220

Neurobiology

Yun Shi , Ph.D

Yun Shi received Ph.D degree in physiology at Georgia State University under the mentoring of Dr. Chun Jiang at Atlanta, USA in 2007. His Ph.D. work focus on the function and regulation of vascular KATP channels. He then had postdoctoral training with Dr. Roger Nicoll in UCSF where he worked on synaptic plasticity. In 2013, he joined the Model Animal Research Center, Nanjing University as a professor and principal investigator.

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The Mechanisms of Neural Plasticity

The central neural system (CNS) is a complex network, in which the appropriate functions depend on the information exchange among neurons through a specified structure named synapse. The neurotransmitters released from presynaptic neurons bind to postsynaptic receptors, enhancing or inhibiting postsynaptic activity. Meanwhile, postsynaptic neurons also release certain regulatory information and modulate presynaptic activity, allowing the feedback to occur. Many of high neuronal functions result from the changes of neurotransmission, or so-called plasticity. Dysfunction of synaptic plasticity is one of the major causes of neurodegeneration diseases. Therefore, studying the synaptic transmission not only help unreal human high neural functions but also improve our understanding on the mechanisms of neural diseases and provide cues for cure.

Glutamate is the major excitatory neurotransmitter in CNS. Two groups of glutamate receptors are located on the post-synaptic membrane, i.e., ionotropic and metabotropic glutamate receptors. Ionotropic receptors include AMPA, NMDA and Kainate receptors; each are composed of different subunits. The normal function of excitatory synapses and the generation of neural plasticity are determined by the composition and expression level of postsynaptic glutamate receptors. However, how the receptors correctly traffic to post-synaptic membrane and how the expression level is appropriately regulated remain unclear.

Hippocampus is a relatively simple structure in brain, which is believed to play an essential role in learning and memory. The CA3-CA1 synapses are arguably the best studied synapses in brain. The plasticity of those synapses, including long-term potentiation (LTP) and long-term depression (LTD), are believed to be the fundament of learning and memory mechanisms.

Mechanosensitive (MS) ion channels are molecular force transducers that specialize in rapidly converting various mechanical stimuli into electrochemical signals for controlling key biological activities such as touch, vascular development, and blood pressure regulation. TMEM63 family of cation channels, the homologs of plant OSCAs in animals, are recently characterized to be osmo- and mechano-sensitive. TMEM63B in SFO neurons was activated by hyperosmotic stress, which leads to depolarization and increased firing rate of these neurons. Therefore, our recent study has demonstrated that TMEM63B is an osmosensor in SFO for generation of thirst perception.

Current research interests in our lab include: 1. The fundament of synaptic plasticity such as LTP and LTD. 2. Diseases associated with glutamate signal pathway. 3. Physiological functions of the mechanosensitive cation channel Tmem63 family.

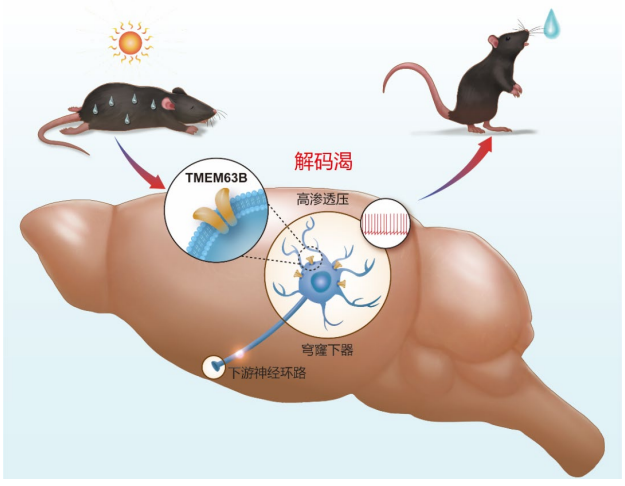


Figure 1. TMEM63B channel is the osmosensor required for thirst drive of interoceptive neurons (Cell discovery 2024).

The interoceptive neurons in SFO are intrinsically osmosensitive, and function as osmoreceptors. TMEM63B in the SFO neurons is both necessary and sufficient for generation of thirst perception.

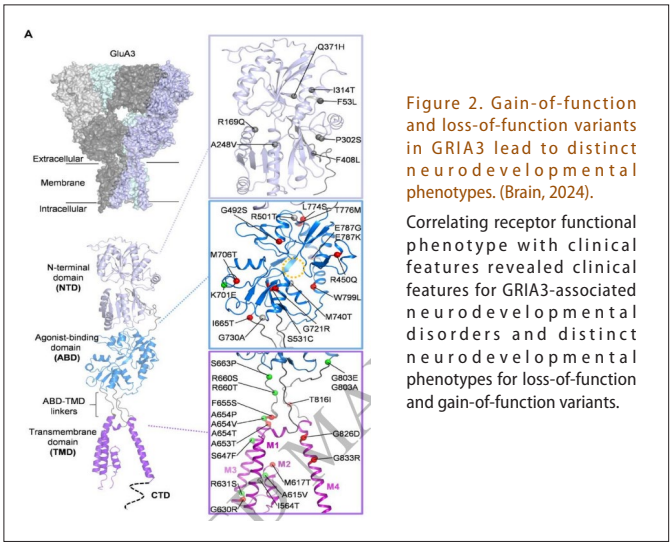
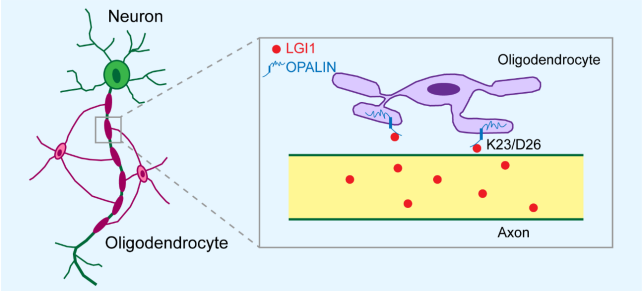


Figure 2. Gain-of-function and loss-of-function variants in GRIA3 lead to distinct neurodevelopmental phenotypes. (Brain, 2024).

Correlating receptor functional phenotype with clinical features revealed clinical features for GRIA3-associated neurodevelopmental disorders and distinct neurodevelopmental phenotypes for loss-of-function and gain-of-function variants.



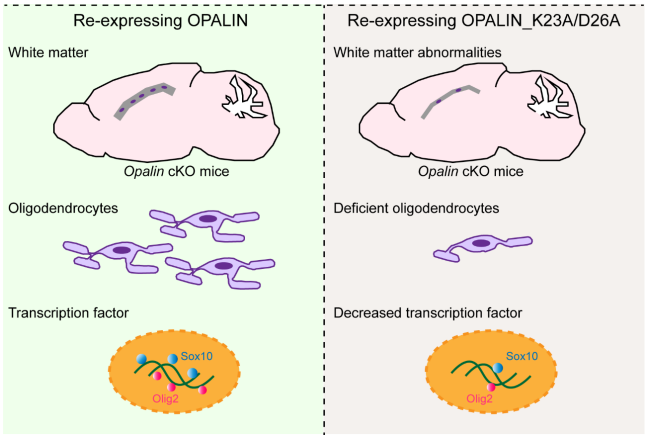


Figure 3. OPALIN is an LGI1 receptor promoting oligodendrocyte differentiation (PNAS, 2024).

OPALIN on the OL membrane serves as an LGI1 receptor, highlighting the importance of the LGI1/OPALIN complex in orchestrating OL differentiation and myelination.

Selected publications

1. Teng XY, Hu P*, Zhang CM, Zhang QX, Yang G, Zang YY, Liu ZX, Chen G*, Shi YS*. (2024) OPALIN is an LGI1 receptor promoting oligodendrocyte differentiation. Proc Natl Acad Sci U S A. 121(32):e2403652121.
2. Yang GL, Jia M, Li GZ, Zang YY, Chen YY, Wang YY, Zhan SY, Peng SX, Wan GQ, Li W*, Yang JJ*, Shi YS*. (2024) TMEM63B channel is the osmosensor required for thirst drive of interoceptive neurons. Cell Discov. 10(1):1.
3. Rinaldi B, Bayat A*, Zachariassen LG, Sun JH, Ge YH, Zhao D, Bonde K, ⋯, Shi YS*, Kristensen AS*. (2024) Gain-of-function and loss-of-function variants in GRIA3 lead to distinct neurodevelopmental phenotypes. Brain. 147(5):1837-1855.
4. Qin YQ, Yu DQ, Wu D, Dong JQ, Li WT, Ye C, Cheung KC, Zhang YY, Xu Y, Wang YQ*, Shi YS*, Dang SY*. (2023) Cryo-EM structure of TMEM63C suggests it functions as a monomer. Nature Commun. 14(1):7265.
5. Peng SX, Pei J, Rinaldi B, Chen Jiang, Ge YH, Jia M, Wang J, Delahaye-Duriez A, Sun J, Zang YY, Shi YY, Zhang N, Gao X, Milani D, Xu X, Sheng N, Gerard B, Chen Zhang C, Bayat A, Liu N*, Yang JJ*, Shi YS*. (2022) Dysfunction of AMPA receptor GluA3 is associated with aggressive behavior in human. Mol Psychiatry. 27(10):4092-4102.
6. Li QQ, Chen J, Hu P, Jia M, Sun JH, Feng HY, Qiao FC, Zang YY, Shi YY, Chen G, Sheng N, Xu Y, Yang JJ*, Xu Z*, Shi YS*. (2022) Enhancing GluN2A-type NMDA receptors impairs long-term synaptic plasticity and learning and memory. Mol Psychiatry. 27(8):3468-3478.
7. He L, Sun J, Gao Y, Li B, Wang Y, Dong Y, An W, Li H, Yang B, Ge Y, Zhang XC*, Shi YS*, Zhao Y*. (2021) Kainate receptor modulation by Neto2. Nature. 599(7884):325-329.
8. Sun JH, Chen J, Ayala Valenzuela FE, Brown C, Masser-Frye D, Jones M, Romero LP, Rinaldi B, Li WL, Li QQ, Wu D, Gerard B, Thorpe E*, Bayat A*, Shi YS*. (2021) X-linked neonatal-onset epileptic encephalopathy associated with a gain-of-function variant p.R660T in GRIA3. PLoS Genet. 17(6):e1009608.
9. Jiang CH, Wei M, Zhang C*, Shi YS*. (2021) The amino-terminal domain of GluA1 mediates LTP maintenance via interaction with neuroplastin-65. Proc Natl Acad Sci U S A. 118(9): e2019194118.
10. Du H, Ye C, Wu D, Zang YY, Zhang L, Chen C, He XY, Yang JJ, Hu P, Xu Z, Wan G*, Shi SY*. (2020) The cation channel TMEM63B is an osmosensor required for hearing. Cell Reports. 31(5):107596.

Group members

Group Leader

Yun Shi

Graduate students

Shiyu Zhan
Guizhou Li
Yanyu Zang
Yuhan Ge
Shuaifei Lu
Xiaofeng Tan
Tianzi Zhang
Jing Li
Jingwen Chen

Former graduate students

Yanjun Li
Jiang Chen
Guifang Duan
Han Du
Dan Wu
Chang Ye
Jiahui Sun
Shixiao Peng
Chaohua Jiang
Xiaoyu Teng
Qingqing Li
Wenmin Cai
Yueying Wang
Guolin Yang
Yangyang Chen
Jingjing Tu.

Guiquan Chen, Ph.D.

Guiquan obtained his PhD in Neuroscience at the University of Edinburgh in Scotland in 2005 and then conducted his postdoctoral research at Harvard Medical School in Boston. He joined the MARC of Nanjing University as a Principle Investigator in December of 2011. His long-term research goal is to understand molecular mechanisms by which the γ–secretase complex regulates neuronal survival and/or death. His lab uses a combination of mouse genetics, molecular biology, cellular and behavioral neuroscience techniques to address this question. Elucidation of molecular mechanisms for age-related neurodegeneration may help identify novel therapeutic targets for the prevention and the treatment of neurodegenerative diseases.

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Molecular and cellular mechanisms for neurodevelopmental and neurodegenerative diseases

1. Molecular mechanisms by which Akt regulates oligodendrocyte differentiation.

As an important protein kinase, Akt has been implicated in diseases with white matter (WM) abnormalities. To study whether and how Akt may regulate OL development, we generated oligodendrocyte (OL) lineage cells-specific Akt1/Akt2/Akt3 triple conditional knockout (Akt cTKO) mice (Fig.1). We show that deletion of Akt three isoforms causes down-regulation of Sox10 and decreased levels of phosphorylated FoxO1 (pFoxO1) in the brain (Fig.2). In vitro analysis reveals that expression of FoxO1 with mutations on phosphorylation sites for Akt significantly represses the Sox10 promoter activity (Fig.2). Together, we have identified a novel phosphorylation-dependent mechanism for Sox10 expression and OL differentiation.

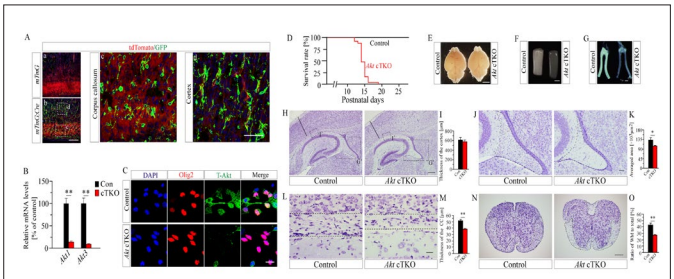


Figure 1. Deficient white matter development in Akt cTKO mice. (A-C) Characterization of Akt cTKO mice. (D) Survival rate. (E-G) Morphology of the brain, the spinal cord (SC) and the optic nerve (ON) in Akt cTKO mice. (H-O) Nissl analyses for the cortex (H), the fimbria (J), the corpus callosum (CC) (L) and the spinal cord (SC) (N).

2. Essential role of Pen-2 in governing the differentiation of oligodendrocyte precursor cells to astrocytes.

Whereas the role of γ-secretase in neurogenesis has been intensively studied, little is known about its role in astrogliogenesis. Recent evidence has demonstrated that astrocytes can be generated from OL precursor cells (OPCs). We generated OL lineage cells specific presenilin enhancer 2 (Pen-2) cKO mice (Fig.3). We show that conditional inactivation of Pen-2 in OL lineage causes enhanced generation of GFAP-expressing astrocytes (Fig.3). Mechanistic analysis reveals that deletion of Pen-2 inhibits the Notch signaling to up-regulate signal transducer and activator of transcription 3 (Stat3) (Fig.4). These findings suggest that Pen-2 may control the differentiation of OPCs to astrocytes through the Stat3 signaling.

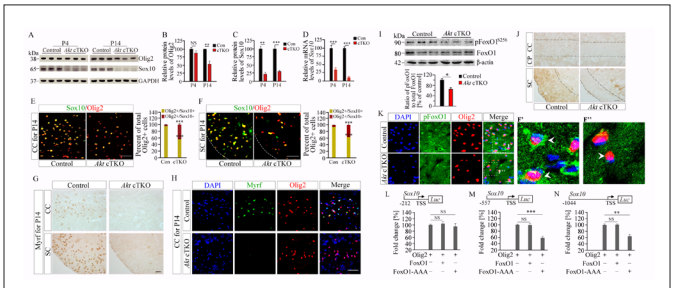


Figure 2. Down-regulation of Sox10 in Akt cTKO mice. (A-D) Decreased expression of Sox10 in Akt cTKO mice at P4 and P14. (E-F) Number of Sox10+/Olig2+ cells in the CC and the SC in Akt cTKO mice. (G,H) IHC analysis of Myrf+ cells in the CC and the SC in Akt cTKO mice at P14. (I-K) Western and IHC analyses on pFoxO1 in Akt cTKO mice. (L-M) Analysis of the promoter activity of Sox10 using cultured N2a cells.

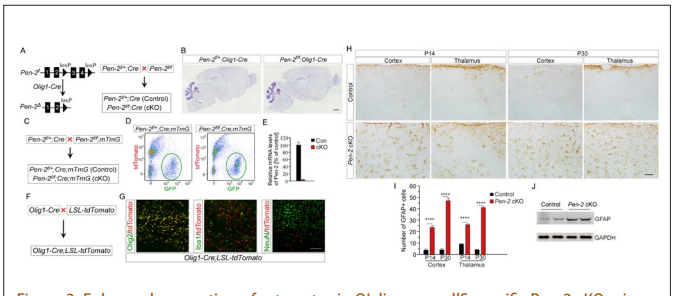


Figure 3. Enhanced generation of astrocytes in OL lineage cells specific Pen-2 cKO mice. (A-D) Characterization of OL lineage cells specific Pen-2 cKO mice. (F,G) Co-staining of Olig2/tdTomato in Olig1-Cre;LSL-tdTomato mice. (H) IHC on GFAP in Pen-2 cKO mice. (I) Number of GFAP+ cells in Pen-2 cKO mice at P14 and P30. (J) Western analysis on GFAP in Pen-2 cKO mice.

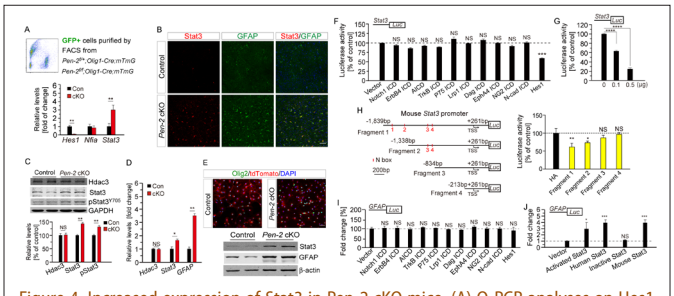
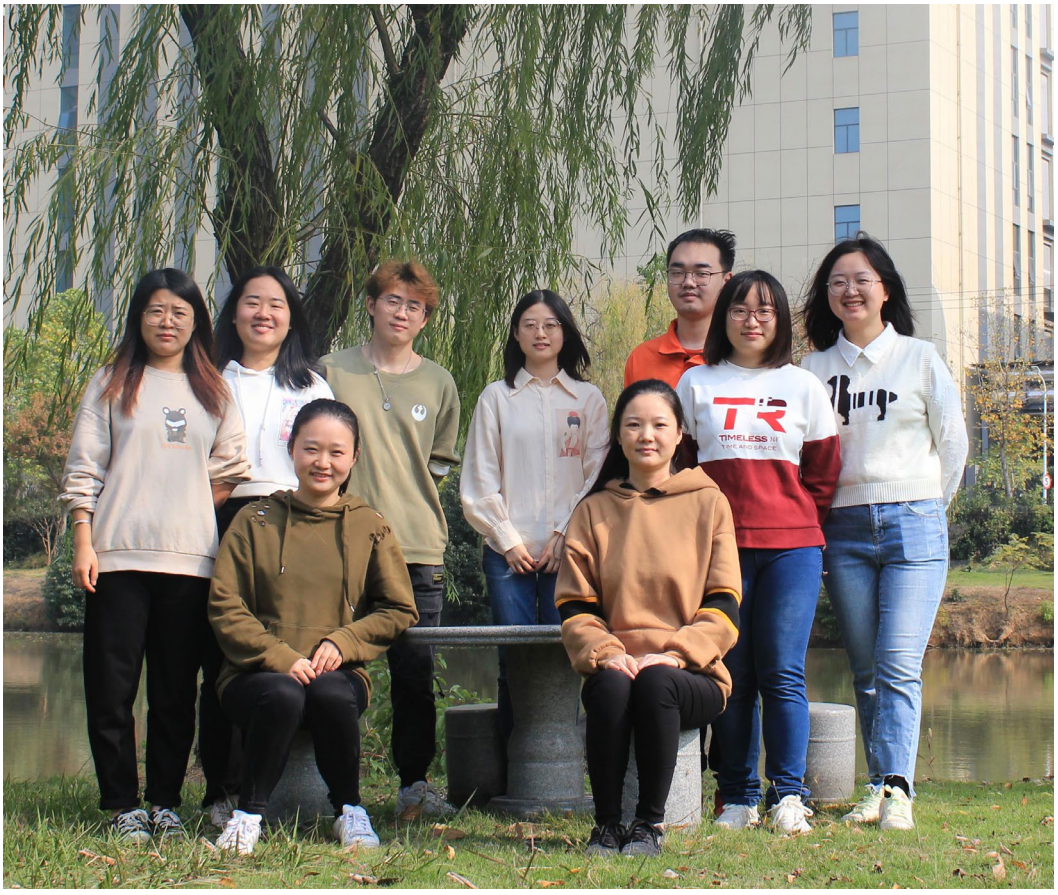


Figure 4. Increased expression of Stat3 in Pen-2 cKO mice. (A) Q-PCR analyses on Hes1, Nfia and Stat3 using Pen-2 cKO RNA samples. (B) IHC of Stat3/GFAP in Pen-2 cKO mice. (C) Western analysis on Hdac3, Stat3 and pStat3 in Pen-2 cKO mice. (D) Q-PCR analyses on Hdac3, Stat3 and GFAP mRNA levels in Pen-2 cKO mice. (E) Western analyses on Stat3 and GFAP using cultured Pen-2 cKO OPCs. (F-H) Analysis of the promoter activity of Stat3 using cultured N2a cells. (I,J) Analysis of the promoter activity of GFAP.

Recent publications (*, Corresponding author)

1. Teng XY, Hu P, Zhang CM, Zhang QX, Yang G, Zang YY, Liu ZX, Chen G* and Shi YS*. OPALIN is an LGI1 receptor promoting oligodendrocyte differentiation. Proceedings of the National Academy of Sciences of the United States of America, 2024 (121), e2403652121.
2. Chen Y, Chen J, Liang L, Dai W, Li N, Dong S, Zhan Y*, Chen G* and Yu Y*. (2024). Compound heterozygous mutations of NTNG2 cause intellectual disability via inhibition of the CaMKII signaling. Journal of Genetics and Genomics, 2024, S1673-8527(24)00198-X.
3. Dai W, Wang H, Zhan Y, Li N, Li F, Wang J, Yan H, Zhang Y, Wang J, Wu L, Liu H, Fan Y, Tao Y, Mo X, Yang J-J*, Sun K*, Chen G* and Yu Y*, CCNK gene deficiency influences neural progenitor cells via Wnt5a signaling in CCNK-related syndrome. Annals of Neurology, 2023 (94): 1136-1154.
4. Xia Y, Zhang Y, Xu M, Zou X, Gao J*, Ji M*, and Chen G*, Presenilin enhancer2 is crucial for the transition of apical progenitors into neurons but into not basal progenitors in the developing hippocampus. Development, 2022. 149: dev.200272.
5. Wang H, Liu M, Ye Z, Zhou C, Bi H, Wang L, Zhang C, Fu H, Shen Y, Yang J, Hu Y*, Chen G*. Akt regulates Sox10 expression to control oligodendrocyte differentiation via phosphorylating FoxO1. Journal of Neuroscience 2021 (41): 8163-8180.
6. Hou J, Bi H, Ye Z, Huang W, Zou G, Zou X, Shi Y, Shen Y, Ma Q, Kirchhoff F, Hu Y*, Chen G*. Pen-2 negatively regulates the differentiation of oligodendrocyte precursor cells into astrocytes in the central nervous system. Journal of Neuroscience 2021 (41):4976-4990.
7. Wang H, Liu M, Zou G, Wang L, Duan W, He X, Ji M, Zou X, Hu Y*, Yang J-J*, Chen G*. Deletion of PDK1 in oligodendrocyte lineage cells causes white matter abnormality and myelination defect in the central nervous system. Neurobiology of Disease 2021 (148): 105212.
8. Bi H, Zhou C, Zhang Y, Cai X, Ji M, Yang J, Chen G*, Hu Y*. Neuron-specific deletion of presenilin enhancer2 causes progressive astrogliosis and agerelated neurodegeneration in the cortex independent of the Notch signaling. CNS Neuroscience & Therapeutics 2021 (27): 174-185.
9. Wu J, Shao C, Ye X, Di X, Li D, Zhao H, Zhang B*, Chen G*, Liu H-K*, Qian Y* (2021) In vivo brain imaging of amyloid- β aggregates in Alzheimer's disease with a near-infrared fluorescent probe. ACS Sensors 2021 (6):863-870.
10. Ma X, Wang Y, Hua J, Xu C, Yang T, Yuan J, Chen G*, Guo Z* and Wang X*. A β -sheet-targeted theranostic agent for diagnosing and preventing aggregation of pathogenic peptides in Alzheimer's disease. Science China Chemistry 2020 (63):73-82.
11. Cheng S, Liu T, Hu Y, Xia Y, Hou J, Huang C, Zou X, Shi Y, Zheng Y, Lu J* and Chen G*. Conditional inactivation of Pen-2 in the developing neocortex leads to rapid switch of apical progenitors to basal progenitors. Journal of Neuroscience 2019 (39):2195-2207.



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Huiming Gao M.D., Ph.D.

Huiming Gao received her M.D. in 1993 and Ph.D. in 2003 from Dalian Medial University. Her Ph.D. thesis was carried out at the National Institute of Environmental Health Sciences (NIEHS)/ National Institutes of Health (NIH) in the USA. After her postdoctoral training at University of Pennsylvania School of Medicine and NIEHS/NIH, Dr. Gao joined the Faculty of Model Animal Research Center (MARC), Nanjing University in 2013. She is now a professor and a principle investigator in MARC.

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Neuroinflammation, neurodevelopment, and neurodegeneration

To investigate driving mechanisms of the decades-long neurodegeneration and disease progression of neurodegenerative diseases is important and urgent. Emerging evidence suggests that chronic neuroinflammation could play a key driving role in progressive neurodegeneration in various neurodegenerative diseases including Parkinson's disease (PD, the second most common neurodegenerative disease). However, what makes the inflammation flip from an acute and beneficial physiological response to a chronic neurodegenerative one remains largely unknown. This study investigated how anti-inflammatory cytokine interleukin-10 (IL-10) regulated the formation of chronic neuroinflammation and consequent neurodegeneration in models of PD. We found that IL-10 deficiency made microglia exhibit more profound activation of NADPH oxidase (NOX2, a major superoxide-producing enzyme complex during inflammation) and produce more intracellular reactive oxygen species (iROS) upon PAMP (pathogen-associated molecular pattern) stimulation. Meanwhile, IL-10-/- microglia displayed more profound NLRP3 inflammasome activation and more IL-1β secretion. Moreover, suppression of NOX2-derived iROS production blocked PAMP-elicited caspase-1 activation and IL-1β secretion in IL-10-/- microglia in the in vitro and in vivo model of PD. One month after an intranigral injection of lipopolysaccharide (LPS), IL-10-/- mice revealed more profound microglial activation and dopaminergic neurodegeneration in the substantia nigra than wildtype mice. Importantly, such PD-like pathological changes were prevented by IL-1β neutralization. Collectively, IL-10 inhibited PAMP-elicited production of NOX2-derived iROS thereby suppressing NLRP3 and caspase-1 activation and IL-1β secretion. By this mechanism, IL-10 prevented chronic neuroinflammation and neurodegeneration. This study suggested boosting anti-inflammatory effects of IL-10 and suppressing NLRP3 activation could be beneficial for PD treatment.

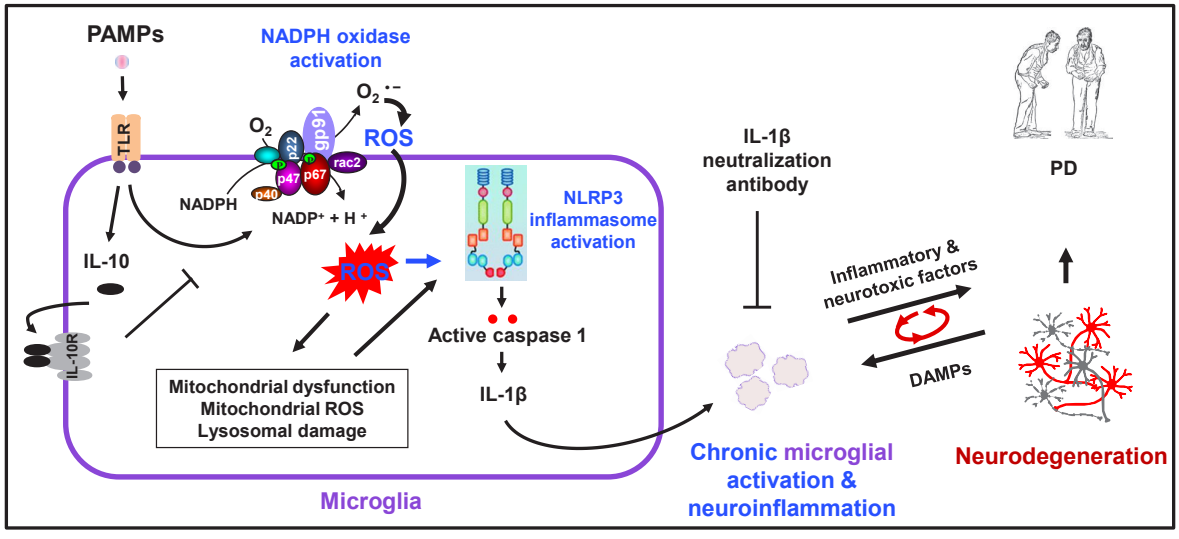

Figure. Through reducing NOX2-derived and consequent NLRP3 activation, IL-10 suppresses IL-1β secretion, thereby preventing chronic neuroinflammation and neurodegeneration

PAMPs: Pathogen-associated molecular patterns; DAMPs: damage-associated molecular patterns; O2.-: superoxide radical

Selected publications(* Corresponding author)

1. R Yang, DD Li, XX Li, XX Yang, H-M Gao, F Zhang* (2024) Dihydroquercetin alleviates dopamine neuron loss via regulating TREM2 activation. International Journal of Biological Macromolecules 269(Pt 2):132179
2. D Tu, R Velagapudi, Y Gao, J-S Hong, H Zhou* and H-M Gao* (2023) Activation of neuronal NADPH oxidase NOX2 promotes inflammatory neurodegeneration. Free Radical Biology and Medicine 200, 47-58
3. S Song*, D Tu, C Meng, J Liu, B Wilson, Q Wang, Y-Y Ian Shih*, H-M Gao*, J-S Hong (2023) Dysfunction of the noradrenergic system drives inflammation, α-synucleinopathy, and neuronal loss in mouse colon. Frontiers in Immunology 14 - DOI 10.3389/fimmu.2023.1083513
4. R Yang, Y Gao, H Li, W. Huang, D Tu, M Yang, X Liu, J-S Hong and H-M Gao* (2022) Posttranslational S-nitrosylation modification regulates HMGB1 secretion and promotes its pro-inflammatory and neurodegenerative effects. Cell Reports 40, 111330
5. Liu D, Zhao Y, Qi Y, Gao Y, Tu DZ, Wang Y, Gao H-M*, Zhou H* (2020) Benzo(a)pyrene exposure induced neuronal loss, plaque deposition, and cognitive decline in APP/PS1 mice. Journal of Neuroinflammation 17(1):258
6. Gao Y, Tu DZ, Yang R, Chu CH, Hong JS and Gao H-M* (2020) Through Reducing ROS Production, IL-10 Suppresses Caspase-1-Dependent IL-1 Maturation, thereby Preventing Chronic Neuroinflammation and Neurodegeneration. International Journal of Molecular Sciences, 21, 465
7. Tu DZ, Gao Y, Yang R, Guan T, Hong JS and Gao H-M* (2019) The pentose phosphate pathway regulates chronic neuroinflammation and dopaminergic neurodegeneration. Journal of Neuroinflammation 16:255
8. Chu CH, Wang S, Chen SH, Wang Q, Lu RB, Gao H-M*, and Hong JS (2016) Neurons and astroglia govern microglial endotoxin tolerance through macrophage colony-stimulating factor receptor-mediated ERK1/2 signals. Brain Behavior and Immunity 55: 260–272

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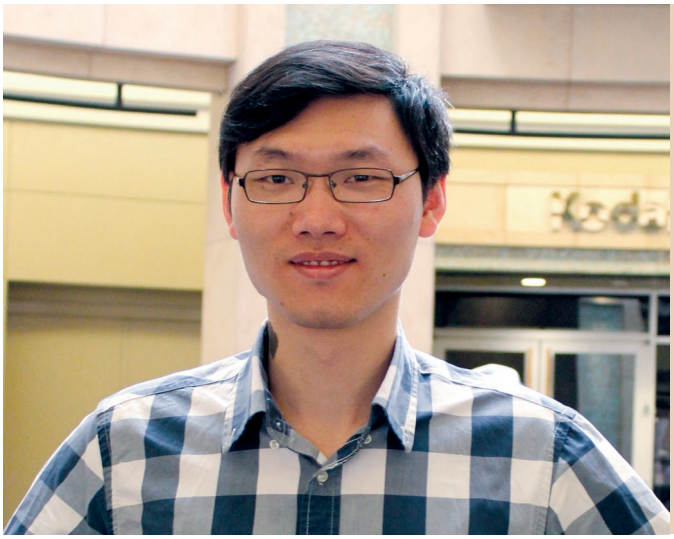

Guoqiang Wan, Ph.D.

Guoqiang Wan received both of his BSc in 2004 and PhD in 2011 from the National University of Singapore. He then had postdoctoral training with Dr Gabriel Corfas first at the Harvard Medical School/Boston Children's Hospital from 2011-2014 and then at the University of Michigan from 2014-2016. He joined MARC of Nanjing University as Principal Investigator in July 2016. Wan lab works on the genetics of hearing and deafness, development and regeneration of cochlear sensory cells and structures, as well as applications of cochlear organoid models for hearing research.

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Development and Regeneration of Auditory Sensory Cells and Structures

In China, 27.8 million people suffer from disabling hearing loss and this number increases by 300,000 every year. Sensorineural hearing loss (SNHL) accounts for 90% of all hearing loss and in most cases it cannot be medically or surgically treated. Mechanistically, SNHL results from damages to the sensory hair cells that are essential for sound detection and/or the spiral ganglion neurons (SGNs) that are required for transmitting the acoustic signals to the brain. Our lab aims to identify novel molecular targets and pathways for the development, degeneration and regeneration of cochlear sensory cells and to explore therapeutic potentials of these targets for treatment of sensorineural hearing loss (Figure 1).

We previously established a high throughput cochlear organoid platform and identified VEGFR-MEK-TGFB1 signaling pathway to promote sensory hair cell regeneration (Stem Cell Rep 2021). Employing the cochlear organoid system, detailed metabolomic characterizations of the expanding and differentiating organoids are performed. We found that hair cell differentiation is associated with increased mitochondrial electron transport chain (ETC) activity and reactive oxidative species generation, with reduced expression of oxidoreductases and tricyclic acid (TCA) cycle metabolites. The metabolic decoupling between ETC and TCA cycle limits the availability of the key metabolic cofactors, α-ketoglutarate (α-KG) and nicotinamide adenine dinucleotide (NAD+). Supplementation of α-KG and NAD+ promotes hair cell reprogramming both in vitro and in vivo. These findings reveal metabolic rewiring as a central cellular process during hair cell differentiation, and highlight the insufficiency of key metabolites as a metabolic barrier for efficient hair cell reprogramming (Figure 2).

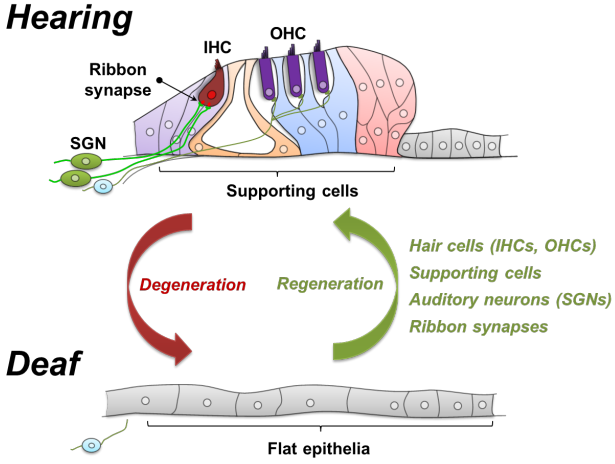

Figure 1. Research overview. In mammalian cochlea, sensory hair cells (IHC and OHC), neurons (SGN), supporting cells and the auditory ribbon synapses are required for normal hearing, damage of these cells and synapses results in deafness.

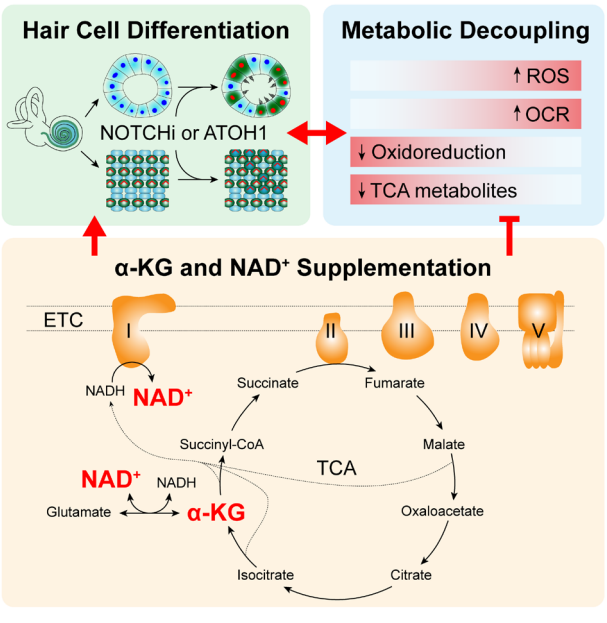

Figure 2. Metabolic decoupling impairing hair cell differentiation that can be remediated by supplementation of α-KG and NAD+.

Selected publications(* Corresponding author)

1. Huang, Y.*, Chen, Z.*, Chen, J.*, Liu, J.*, Qiu, C., Liu, Q., Zhang, L., Zhu, G.J., Ma, X.#, Sun, S.#, Shi, Y.S.#, Wan, G.# (2024). Direct reprogramming of fibroblasts into spiral ganglion neurons by defined transcription factors. Cell Proliferation, e13775.
2. Qiu, C.*, Zhang, L.*, Yong, C., Hu, R., Sun, Y., Wang, B., Fang, L., Zhu, G.J., Lu, Q., Wang, J.#, Ma, X.#, Zhang, L.#, Wan, G.# (2024). Stub1 promotes degradation of the activated Diaph3: A negative feedback regulatory mechanism of the actin nucleator. Journal of Biological Chemistry, 300(10):107813.
3. Huang, Y., Zhang, L., Sun, Y., Liu, Q., Chen, J., Qian, X., Gao, X.#, Zhu, G.J.#, Wan, G.# (2024). A human-specific cytotoxic neopeptide generated by the deafness gene Cingulin. Journal of Genetics and Genomics, 51(11):1215-1227.
4. Liu, Q.*, Zhang, L.*, Chen, Z., He, Y., Huang, Y., Qiu, C., Zhu, C., Zhou, D., Gan, Z.#, Gao, X.#, Wan, G.# (2024). Metabolic Profiling of Cochlear Organoids Identifies α-Ketoglutarate and NAD+ as Limiting Factors for Hair Cell Reprogramming. Advanced Science, e2308032.
5. Ye, C., Zhang, T.Z., Zang, Y.Y., Shi, Y.S.#, and Wan, G.# (2024). TMEM63B regulates postnatal development of cochlear sensory epithelia via thyroid hormone signaling. Journal of Genetics and Genomics, 51(6):673-676.
6. Zhu, G.J.*, Huang, Y.*, Zhang, L.*, Yan, K.*, Qiu, C., He, Y., Liu, Q., Zhu, C., Morín, M., Moreno-Pelayo, M.Á., Zhu, M.S., Cao, X., Zhou, H., Qian, X., Xu, Z.#, Chen, J.#, Gao, X.#, Wan, G.# (2023). Cingulin regulates hair cell cuticular plate morphology and is required for hearing in human and mouse. EMBO Molecular Medicine, e17611.
7. Liu, Q., Zhang, L., Zhu, M.S., and Wan, G. (2021). High-throughput screening on cochlear organoids identifies VEGFR-MEK-TGFB1 signaling promoting hair cell reprogramming. Stem Cell Reports, 16:2257-2273.
8. Zhu, G.J.*, Gong, S.*, Ma, D.B.*, Tao, T.*, He, W.Q.*, Zhang, L., Wang, F., Qian, X.Y., Zhou, H., Fan, C., Wang, P., Chen, X., Zhao, W., Sun, J., Chen, H., Wang, Y., Gao, X., Zuo, J., Zhu, M.S.#, Gao, X.#, Wan, G.# (2020). Aldh inhibitor restores auditory function in a mouse model of human deafness. PLOS Genetics, 16(9):e1009040.
9. Du, H.*, Ye, C.*, Wu, D.*, Zang, Y.Y., Zhang, L., Chen, C., He, X.Y., Yang, J.J., Hu, P., Xu, Z., Wan, G.# and Shi, Y.S.# (2020). The cation channel TMEM63B is an osmosensor required for hearing. Cell Reports, 31(5):107596.

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Chenxuan Yong (PhD student)
Dr. Guoqiang Wan (PI)
Sihao Gong (PhD student, holding her son)
Wenya Fan (PhD student)
Yuanning Guo (Graduate student)
Xinyu Wang (Graduate student)
Shu Wang (Graduate student)
Yuxi Diao (PhD student)
Cui Qiu (PhD student, not in the picture)


Organogenesis

Jiong Chen Ph.D.

Jiong Chen received his Bachelor in Biochemistry (1995) and his Ph.D. in Molecular, Cell and Developmental Biology (2002), both from University of California, Los Angeles (UCLA). His Ph.D. thesis was carried out in Frank Laski's lab and it was focused on the genetics and developmental studies of cell movement processes in the Drosophila ovary. From 2002 to 2004, Jiong did his postdoctoral research in Drosophila eye development under the guidance of Utpal Banerjee at UCLA, and it was combined with an undergraduate teaching experience that was funded by a HHMI teaching/research grant. He joined the Faculty of Model Animal Research Center (MARC), Nanjing University full time early 2005. He is now a professor of genetics and developmental biology and a principal investigator in MARC.

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Understanding the driving forces underlying collective cell Migration

Cells do not always migrate individually; they often migrate collectively as a cluster, a sheet, or a strand under physiological, developmental and cancer metastatic conditions. Collective cell migration has recently received much attention from cell and developmental biologists, and it has emerged as an important field of study with many characteristics distinct from those of single cell migration. As a new field, collective migration still has many fundamental questions unresolved. For example, what intrinsic factors or signals pre-determine the migratory fate of a group of cells that will later collectively detach and migrate away from the host tissue (likened to a group of runners pre-selected from a larger group of candidate runners)(Figure 1)? How can the group of cells communicate with each other and collectively know the front vs. back, top vs. bottom and inside vs. outside during migration (Figures 2 and 3)? Finally, what powers the group to migrate collectively (Figure 3)?

A recent and primary focus of my lab has been to address these key questions. We utilize the border cells in Drosophila ovary to study collective migration during development, and they are genetically tractable and amenable to live imaging and optogenetic manipulation.

Cell growth regulates fate determination of border cells. Recently, my lab found that the fate determination of border cells was negatively regulated by the growth-promoting InR/Akt/TORC1 signaling pathway (Fig 1; Kang et al., Dev Cell, 2018). During development, cell growth and cell differentiation are two distinct yet coupled fundamental processes to give rise to tissues or organs. However, the mechanisms underlying the coordination or coupling between cell growth and cell differentiation are largely unknown. Our novel finding suggests that specification and differentiation of migratory cells is negatively coupled to cell growth during development.

Control of front-back polarity. It is known that the chemotactic migration of border cells is guided by the guidance receptor PVR, in response to extracellular signals secreted from oocyte. But, how guidance signaling sets up the front-back polarity of the entire border cell cluster is not well understood. We've made an interesting discovery that the guidance receptor PVR mediates the asymmetric distribution of exocyst and recycling endosome to set up the front-back polarity. (Wan et al., Development, 2013). Furthermore, we find that molecules crucial in apical-basal polarity, including aPKC and Crumbs complex, are required for the establishment of front-back polarity (Fig 3; Wang et al., Development, 2018). In addition, we find interesting coordination among the front-back, apical-basal and inside-outside polarities within the border cell cluster.

Power control of collective migration. We found that the actin depolymerizing factor Cofilin is required for the formation of actin-based lamellipodia, whose protrusion and adhesion provide force for migration of border cells (Zhang et al., Development, 2011). Moreover, Cofilin localization and phosphorylation are regulated by guidance receptor (PVR) signaling in such a way that active and unphosphorylated Cofilin are enriched in the leading border cell, resulting in the predominant protrusion forming only at the front of border cell cluster.

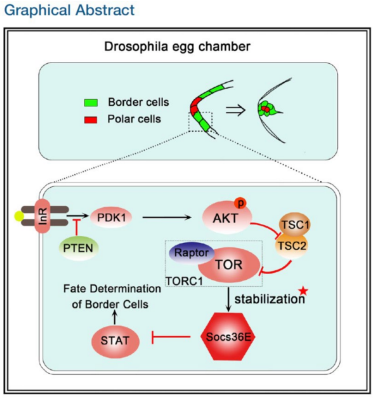

Figure 1. The growth promoting InR/Akt/TORC1 pathway attenuates migratory cell fate of border cells by down-regulation of JAK/STAT and destabilization of Socs36E. (from Kang et al., 2018)

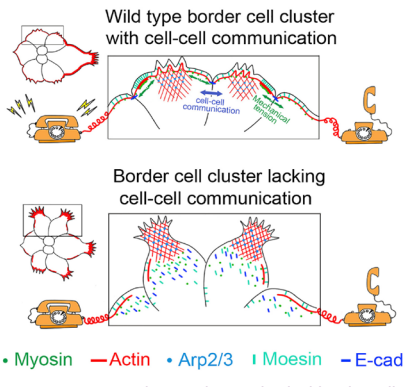

Figure 2. Diagram showing how individual border cells communicate with each other via supracellular actin-myosin network. Disruption of the supracellular network results in lack of cell-cell communication and defects in collective cell migration (from Wang H. et al., 2020)

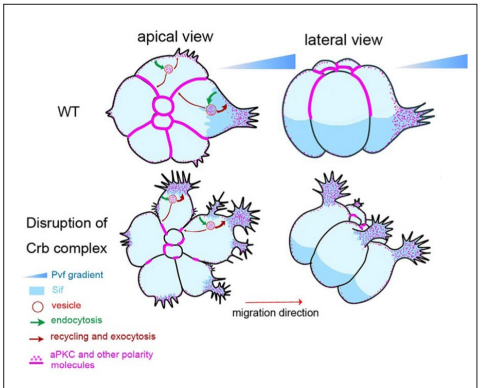

Figure 3. Diagram showing WT and Crb complex-deficient border cells in apical and lateral views. The model proposes how the two pools of aPKC and three distinct cell polarities are established by the Crb and Par complexes and endocytic recycling machinery. (from Wang et al., 2018)

Selected Publications

1. Wang, H. and Chen, J.* Cell migration: Collective cell migration is intrinsically stressful. Current Biology, 34(7): R275-R278 (2024)
2. Qu, C., Kan, Y., Wu, M., Dong, Z., Wang, X., Zhang, Q., Wang, H., Wang, D. and Chen, J. * Actin polymerization induces mitochondrial distribution during collective cell migration. Journal of Genetics and Genomics (2023)
3. Qu, C., Yang, W., Kan, Y., Zuo, H., Wu, M., Zhang, Q., Wang, H., Wang, D. and Chen, J. * RhoA/ROCK Signaling Regulates Drp1-Mediated Mitochondrial Fission During Collective Cell Migration. Frontiers in Cell and Developmental Biology (2022)
4. Wang, X., Wang, H. *, Liu, L., Li, S., Emery, G. and Chen, J. * Temporal coordination of collective migration and lumen formation by antagonism between two nuclear receptors. Iscience (2020)
5. Wang, H. *, Guo, X., Wang, X., Wang, X. and Chen, J. * Supracellular actomyosin mediates cell-cell communication and shapes collective migratory morphology. Iscience (2020)
6. Guo, X., Luo, J., Wang, H.*, and Chen, J*. SERCA regulates collective cell migration by maintaining cytoplasmic Ca2+ homeostasis, Journal of Genetics and Genomics (2019)
7. Wang, H., Qiu, Z., Xu, Z., Chen, S., Luo, J., Wang, X.*and Jiong Chen*. aPKC is a key polarity molecule coordinating the function of three distinct cell polarities during collective migration, Development (2018)
8. Kang, D., Wang, D., Xu, J., Quan, C., Guo1, X., Wang, H., Luo, J., Yang, Z., Chen, S.*, Chen, J.*. The InR/Akt/TORC1 growth-promoting signaling negatively regulates JAK/STAT activity and migratory cell fate during morphogenesis, Developmental Cell (2018)
9. Wan, P., Wang, D., Luo, J., Chu, D., Wang, H., Zhang, L., and Chen, J.* Guidance receptor promotes asymmetric distribution of Exocyst and recycling endosome during collective cell migration Development (2013).
10. Zhang, L., Luo, J., Wan, P., Wu, J., Laski, F. and Chen, J.* Regulation of cofilin phosphorylation and asymmetry in collective cell migration during morphogenesis. Development 138, 455-64. (2011)

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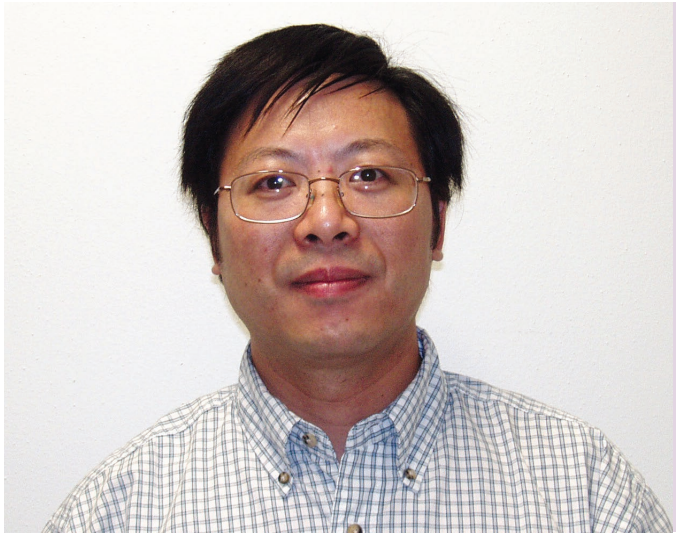

Qing Zhang, Ph.D

Qing Zhang received his Ph.D in Microbiology from Fudan University in 2002. Afterwards, he had had his postdoctoral training in Department of Developmental Biology of UT Southwestern Medical Center at Dallas for six years. In 2009, he joined the Model Animal Research Center of Nanjing University as a professor and principle investigator.

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Regulation of mitochondrial homeostasis

mtDNA extramitochondrial replication mediates mitochondrial defect effects

A high ratio of severe mitochondrial defects causes multiple human mitochondrial diseases. However, until now, the in vivo rescue signal of such mitochondrial defect effects has not been clear. Here, we built fly mitochondrial defect models by knocking down the essential mitochondrial genes dMterf4 and dMrps23. Following genome-wide RNAi screens, we found that knockdown of Med8/Tfb4/mtSSB/PolG2/mtDNA-helicase rescued dMterf4/dMrps23 RNAi-mediated mitochondrial defect effects. Extremely surprisingly, they drove mtDNA replication outside mitochondria through the Med8/Tfb4-mtSSB/PolG2/mtDNA-helicase axis to amplify cytosolic mtDNA, leading to activation of the cGAS-Sting-like IMD pathway to partially mediate dMterf4/dMrps23 RNAi-triggered effects. Moreover, we found that the Med8/Tfb4-mtSSB/PolG2/mtDNA-helicase axis also mediated other fly mitochondrial gene defect-triggered dysfunctions and Drosophila aging. Overall, our study demarcates the Med8/Tfb4-mtSSB/PolG2/mtDNA-helicase axis as a candidate mechanism to mediate mitochondrial defect effects through driving mtDNA extramitochondrial replication; dysfunction of this axis might be used for potential treatments for many mitochondrial and age-related diseases.

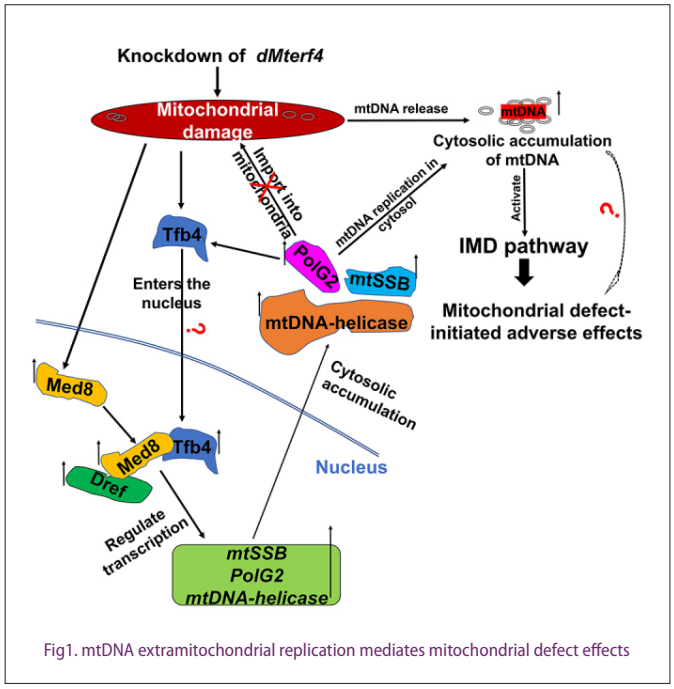

Fig1. mtDNA extramitochondrial replication mediates mitochondrial defect effects

Highlights

- Med8/Tfb4-mtSSB/PolG2/mtDNA-helicase axis mediates mitochondrial defect effects
- The above axis drives mtDNA extramitochondrial replication
- Cytosolic mtDNA replication triggers innate immune response to mediate the effects
- Med8/Tfb4-mtSSB/PolG2/mtDNA-helicase axis also modulates Drosophila lifespan

Selected publications (*Correspondence author)

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7. Liu C, Zhou Z, Chen P, Su MY, Chang CJ, Yan J, Jiang J*, Zhang Q*. Hedgehog signaling downregulates Suppressor of Fused through the HIB/SPOP-Crn axis in Drosophila. Cell Research. 2014; 24,595-609.
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11. Jia J#, Zhang L#, Zhang Q#, Tong C, Wang B, Hou F, Amanai K, Jiang J. Phosphorylation of Cubitus interruptus by Double-time/CKIe and CKIa targets it for Slimb/b-TRCP mediated proteolytic processing. Dev Cell. 2005; 9, 819-830.

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Ying Cao, Ph.D.

Cao Ying made the PhD study at the University of Essen (now University of Duisburg-Essen), Germany, from 1998 to 2002. During the period he studied developmental biology and made a research on embryonic development using an amphibian species (Xenopus leavis) as a model organism. He received the degree Dr. rer. nat. and graduated summa cum laude in 2002. Afterwards during the years from 2002 to 2008 he joined the Institute of Biochemistry, Ulm University, Germany, and continued the study on developmental biology. In October 2008, he set up the laboratory in MARC for developmental biology and cancer biology. The results in his group elucidated systemic rules that are critical for understanding cancer, a complex systemic disease. The rules are: 1) The core property of cancer (tumorigenic) cells is neural stemness, which is the general stemness; 2) Evolutionarily predetermined advantage of neural stemness determines and unifies pluripotent differentiation potential and tumorigenicity; 3) Pluripotency and tumorigenicity are both but different manifestations of the general stemness, represented by neural stemness, during embryonic and postnatal stages of animal life, respectively; 4) Tumorigenesis represents a process of progressive loss of original cell identity and gain of neural stemness; 5) Tumorigenicity is by nature the manifestation of aberrant occurrence of pluripotent state or neural stemness in a postnatal animal/human; 6) Neural induction drives body axis formation during embryogenesis (and ectopic neural induction causes a conjoined twin), whereas a neural induction-like process drives tumorigenesis in postnatal animals/human. Moreover, he also elucidated that epithelial-mesenchymal transition (EMT) and its related concepts are groundless and scientifically meaningless.

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Unification of embryogenesis and tumorigenesis

Anatomy of epithelial-mesenchymal transition (EMT) and its related concepts revealed that they are poorly defined irrational 'concepts' and scientifically meaningless.

EMT and its related concepts, mesenchymal-epithelial transition (MET) and endothelial-mesenchymal transition (EndMT), have been investigated for more than 50 years and become 'mainstream concepts' in biomedical sciences with more than 50,000 papers published. However, after >50 years of research, what has been clear about these concepts? Almost nothing, not even a hint of rationale in these concepts. The points:

First, epithelial and mesenchymal cells being classified as two cell types is not appropriate. Epithelial and mesenchymal cells are defined according to their shapes and adhesiveness only, and both include many different cell types from embryonic stage to adulthood. It is difficult to generalize their cell state/property from the heterogeneity in epithelial and mesenchymal cells, and find suitable markers or the core regulatory networks to distinguish these cells from other cell types ambiguously. Second, cells are generally labeled as epithelial and mesenchymal from embryos to adults, and then EMT/MET are considered as a universal dogma dictating development and pathology. This is a circular, self-fulfilling argument. Third, no evidence confirms that EMT and MET could function as driving forces to promote embryogenesis and tumorigenesis. By contrast, the change in cell shape and adhesiveness should be the consequence rather than the cause of developmental process and cancer progression. Fourth, EMT is interpreted as a transition from stationary to migratory state. However, there is no clear-cut distinction in the migratory feature of epithelial and mesenchymal cells. Fifth, cells of a particular type exhibit features like shape, adhesiveness, mobility, and physiological functions. They are coupled together and defined by cell type-specific regulatory networks. Therefore, interpretation of change in cell property or state solely by the change in shape and adhesiveness is a sheer bias. Sixth, EMT cannot be described in a molecular way because of lack of reliable and universal EMT markers or factors.

It is time to face the contradictions and irrationality in EMT and its related concepts, reassess their value as general rules dictating developmental biology and pathology as shown in literatures, and reassess their value as research subjects.

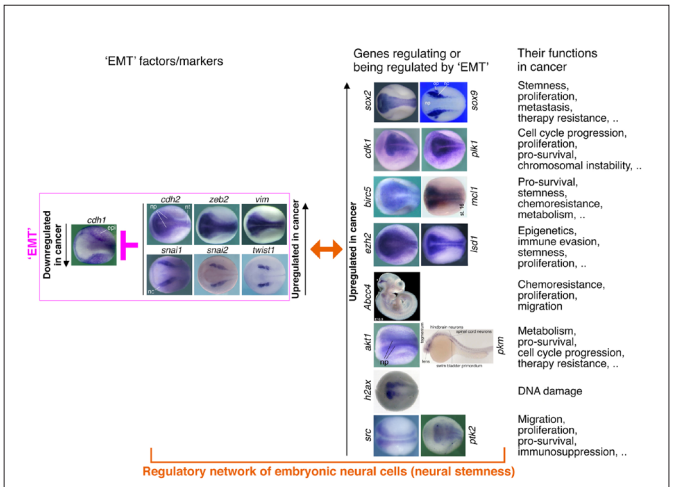

Figure 1. Localized embryonic expression of 'EMT' factors/markers and the genes regulating or being regulated by 'EMT' in cancer reveals that they are components of the regulatory networks of embryonic neural cells, suggesting the key role of neural stemness rather than the unknown mesenchymal state in the determination of different features of cancer cells. This means EMT misattributes the role of neural stemness to mesenchymal state when interpreting the properties of cancer cells, and misattributes the intrinsic property of neural crest cells to mesenchymal state when interpreting neural crest cell migratory property.

Selected publications (*Correspondence author)

1. Cao Y. Lack of basic rationale in epithelial-mesenchymal transition and its related concepts. Cell Biosci. 2024 Aug 20;14(1):104.
2. Cao Y*. Neural induction drives body axis formation during embryogenesis, but a neural induction-like process drives tumorigenesis in postnatal animals. Front Cell Dev Biol. 2023 May 9;11:1092667.
3. Zhang M, Liu Y, Shi L, Fang L, Xu L, Cao Y*. Neural stemness unifies cell tumorigenicity and pluripotent differentiation potential. J Biol Chem. 2022 Jul;298(7):102106.
4. Cao Y*. Neural is Fundamental: Neural Stemness as the Ground State of Cell Tumorigenicity and Differentiation Potential. Stem Cell Rev Rep. 2022 Jan;18(1):37-55.
5. Chen L, Zhang M, Fang L, Yang X, Cao N, Xu L, Shi L, Cao Y*. Coordinated regulation of the ribosome and proteasome by PRMT1 in the maintenance of neural stemness in cancer cells and neural stem cells. J Biol Chem. 2021 Oct 4;297(5):101275.
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9. Zhang Z, Lei A, Xu L, Chen L, Chen Y, Zhang X, Gao Y, Yang X, Zhang M, Cao Y*. 2017. Similarity in gene-regulatory networks suggests that cancer cells share characteristics of embryonic neural cells. J Biol Chem. 292(31):12842-12859.
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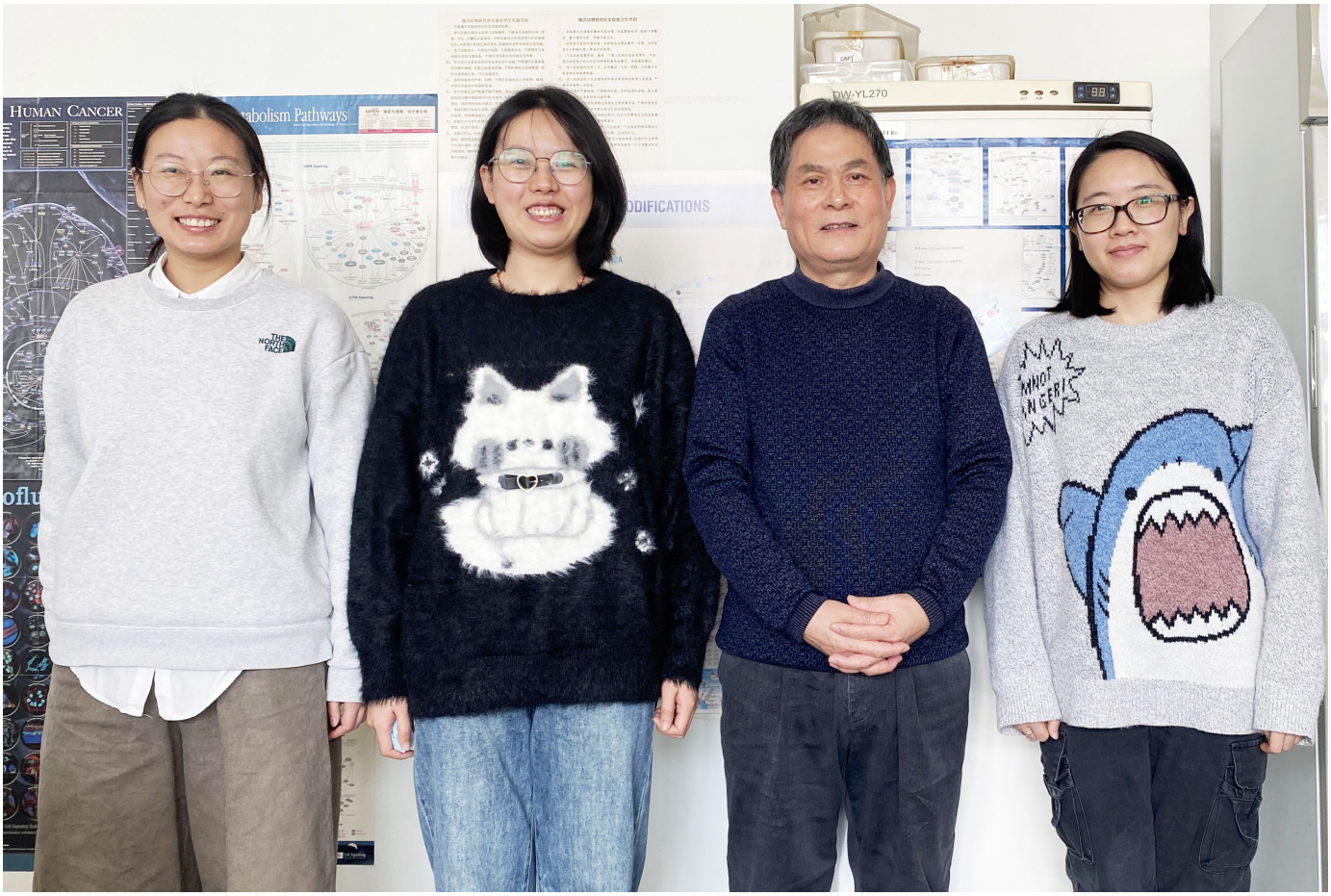

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Qingshun Zhao, Ph.D

Qingshun obtained his B.S. degree in 1987 and M.S. degree in 1990 from Nanjing University (Nanjing, Jiangsu, China), and received his Ph.D. degree in 2001 from Purdue University (West Lafayette, Indiana, USA). His Ph.D. dissertation was carried out in Dr. Paul Collodi's Lab and it was focused on identification and characterization of fibronectin isoforms during zebrafish development. From 2001 to 2003, Qingshun did his postdoctoral research on roles of retinoid signaling in zebrafish hindbrain development under the guidance of Dr. Elwood Linney in Duke University Medical Center (Durham, North Carolina, USA). In 2003, he became an associate professor and a principal investigator in Model Animal Research Center, Nanjing University. In 2006, Qingshun was promoted full professor of Nanjing University.

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Zebrafish development

The research interests of the lab focus on investigating the molecular mechanism underlying vertebrate early development using zebrafish as a model animal.

RA (retinoic acid) plays essential roles in vertebrate embryogenesis. Its homeostasis in embryos is determined by the presence of Aldh1A that produces RA and Cyp26 that metabolizes RA into bio-inactive metabolites. Unlike mammals, zebrafish only have aldh1a2, aldh1a3 and aldh8a1 but not aldh1a1. Because both aldh1a3 and aldh8a1 are expressed in late organogenesis, aldh1a2 is the gene that is responsible for RA synthesis in zebrafish early development (Liang et al, 2008). Like mammals, zebrafish possesses a third cyp26 gene (cyp26c1) (Gu et al., 2005) in addition to cyp26a1 and cyp26b1. The Cyp26c1 metabolizes RA but not retinol or retinal in a similar way to Cyp26a1, the major gene that is responsible for RA metabolism in zebrafish early development (Gu et al., 2006). Like cyp26a1, proper expression of cyp26c1 at early developmental stage is essential for the development of anterior–posterior axis and left–right symmetry in zebrafish embryos (Gu et al., 2005; Gu et al., 2006). Analyzing the promoter of cyp26a1, we reveal that zebrafish cyp26a1 possesses three conserved RAREs in response to RA signal and therefore maintains RA homeostasis in a feedback way (Hu et al., 2008; Li et al., 2012). Other than Cyp26s that can limit RA signaling, Ncor1 (nuclear receptor co-repressor) is essential for patterning the anterior–posterior axis of zebrafish hindbrain by actively repressing RA signaling (Xu et al., 2009). Consistent with these results, znfl1 whose expressions are in response to RA signaling, mediate the roles of RA in patterning zebrafish posterior neuroectoderm by acting upstream of pou5f3 and sall4 (Dong et al., 2017). Additionally, Znfl1s regulate left-right asymmetry patterning through controlling the expression of fgfr1a (Li et al., 2019).

RA signaling is also essential to vertebrate mesoderm differentiation. It plays a restrictive role in primitive myelopoiesis by inhibiting the specification of ventral mesoderm cells into anterior hemangioblasts through acting downstream of gata4/5/6 and upstream to scl in a dose dependent manner (Liang et al., 2012). Furthermore, zebrafish microRNA miR-210-5p inhibits primitive myelopoiesis by silencing foxj1b and slc3a2a mRNAs downstream of gata4/5/6 transcription factor genes (Figure 1; Jia et al., 2019). Moreover, RA is also essential for valvulogenesis by affecting endocardial cushions formation in zebrafish embryos (Li et al., 2016). Additionally, Ncor1 and Ncor2 play essential but distinct roles in zebrafish primitive myelopoiesis (Li et al., 2014). On the other hand, the differentiation of ventral mesoderm is affected by environmental factors, excessive sodium nitrite affects zebrafish valve leaflet formation by producing too much NO signaling (Li et al., 2014).

RA signaling is genetically controlled by upstream genes. Foxc1a is a member of the forkhead transcription factors. By generating foxc1a knockout zebrafish using TALEN (transcription activator-like effector nuclease) technology, we demonstrate that foxc1a is essential for somitogenesis by controlling Fgf and Notch signaling through restricting the expression of aldh1a2 in zebrafish paraxial mesoderm directly (Li et al., 2015) and plays essential roles in zebrafish cardiogenesis by directly activating the expression of nkx2.5, encoding a transcriptional regulator of cardiac progenitor cells (Yue et al., 2018), and directly inhibiting the expression of aldh1a2 in foxc1a-expressing cells (Gu et al., Unpublished data). In human cells, we demonstrate that FOXC1 does regulate human NKX2-5 expression in a dose-dependent manner via direct binding to its proximal promoter. A comparison of FOXC1 mutant function in the rat cardiac cell line H9c2 and zebrafish embryos suggested that the zebrafish embryos might serve as a more representative model system than the H9c2 cells. Three of the Axenfeld-Rieger syndrome FOXC1 mutations tested increased whereas a fourth repressed the expression of NKX2-5 implying that mutant FOXC1s might play etiological roles in CHD by abnormally regulating NKX2-5 in the patients. To sum up, zebrafish embryos can serve as a useful in vivo platform for rapidly evaluating disease-causing roles of mutated genes (Zhang et al., 2020).

Engineered endonuclease including ZFN, TALEN and CRISPR/Cas9 are powerful tools to create genome edited animals without species limitation. Employing ZFN and TALEN, we produced heritable targeted inactivation of myostatin genes in yellow catfish, the first endogenous gene knockout in aquaculture fish (Dong et al., 2011, Dong et al., 2014), and the mstna null yellow catfish exhibit double muscle phenotype with muscle hyperplasia (Zhang et al., 2019). By co-microinjecting yfp-nanos3 mRNA with genome editing tools to make founders and then screen them with the help of tentatively fluorescent-labeled PGCs, we invent a new method that significantly increases the ease and speed of generating heritable knockin animals with CRISPR/Cas9 (Dong et al., 2014). Using this method, we develop "two-step strategy" to generate an aldh1a2 floxed zebrafish line (aldh1a2flox/flox) by first inserting mloxP sites into its 3rd intron and then into its 4th intron. With the systemic expression of Cre in the eggs of aldh1a2flox/flox zebrafish, we obtained an aldh1a2 conventional knockout zebrafish line (aldh1a2+/-) (Gu et al., Unpublished data). Interestingly, the embryos whose primordial germ cells are eliminated at early development grow up as all-male-like sterile zebrafish (Zhou et al., 2018). Collaborating with the groups of Professors Zhou and Zhu, we developed an alternative novel tool for DNA editing (SGN: structure-guided nuclease) without target sequence limitation (Xu et al., 2016). Unfortunately, our further efforts do not support that the system works in human colorectal carcinoma cell line (HCT116), nor in producing any germline transmission zebrafish mutants (Zhang et al., Unpublished data)

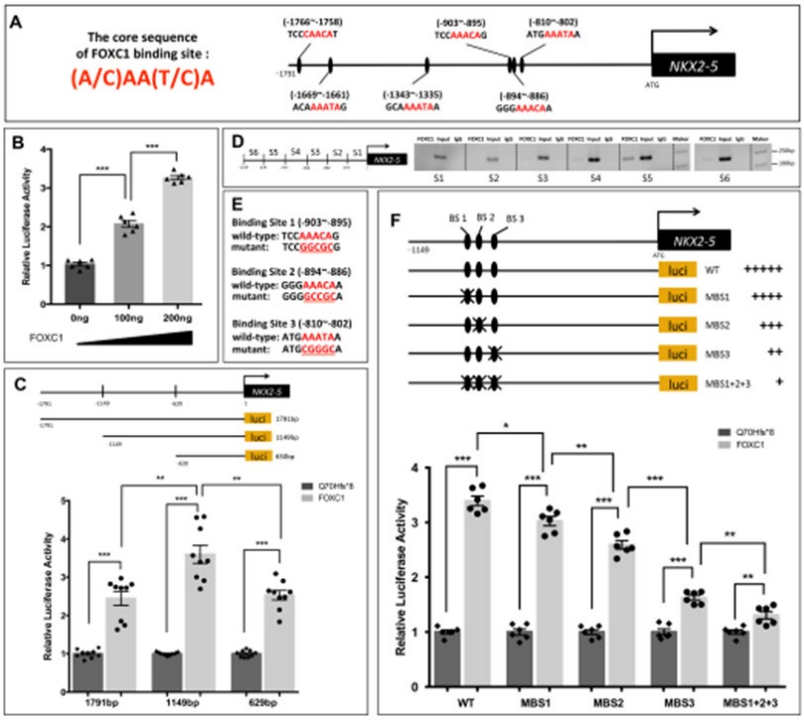

Figure 1. FOXC1 directly regulates the expression of NKX2-5 by binding to its proximal promoter in H9c2 cells.

A, Schematic showing putative FOXC1 transcription factor binding sites in 1791 bp 5′-flanking sequence upstream of NKX2-5 translation start site (ATG). B, Results of Dual-Luciferase Reporter Assay showing the responses of NKX2-5 promoter to different doses of FOXC1. C, Schematic (top) showing the firefly luciferase reporter expression constructs comprising the different lengths of upstream regulatory sequence ofNKX2-5, namely 1791 bp, 1149 bp or 630 bp, and the coding sequences of NKX2-5 or firefly luciferase, and the results (below) of Dual-Luciferase Reporter Assay on the three expression constructs. D, Schematic (left) showing the dissection of the 1149 bp regulatory sequences ofNKX2-5 into S1-S6 regions and the results of ChIP-PCR assay (right) indicating that S5contains FOXC1-binding sites. E, The wild-type sequences and location of FOXC1-binding sites (BS) in S5 of NKX2-5 regulatory sequence (top), and the mutant FOXC1 binding sites (MBS) with changed core sequence. F, Schematic (top) showing the reporter expression constructs carrying wild-type BS or MBS of FOXC1, and the results (below) of Dual-Luciferase Reporter Assay on the five expression constructs. X-axis (B, C, F): The amount of overexpressed FOXC1 (B), the reporter expression constructs with different lengths of regulatory sequences (C), or the reporter expression constructs carrying wild-type BS or MBS of FOXC1 (F). Light grey columns (C, F): transfected with wild-type FOXC1;Dark grey columns (C, F): transfected with the same amount of functional null mutated FOXC1(p.Q70Hfs*8) as control. Y-axis (B, C, F): Relative activity of firefly luciferase reporter.

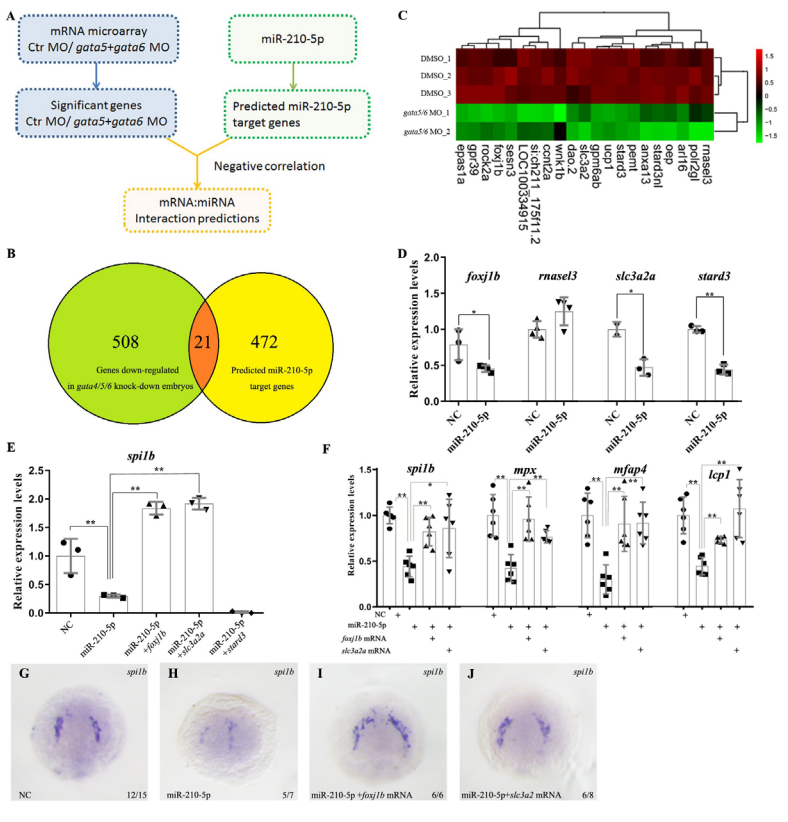

Figure 2. Both foxj1b and slc3a2a work downstream of miR-210-5p to mediate its role in inhibiting zebrafish primitive myelopoiesis.

(A) Schematic showing the workflow to screen the candidate downstream genes of miR-210-5p to mediate its role in inhibiting zebrafish primitive myelopoiesis. (B) Venn map showing the candidate target genes of miR-210-5p to mediate its roles in inhibiting zebrafish primitive myelopoiesis. (C) Heat map showing the clustering analysis of 21 candidate genes working downstream of miR-210-5p to inhibit the primitive myelopoiesis. (D) qRT-PCR results showing the expression changes of candidate target genes in the miR-210-5p overexpressed embryos at 14 hpf. (E) Overexpressions of foxj1b and slc3a2a but not stard3 effectively rescued the expression of spi1b that was inhibited in the 14 hpf embryos overexpressed with miR-210-5p. (F) Overexpressions of foxj1b and slc3a2a effectively rescued the expressions of spi1b, mpx, mfap4 and lcp1 in the zebrafish embryos at 14 hpf and 26 hpf, respectively. (G-J) Whole mount in situ hybridization results showing the expressions of spi1b in the 14 hpf embryos microinjected with NC, miR-210-5p mimic alone or miR-210-5p mimic together with foxj1b or slc3a2a mRNA, respectively.

Selected Publications (*corresponding author;**co-corresponding author)

1. Li N, Jiang D, He L, Yue Y, Zhang Q, Wang S, Zhang Y, Wei Y, Zhao Q. Both prokaryotes and eukaryotes produce an immune response against plasmids with 5'-GTTTGTT-3'. Cell Biosci. 2022 Jun 11;12(1):87. doi: 10.1186/s13578-022-00825-3. PMID: 35690839; PMCID: PMC9188160.
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3. Qinxin Zhang, Dong Liang, Yunyun Yue, Luqingqing He, Nan Li, Dongya Jiang, Ping Hu, Qingshun Zhao*. 2020. Axenfeld-Rieger syndrome-associated mutants of the transcription factor FOXC1 abnormally regulate NKX2-5 in model zebrafish embryos. The Journal of Biological Chemistry, 295(33):11902-11913.
4. Wenshuang Jia, Dong Liang; Nan Li, Meijing Liu, Zhangji Dong, Jingyun Li, Xiaohua Dong, Yunyun Yue, Ping Hu, Jihua Yao, Qingshun Zhao*. 2019. Zebrafish microRNA miR-210-5p inhibits primitive myelopoiesis by silencing foxj1b and slc3a2a mRNAs downstream of gata4/5/6 transcription factor genes. The Journal of Biological Chemistry, 294(8):2732-2743.
5. Yunyun Yue, Mingyang Jiang, Luqingqing He, Zhaojunjie Zhang, Qinxin Zhang, Chun Gu, Meijing Liu, Nan Li, Qingshun Zhao*. 2018. The transcription factor Foxc1a in zebrafish directly regulates expression of nkx2.5, encoding a transcriptional regulator of cardiac progenitor cells. The Journal of Biological Chemistry, 293(2):638-650.
6. Xiaohua Dong, Jingyun Li, Luqingqing He, Chun Gu, Wenshuang Jia, Yunyun Yue, Jun Li, Qinxin Zhang, Lele Chu, Qingshun Zhao*. 2017. Zebrafish Znfl1s control the expression of hoxb1b in the posterior neuroectoderm by acting upstream of pou5f3 and sall4. The Journal of Biological Chemistry, 292(31):13045-13055.
7. Shu Xu, Shasha Cao, Bingjie Zou, Yunyun Yue, Chun Gu, Xin Chen, Pei Wang, Xiaohua Dong, Zheng Xiang, Kai Li, Minsheng Zhu**, Qingshun Zhao**, Guohua Zhou*. 2016. An alternative novel tool for DNA editing without target sequence limitation: the structure-guided nuclease. Genome Biology. 17(1):186.
8. Junbo Li, Yunyun Yue, Qingshun Zhao*. 2016. Retinoic acid signaling is essential for valvulogenesis by affecting endocardial cushions formation in zebrafish embryos. Zebrafish, 13(1):9-18. (Cover)
9. Jingyun Li, Yunyun Yue, Xiaohua Dong, Wenshuang Jia, Kui Li, Dong Liang, Zhangji Dong, Xiaoxiao Wang, Xiaoxi Nan, Qinxin Zhang, Qingshun Zhao*. 2015. Zebrafish foxc1a plays a crucial role in early somitogenesis by restricting the expression of aldh1a2 directly. The Journal of Biological Chemistry, 290(16):10216-28.
10. Zhangji Dong, Xiaohua Dong, Wenshang Jia, Shasha Cao, Qingshun Zhao*. 2014. Improving the efficiency for generation of genome-edited zebrafish by labelling primordial germ cells. The International Journal of Biochemistry & Cell Biology, 55:329-34.

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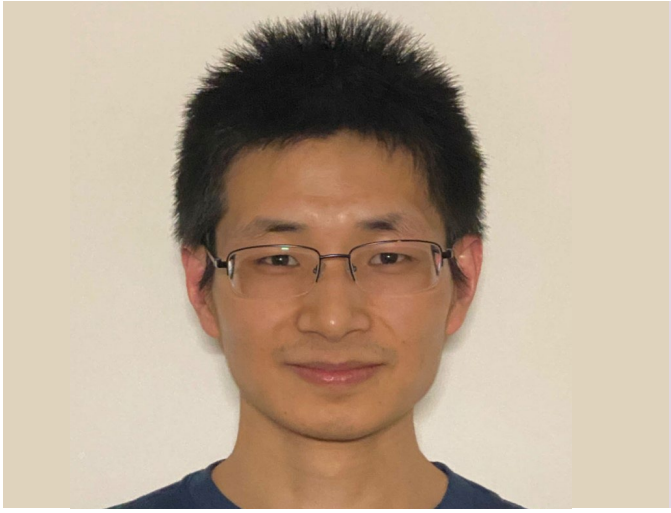

Liang Chi Ph.D.

Dr. Liang Chi graduated with a bachelor's degree in biology from Lanzhou University in 2014. In 2020, he earned his Ph.D. from the Department of Environmental Sciences and Engineering at the University of North Carolina at Chapel Hill, under the mentorship of Professor Kun Lu. In 2024, he completed postdoctoral training at the National Institute of Allergy and Infectious Diseases (NIAID) at the NIH, under the guidance of Academician Yasmine Belkaid. Dr. Chi was appointed as an Associate Professor at the Model Animal Research Institute of Nanjing University in 2024.His lab primary research focuses on the interactions between symbiotic microbiota, the immune system, and the endocrine system, as well as the influence of environmental factors on these interactions. Dr. Chi's research findings have been published in leading journals such as Science, Environmental Health Perspectives, npj Biofilms and Microbiomes, and Archives of Toxicology.

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Revealed the Mechanism of Sex Differences in the Skin Immune System

Individual differences in disease susceptibility and drug response are critical for advancing personalized medicine, with sex differences playing a pivotal role in these variations. Recent studies reveal significant disparities in immune function, disease prevalence, and severity between males and females, yet the mechanisms underlying these immune sex differences remain incompletely understood. Additionally, while symbiotic microbiota and environmental factors are essential for maintaining immune homeostasis, their roles in shaping sex differences are largely unexplored. Understanding how microbiota and environmental factors interact within the immune systems of different sexes is crucial for bridging these knowledge gaps and optimizing immune-targeted therapies. The interplay among sex hormones, microbiota, and environmental factors in shaping immune systems across sexes is key to addressing these gaps and advancing therapeutic strategies.

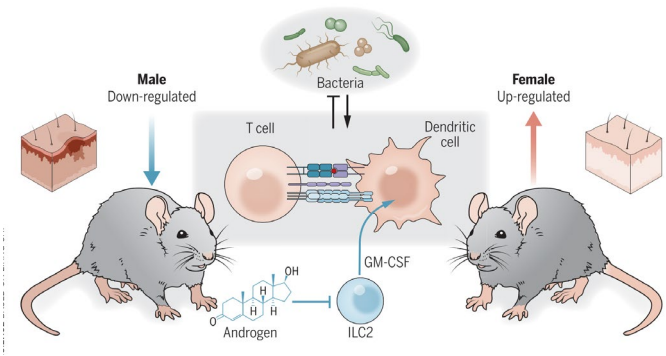
Our lab's long-term goal is to uncover the mechanisms driving sex and individual differences in immune and metabolic systems, with a focus on the roles of microbiota, nutrition, environmental influences, and hormonal regulation. This research aims to pave new pathways for personalized disease prevention and management. To realize this vision, we have identified three core research directions: exploring tissue-specific hormone microenvironments, investigating microbiota influenced by sex differences, and examining the impact of diet and environmental factors on immune regulation:

1. Hormone Microenvironments and Their Impact on Tissue-Specific Immunity:
Understanding how unique hormone microenvironments in different tissues influence local immune and metabolic functions is essential for elucidating the role of sex differences in disease susceptibility. Our preliminary findings indicate significant sex-specific differences in immune responses across tissues, driven by tissue-specific synthesis and metabolism of sex hormones, which create localized hormonal microenvironments. This project aims to systematically investigate the formation of these tissue-specific hormone microenvironments and their roles in driving sex-specific immune regulation.

2. Sex Hormones, Microbiota Composition, and Immune Regulation:
Investigating how sex hormones shape sex-specific microbiota composition and how these differences impact immune regulation is critical for understanding immune modulation from a sex-specific perspective. Previous studies have demonstrated significant differences in microbiota composition between sexes, which undergo notable shifts during hormonal changes such as pregnancy and aging. Our preliminary data suggest that microbiota significantly influence immune sex differences. This research direction aims to uncover the molecular mechanisms by which sex hormones regulate microbiota composition and their sex-specific impacts on immune responses.

3. Dietary Factors and Sex-Specific Immune Regulation:
Understanding how different dietary patterns and nutritional components influence immune regulation and contribute to sex differences will aid in developing effective intervention strategies. Our prior work shows that inhibiting fatty acid metabolism significantly alters immune cell composition in the skin and impacts sex differences, with different fatty acids exerting varying effects on skin immunity. This project will explore how diverse dietary patterns shape immune function and their roles in mediating sex-specific effects.

Through these interconnected research areas, our lab is dedicated to building a comprehensive framework for understanding the mechanisms behind sex and individual differences in immune and metabolic systems. By elucidating the roles of hormone microenvironments, microbiota, and dietary factors in immune regulation, our research will support the development of personalized, sex-specific therapeutic strategies. This integrated approach aims to fill critical knowledge gaps and advance fields such as sex-based medicine, nutritional science, and microbiota research, driving innovations in personalized healthcare.



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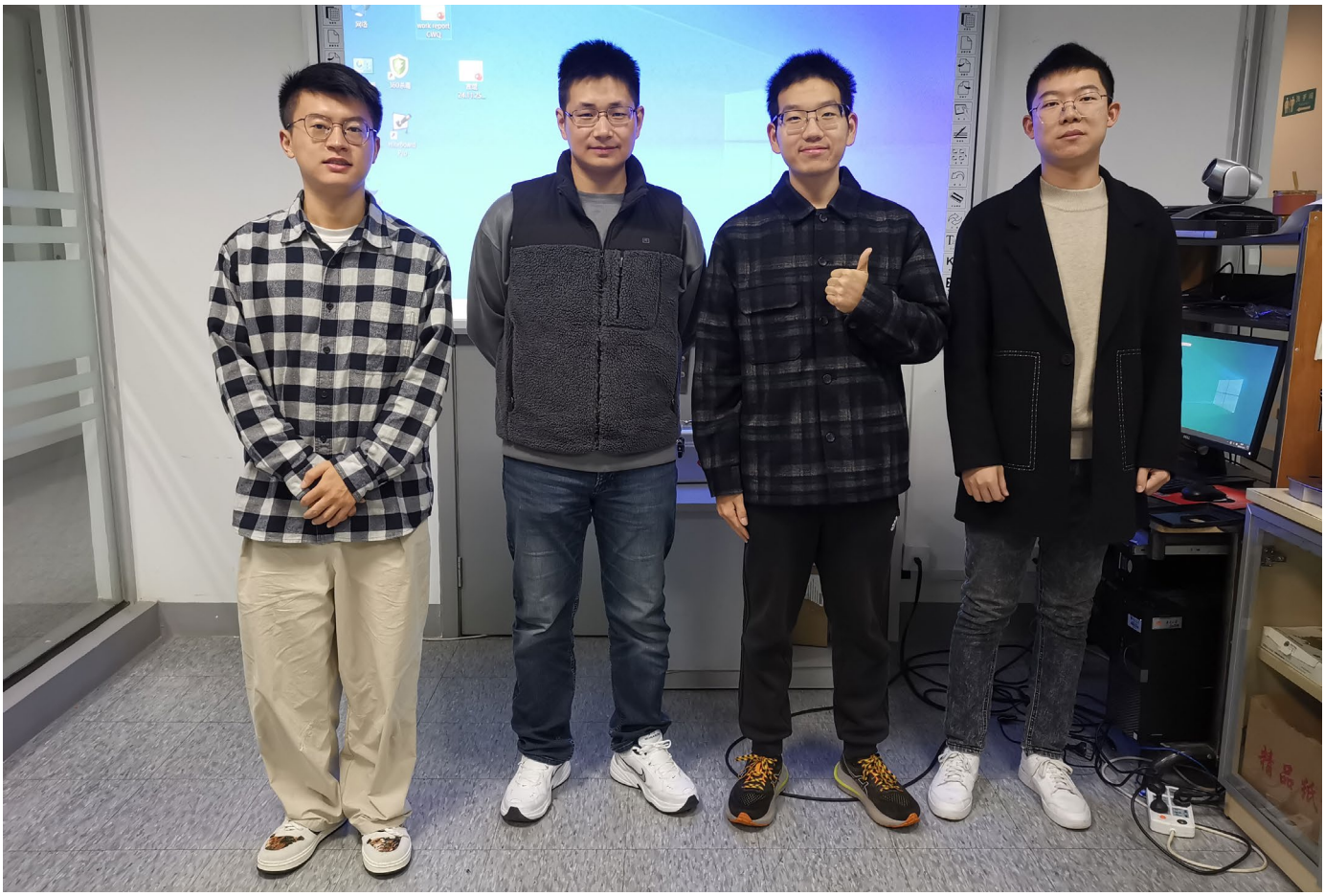

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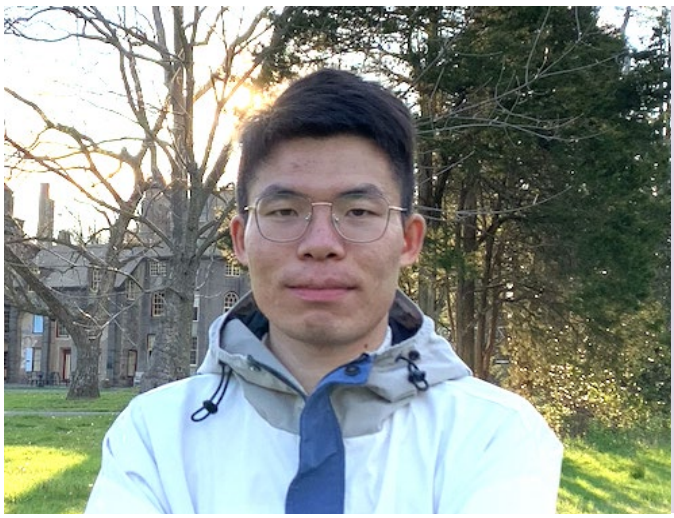
Yi Kun



Yongzhen Liu, Ph.D.

Yongzhen Liu received his Ph.D. degree in Microbiology from Peking University School of Basic Medical Sciences in 2019. From 2019 to 2024, he worked as a postdoctoral fellow at Princeton University with Prof. Alexander Ploss. In 2024, he joined the Model Animal Research Center (MARC) of Nanjing University as a principal investigator and associated professor of microbiology.

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Hepatitis virus infection and pathogenesis

Infectious diseases account for at least 15 million deaths each year - almost a quarter of all human deaths worldwide. Among which, the hepatitis B virus (HBV) epidemic is an ongoing threat to global health. According to the WHO, an estimated 296 million people worldwide were living with hepatitis B in 2019, with approximately one third of these individuals living in China. According to the fourth national seroepidemiological survey, the HBsAg prevalence in 1–69-year-olds was 5.86% in China. HBV is one of the most common causes of liver cirrhosis, liver cancer, and viral hepatitis related death. Hepatitis delta virus (HDV), the sole member of the Delta virus genus, is a small circular single-stranded negative sense RNA (1700 nucleotides) virus which can cause hepatitis D. Compared with chronic HBV infection alone, HBV and HDV dual infection is frequently associated with the most severe form of viral hepatitis, accelerated liver disease progression, and can lead to the development of cirrhosis in 70–80% of cases within 5–10 years. Moreover, upwards of 50% of patients die from liver disease within 10 years of diagnosis. The rates of HCC and hepatic decompensation also are about 2–3-fold higher than for HBV mono-infection.

Our lab focuses on the HBV infection tropism exploration and the development of HBV infection animal model. The infection tropism of HBV is very narrow, and is limited to humans and chimpanzees. Previous research showed that HBV cannot infect old world monkeys like rhesus macaque and new world monkeys like squirrel monkeys. Neither the commonly used rat or mouse models. The apparent block in interspecies transmission in non-human primates can be largely attributed to differences in the amino acid (AA) sequence of the HBV receptor NTCP. We developed a very efficient and scalarable technology to investigate HBV binding ability on hepatocytes of different species. Mechanistically, human hepatoma cells HepG2 were used to ectopically express NTCPs (tagged with red fluorescent protein) of different species by lentiviruses (Fig. 1A). Then myristoylated HBV preS1[2–48]-FITC peptides were synthesized and the virus binding capacity can be detected by imaging and flow cytometry (Fig. 1B). Because HDV can only propagate with HBV envelop and enter the target cells use the same functional receptor, we also established the HBV entry detection by using HDV infection (Fig. 1C).

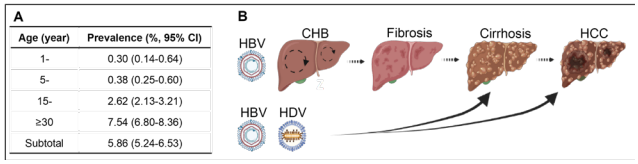

Figure 1. HBV prevalence and pathogenesis. (A) Age-specific HBV prevalence in China in 2020 (Zheng et al. 2024). The HBV infection was characterized by serological HBsAg detection. (B) Compared with chronic HBV infection alone, HBV and HDV dual infection is associated with accelerated liver disease progression.

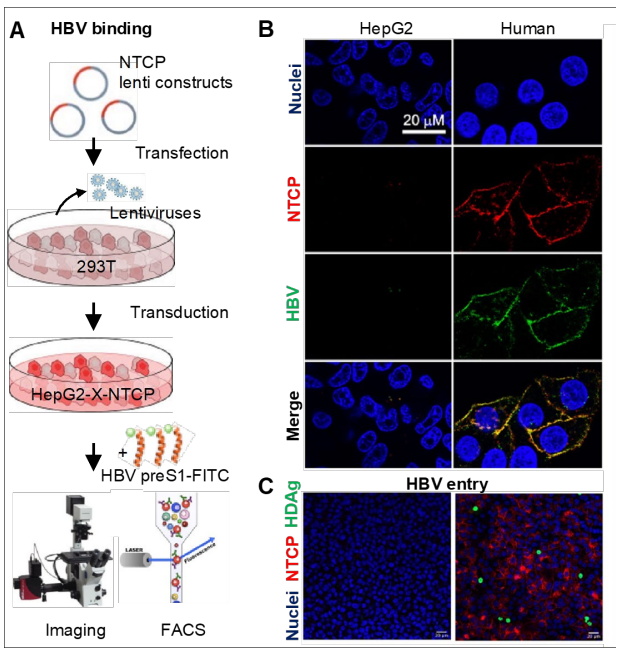

Figure 2. HBV binding and entry detection system. (A) The schematic of how the virus binding was investigated. (B) As a proof-of-concept, HBV binding on HepG2 cells expressing human NTCP was shown by confocal imaging. (C) HBV entry detection system was established by HDV antigen (HDAg) staining. Based on this efficient system, we are currently working on exploring the species that can support HBV/HDV infection.

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1. Liu Y#, Maya S, Carver S, O' Connell A.K., Zen A, Gertje H.P., Crossland N., Ploss A*.. Development of a dual channel detection system for pan-genotypic simultaneous quantification of hepatitis B and delta viruses. Emerging Microbes & Infections. 2024 April; (13): 2350167.
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	Ziyue Wang

Lei Dong, Ph.D.

Lei Dong received his Bachelor in Biotechnology (2003) and Ph.D. in Biochemistry and Molecular Biology (2007) both from Nanjing University. Lei then undertook his postdoctoral training at School of Chemistry & Chemical Engineering, Nanjing University before he joined in the faculty of School of Life Sciences, Nanjing University at 2010. Lei is currently a professor of Pharmaceutics and Biomaterials as well as a principal investigator at Nanjing University. He also serves as the Associate Dean of the School of Life Sciences and the Director of NJU Xishan Institute of Applied Biotechnology (Wuxi).

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Organ function remodeling

Tissue engineering holds immense potential for regenerating failing organs. However, the functional regeneration of large and complex organs remains a significant challenge due to limitations, such as insufficient seed cells, immune rejection, and the lack of effective techniques for constructing mature vascular systems. A breakthrough solution to these barriers lies in utilizing the mature blood vessel networks of existing, dispensable organs. Among these, the spleen is particularly promising due to its unique structural and physiological properties. Once remodeled into a pro-regenerative niche, the spleen can be repurposed to compensate for the functional deficits of failing native organs.

Our previous studies demonstrated the feasibility of transforming or reprogramming spleen into a liver-like organ through targeted remodeling, creating an environment conducive to hepatocyte transplantation. This "hepatized" spleen effectively performed typical hepatic functions, including glycogen storage, lipid metabolism, and drug detoxification, significantly improving survival rates in mice undergoing 90% hepatectomy and severe liver damage. Additionally, the spleen's capacity to regenerate functional tissues such as islets, thyroid, and thymus underscores its versatility and opens new avenues in tissue engineering (Figure 1).

Building on this foundation, our current study introduces a novel biomaterials-based strategy for spleen remodeling (Figure 2). Utilizing a cross-linked sulphated hyaluronic acid system (sHA-X), we achieved the mechanical activation of latent transforming growth factor-beta (TGF-β) stored in the spleen. This activation induced extensive ECM remodeling, creating an ECM-rich niche ideally suited for hepatocyte transplantation. Unlike earlier approaches, this method requires no exogenous genetic or protein modifications, relying entirely on the spleen's intrinsic regenerative potential. It provides promising prospects for clinical transformation of "organ function remodeling" as a strategy to treat end-stage liver diseases.

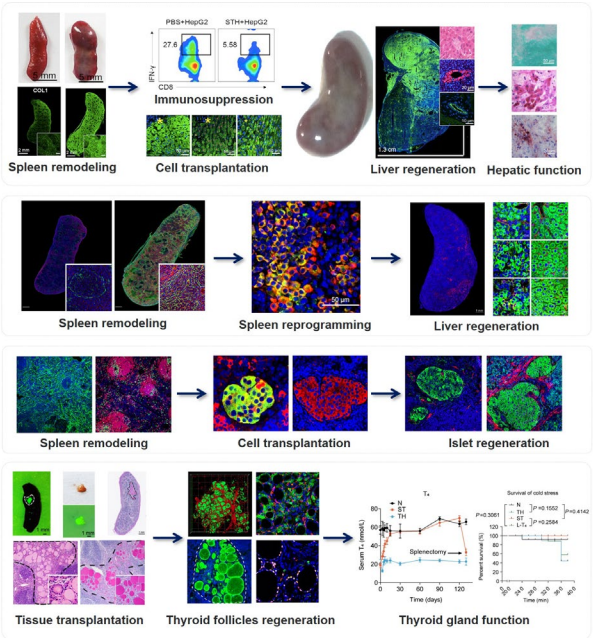

Figure 1. Function reconstruction of complex organs and tissues in the spleen

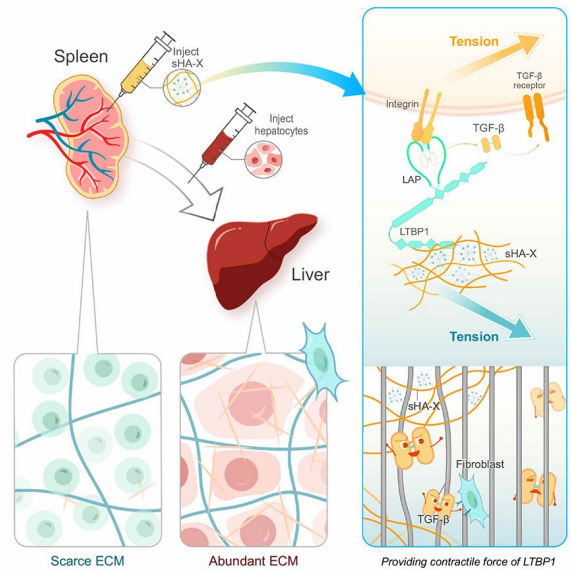

Figure 2. Graphical abstract illustrating the establishment of liver functions within the spleen through in situ activation of transforming growth factor-beta (TGF-β). This method leverages the spleen's abundant storage of TGF-β in its latent, inactive form. Utilizing a chemically engineered polysaccharide designed to mechanically release TGF-β to exceptionally high levels, this innovative approach creates an environment that promotes the adhesion and growth of transplanted allogenic liver cells, ultimately transforming the spleen into a functional "hepatized" organ.

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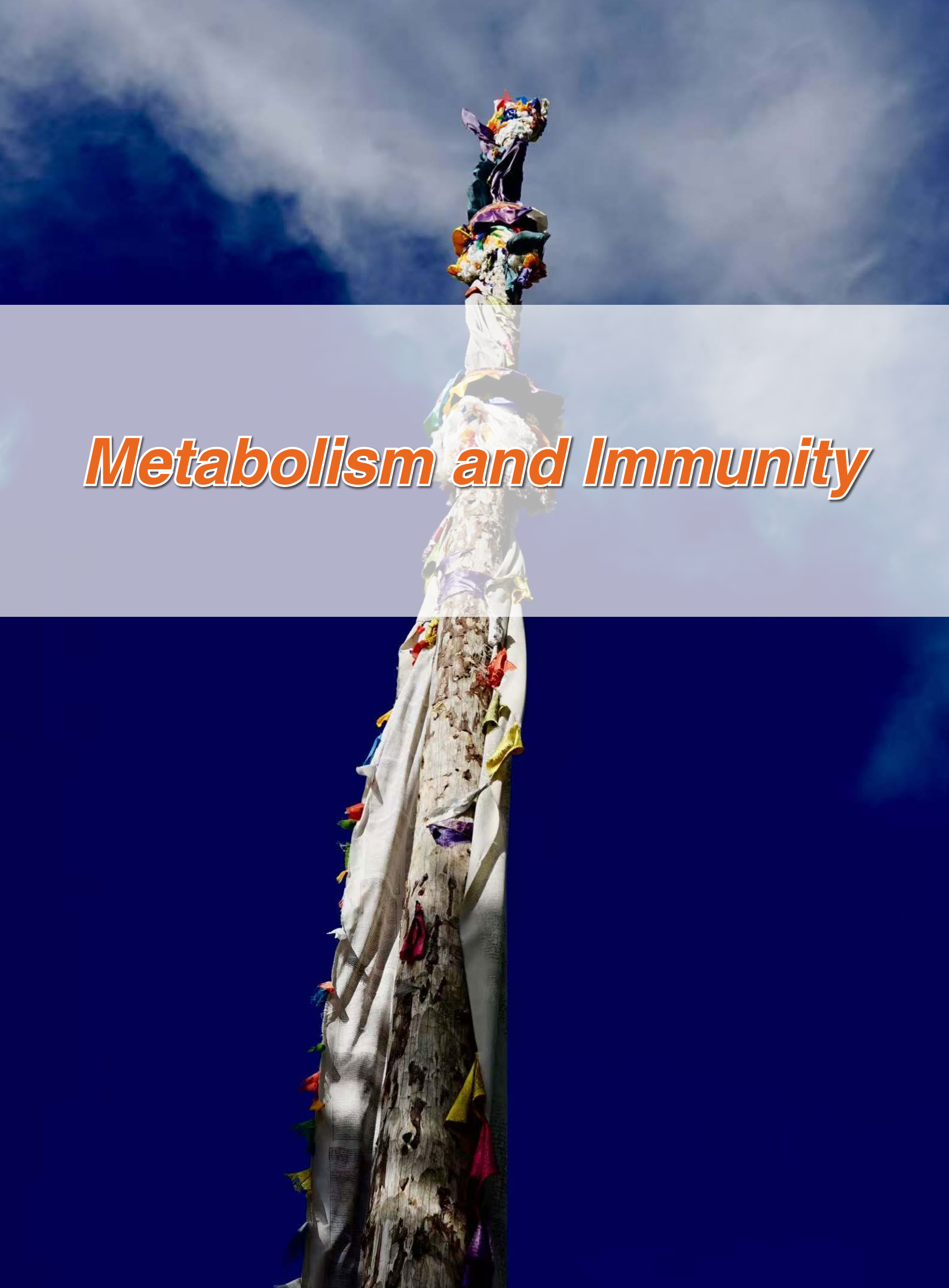

Metabolism and Immunity

Xiang Gao, Ph.D.

Xiang was an alumina of Nanjing University. He received his Ph.D. degree from Thomas Jefferson University in 1994, then did his postdoctoral training at the Jackson Laboratory and University of North Carolina at Chapel Hill. In 2000, Xiang was recruited back to Nanjing University. He later founded both MARC and National Resource Center of Mutant Mice of China. He is also the current director for the State Key Laboratory of Pharmaceutical Biotechnology. Xiang is the recipient for Cheung Kong Scholar from Ministry of Education and Distinguished Young Scholar from National Science Foundation.

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Physiological regulation and metabolic homeostasis

The advance of modern technologies, especially the NGS and gene editing, transform the biomedical fields. The complicated metabolic regulatory networks crossing the variety of tissues and organs are becoming tangible with these new tools. We are excited to embrace these promising progresses for identifying the previous unsolvable biological questions. In my laboratory, we are more interested in defining the global regulators for crucial physiological processes. Following are some of our publications:

1. Senp7 deficiency impairs lipid droplets maturation in white adipose tissues via Plin4 deSUMOylation (Figure 1)

Lipid metabolism is important for the maintenance of physiological homeostasis. Several members of the small ubiquitin-like modifier (SUMO)-specific protease (SENP) family have been reported as the regulators of lipid homeostasis.

However, the function of Senp7 in lipid metabolism remains unclear. In this study, we generated both conventional and adipocyte-specific Senp7 KO mice to characterize the role of Senp7 in lipid metabolism homeostasis. Both Senp7-deficient mice displayed reduced white adipose tissue mass and decreased size of adipocytes. By analyzing the lipid droplet morphology, we demonstrated that the lipid droplet size was significantly smaller in Senp7-deficient adipocytes. Mechanistically, Senp7 could deSUMOylate the perilipin family protein Plin4 to promote the lipid droplet localization of Plin4. Our results reveal an important role of Senp7 in the maturation of lipid droplets via Plin4 deSUMOylation.

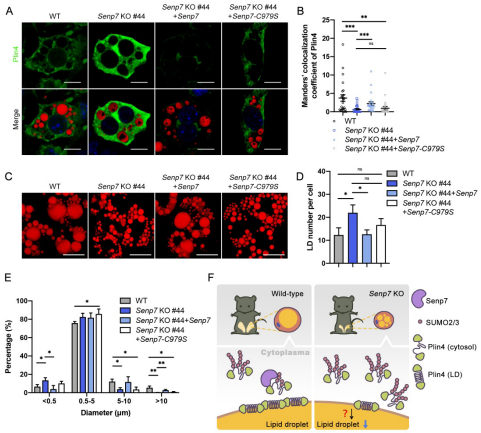

Figure 1. Senp7 deficiency impairs lipid droplets maturation in white adipose tissues via Plin4 deSUMOylation

2. Depletion of Gsdma1/2/3 alleviates PMA-induced epidermal hyperplasia by inhibiting the EGFR-Stat3/Akt pathway (Figure 2)

Homeostasis of the skin barrier is essential for maintaining normal skin function. Gasdermin A (GSDMA) is highly expressed in the skin and is associated with many skin diseases, such as melanoma and psoriasis. In mice, GSDMA is encoded by three gene homologues, namely Gsdma1, Gsdma2, and Gsdma3. Although Gsdma3 gain-of-function mutations cause hair loss and skin inflammation, Gsdma3-deficient mice show no phenotypes in skin or hair structures. To explore the physiological function of GSDMA, we generated conventional Gsdma1/2/3 knockout (KO) mice. We found that Gsdma1/2/3 KO mice showed significantly decreased epidermal hyperplasia and inflammation induced by phorbol 12-myristate 13-acetate (PMA). Furthermore, we found that the alleviation of epidermal hyperplasia depends on Gsdma1/2/3 expressed specifically in keratinocytes. Mechanistically, Gsdma1/2/3 depletion downregulated epidermal growth factor receptor (EGFR) ligands, leading to decreased EGFR-Stat3/Akt signalling. These results demonstrate that depletion of Gsdma1/2/3 alleviates PMA-induced epidermal hyperplasia partially by inhibiting the EGFR-Stat3/Akt pathway.

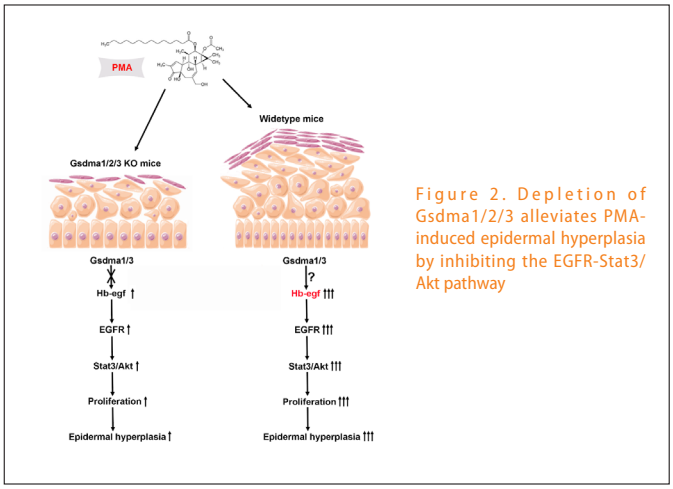

Figure 2. Depletion of Gsdma1/2/3 alleviates PMA-induced epidermal hyperplasia by inhibiting the EGFR-Stat3/Akt pathway

Selected publications

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2. Liu, Q., M. Li, M. Sun, R. Xin, Y. Wang, Q. Chen, X. Gao*, and Z. Lin*, Depletion of Gsdma1/2/3 alleviates PMA-induced epidermal hyperplasia by inhibiting the EGFR-Stat3/Akt pathway. J Mol Cell Biol, 2024. 16(1).
3. Li, X., T. Zhang, L. Kang, R. Xin, M. Sun, Q. Chen, J. Pei, Q. Chen, X. Gao*, and Z. Lin*, Apoptotic caspase-7 activation inhibits non-canonical pyroptosis by GSDMB cleavage. Cell Death Differ, 2023. 30(9): p. 2120-2134.
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Dr. Shuai Chen received his Ph.D. degree from University of Halle-Wittenberg (Germany) in 2005. After his postdoctoral training in the field of cell signaling and molecular physiology at the MRC Protein Phosphorylation Unit, University of Dundee (UK) from 2006 to 2011, Dr. Chen joined MARC as a principle investigator and a professor in Metabolic Biology in 2012. He is the recipient for Distinguished Young Scholars from the National Natural Science Foundation (2020) and New Century Excellent Talents from the Ministry of Education (2013).

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Metabolic Signaling, Physiology and Diseases

Metabolic diseases including type 2 diabetes mellitus (T2DM), obesity and non-alcoholic fatty liver disease (NAFLD) have become prevalent world-wide in the last few decades, which urges a better understanding of their pathogenesis as well as new therapeutic strategies to combat these diseases. Insulin resistance is a common cause for the pathogenesis of these metabolic diseases, whose underlying mechanism is still not clear. Insulin actions exhibit a tissue/pathway-dependent manner. One of the goals of my laboratory is to understand the molecular basis of tissue/pathway-specific insulin actions, the pathogenic mechanisms of metabolic diseases, and discoveries of leading compounds to combat these diseases. Energy sensing through the critical sensor AMP-activated protein kinase (AMPK) plays a key role in regulating glucose and lipid homeostasis. Activation of the AMPK improves insulin sensitivity through multiple mechanisms, which may be targeted to combat metabolic disease. Therefore, we are currently running three research programs in the laboratory: (1) tissue/pathway-specific insulin actions and diabetic complications, (2) energy sensing in control of metabolic homeostasis, (3) discoveries of therapeutic targets and agents for metabolic diseases.

The recent progresses of my lab is as follows:

1. Rab8a as a mitochondrial receptor for lipid droplets in skeletal muscle

Dynamic interaction between lipid droplets (LDs) and mitochondria controls mobilization of long-chain fatty acids (LCFAs) from LDs for mitochondrial β-oxidation in skeletal muscle under energy stress conditions such as exercise. However, it remains unclear about the composition and regulation of the tethering complex mediating LD-mitochondrion interaction. We identify Rab8a as a mitochondrial receptor for LDs forming the tethering complex with the LD-associated PLIN5 in skeletal muscle. In rat L6 skeletal muscle cells, the energy sensor AMPK increases the GTP-bound active Rab8a that promotes LD-mitochondrion interaction through binding to PLIN5 upon starvation. The assembly of Rab8a-PLIN5 tethering complex also recruits the adipose triglyceride lipase (ATGL), which couples LCFA mobilization from LDs with its transfer into mitochondria for β-oxidation. Rab8a deficiency impairs fatty acid utilization and decreases endurance during exercise in a mouse model. These findings may help to elucidate the regulatory mechanisms underlying the beneficial effects of exercise on lipid homeostasis control. (Ouyang Q., …, Wang H.Y.*, Chen S.* 2023 Dev Cell).

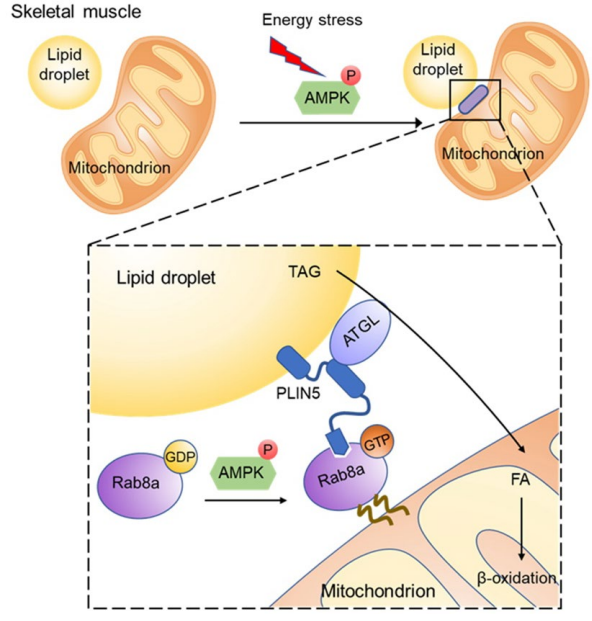

Figure 1 A model for Rab8a as a mitochondrial receptor for lipid droplets in skeletal muscle.

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1. Ouyang Q, Chen QL, Ke SY, Ding LF, Yang XY, Rong P, Feng WK, Cao Y, Wang Q, Li M, Su S, Wei W, Liu MJ, Liu J, Zhang X, Li JZ, Wang HY* and Chen S* (2023) Rab8a as a mitochondrial receptor for lipid droplets in skeletal muscle. Dev Cell 58, 289-305 (* corresponding authors)
2. Quan C, Zhu SS, Wang RZ, Chen JM, Chen QL, Li M, Su S, Du Q, Liu MJ, Wang HY* and Chen S* (2022) Impaired SERCA2a phosphorylation causes diabetic cardiomyopathy through impinging on cardiac contractility and precursor protein processing. Life Metabolism DOI: 10.1093/lifemeta/loac013 (* corresponding authors)
3. Zhu SS, Quan C, Wang RZ, Liang DR, Su S, Rong P, Zhou K, Yang XY, Chen QL, Li M, Du Q, Zhang JZ, Fang L, Wang HY* and Chen S* (2022) The RalGAP α 1 RalA signal module protects cardiac function through regulating calcium homeostasis. Nat Commun 13: 4278 DOI: 10.1038/s41467-022-31992-z (* corresponding authors)
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5. Zhou K, Chen QL, Chen JM, Liang DR, Feng WK, Liu MJ, Wang Q, Wang RZ, OuYang Q, Quan C* and Chen S* (2022) Spatiotemporal regulation of insulin signaling by liquid-liquid phase separation. Cell Discov 8(1): 64 DOI: 10.1038/s41421-022-00430-1 (* corresponding authors)
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8. Quan C, Du Q, Li M, Wang RZ, Su S, Zhu SS, Chen QL, Sheng Y, Chen L, Wang H, Campbell DG, MacKintosh C, Yang ZZ, Ouyang KF, Wang HY* and Chen S* (2020) A PKB-SPEG signaling nexus links insulin resistance with diabetic cardiomyopathy by regulating calcium homeostasis. Nat Commun 11(1): 2186 doi: 10.1038/s41467-020-16116-9 (* corresponding author)
9. Quan C, Li M, Du Q, Chen QL, Wang H, Campbell D, Fang L, Xue B, MacKintosh C, Gao X, Ouyang KF, Wang HY and Chen S* (2019) SPEG controls calcium re-uptake into the sarcoplasmic reticulum through regulating SERCA2a by its second kinase-domain. Circ Res 124(5): 712-726 (* corresponding author)

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Maintaining cellular metabolic homeostasis

Our research group focuses on the relationship between metabolism and disease, utilizing genome editing technology to establish mouse models of major human diseases or developmental defects. We investigate the function of disease-related genes and uncover the molecular mechanisms underlying major diseases. Our primary interest lies in the maintenance of the body's internal environmental homeostasis and the relationship between homeostasis imbalance and the onset of disease.

The metabolic homeostasis of the body relies on regulation at three levels: first, the functional coordination of various organs and tissues under the guidance of the neuroendocrine system; second, the metabolic coupling between different cell types within tissues and organs; and third, the synergistic action of different metabolic pathways within cells. For instance, specific patterns of glucose metabolism (such as gluconeogenesis and glycolysis) and lipid metabolism (like fatty acid oxidation and fatty acid synthesis) are crucial for the normal functioning of cells. The metabolic patterns differ among various cells within tissues and organs, and their metabolic coupling is fundamental for organ function. Furthermore, different organs maintain metabolic homeostasis and physiological functions through coordination via the neuroendocrine system, exosomes, and metabolic intermediates.

Therefore, our research group's interests are mainly focused on: the mechanisms by which various metabolic pathways within cells coordinate to regulate cellular functions, the ways in which metabolic coupling between cells governs the functioning of tissues and organs, and the molecular mechanisms through which different organs coordinate their functional states to regulate the body's metabolic homeostasis.

1. Egr-1 regulation of skeletal muscle during physiological states or muscle atrophy (Figure1)

Skeletal muscle exhibits significant plasticity in response to external stimuli. Disuse, aging, or cachexia-related muscle loss leads to dysfunction of skeletal muscle, resulting in poor health and a reduced quality of life. However, effective methods to alleviate or prevent muscle atrophy remain elusive. Here, we demonstrate that Egr-1, a transcription factor, plays a role in regulating skeletal muscle mass in response to muscle atrophy. In humans and mice, the expression of muscular Egr-1 increases continuously under conditions causing muscle atrophy, and its deletion can significantly alleviate skeletal muscle loss. Muscular Egr-1 deficiency mitigates muscle loss, a protective effect achieved by enhancing homeostatic autophagy through the inhibition of BCAA-mediated mTORC1 hyperactivation. Thus, this study uncovers a pivotal role of Egr-1-dependent mTORC1 hyperactivation in leading to skeletal muscle atrophy, and provides a strategic approach for the treatment of muscle atrophy.

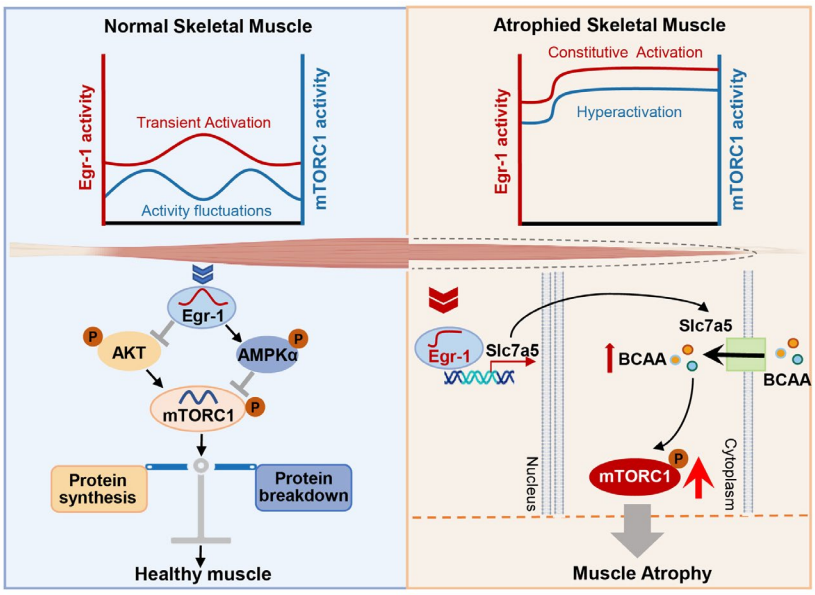

Figure1. Schematic for Egr-1 regulation of skeletal muscle during physiological states or muscle atrophy.

2. Postnatal decline of insulin and elevation of glucagon regulates heart regenerative capacity by promoting glucose/lipid metabolic shift (Figure2)

The adult heart has a limited regenerative capacity and cannot self-renew after damage, while both embryonic and neonatal hearts can effectively regenerate following injury. However, this regenerative ability diminishes shortly after birth due to cell cycle arrest. Our research indicates that during the perinatal stage, insulin levels decrease while glucagon levels increase, leading to a shift in metabolic preference from glucose to lipids, which ultimately inhibits cardiomyocyte proliferation. Reversing this metabolic shift in neonatal hearts by deleting the Cpt2 gene to enhance glycolysis can improve cardiac regeneration capacity. Additionally, the glucose/lipid metabolic shift is associated with a significant reduction in the lactylation of metabolic enzymes in neonatal hearts, affecting both glucose and lipid metabolism. This modification regulates the activity of these metabolic enzymes and inhibits cardiomyocyte proliferation. Overall, our findings suggest that the metabolic environment in neonates plays a critical role in regulating metabolic reprogramming and cardiac regeneration in neonatal hearts.

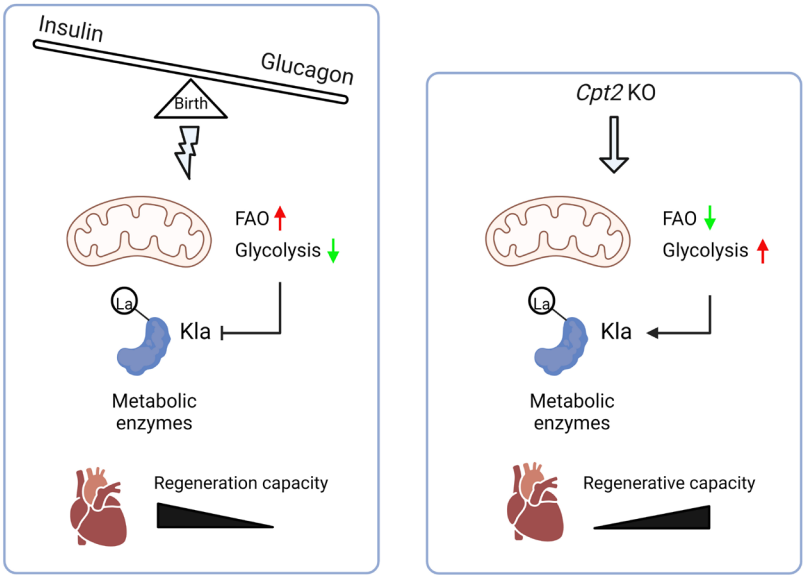

Figure2. Working modelforKetone bodies promote epididymal white adipose expansion to alleviate liver steatosis in response to a ketogenic diet.

3. Elevated mevalonolactone from Ruminococcus torques contributes to Metabolically Abnormal Obesity development (Figure3)

Obese individuals are categorized as either "Metabolically Abnormal Obesity" (MAO) or "Metabolically Healthy Obesity" (MHO) based on their insulin resistance and metabolic disorders. However, the intrinsic mechanism remains largely unknown. Through examining gut microbiota and fecal metabolome of MAO and MHO patients, we identified intestinal microorganism Ruminococcus torques (R. torques) and its metabolite mevalonolactone (MVL) as risk factors for insulin resistance and metabolic disorders. Both R. torques and MVL administration results in MAO phenotype in mice. In general, MVL is an intermediate metabolite in the eukaryotic mevalonate (MVA) pathway, however we found that prokaryote R. torques, has the potential to produce MVL. We further showed that MVL could directly bind to the transcription factor ZNF384, triggering its nucleation and subsequent binding to the promoter regions of Ggps1. Ggps1 enhance Ras prenylation and promotes insulin resistance. In conclusion, the abnormal colonization of R. torques in gut leads to an increased level of MVL in patients. This, in turn, affects the expression of Ggps1 via ZNF384, ultimately contributing to the development of MAO.

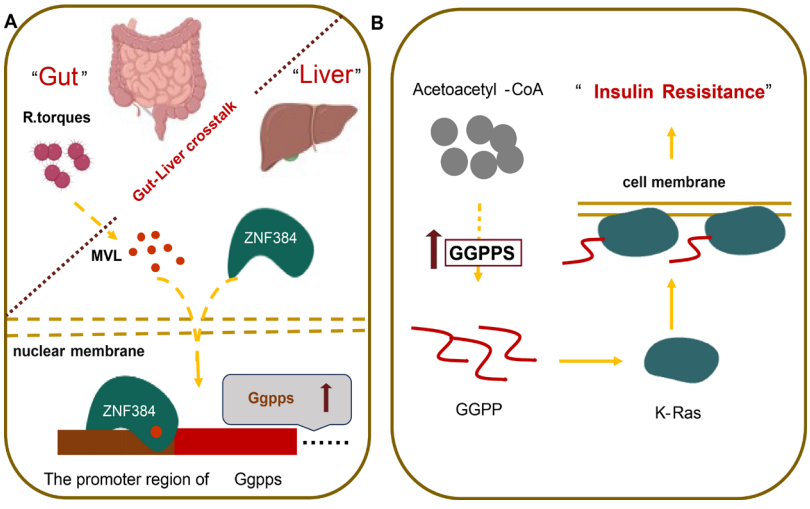

Figure 3. MVL driven by R.torques affects insulin resistance and cholesterol synthesis associated with MAO.

Selected Publications (#:Co-first authors; *:Co-corresponding authors)

1. Hai-Quan Wang, Xiao-Long Wu, Jing Zhang, Si-Ting Wang, Yong-Juan Sang, Kang Li, Chao-Fan Yang, Fei Sun, Chao-Jun Li. 2024. Meiotic transcriptional reprogramming mediated by cell-cell communications in humans and mice revealed by scATAC-seq and scRNA-seq. Zoological Research, 45(3): 601-616. DOI: 10.24272/j.issn.2095-8137.2023.414
2. Zhang T, Zhu Y, Wang X, Chong D, Wang H, Bu D, Zhao M, Fang L, Li C. The characterization of protein lactylation in relation to cardiac metabolic reprogramming in neonatal mouse hearts. J Genet Genomics. 2024 Jul;51(7):735-748. doi: 10.1016/j.jgg.2024.02.009. Epub 2024 Mar 11. PMID: 38479452.
3. Zhao MF, Zhang XG, Tang YP, Zhu YX, Nie HY, Bu DD, Fang L, Li CJ. Ketone bodies promote epididymal white adipose expansion to alleviate liver steatosis in response to a ketogenic diet. J Biol Chem. 2024 Feb;300(2):105617. doi: 10.1016/j.jbc.2023.105617. Epub 2024 Jan 3. PMID: 38176653; PMCID: PMC10847776.
4. Wu J, Bu D, Wang H, Shen D, Chong D, Zhang T, Tao W, Zhao M, Zhao Y, Fang L, Li P, Xue B, Li CJ. The rhythmic coupling of Egr-1 and Cidea regulates age-related metabolic dysfunction in the liver of male mice. Nat Commun. 2023 Mar 24;14(1):1634. doi: 10.1038/s41467-023-36775-8. PMID: 36964140; PMCID: PMC10038990.
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Zhenji Gan, Ph.D.

Zhenji received his Ph.D. degree in Biochemistry and Molecular Biology (2003 - 2008) from the Shanghai Institutes for Biological Sciences, Chinese Academy of Sciences. His Ph.D. work was carried out in Dr. Yong Liu's lab focused on metabolic diseases. From 2008 to 2013, Zhenji pursued his post-doctoral training in the areas of nuclear receptor signaling and energy metabolism under the guidance of Dr. Daniel Kelly at Sanford-Burnham Medical Research Institute. In 2013, he started a Principal Investigator position in the Model Animal Research Center (MARC) of Nanjing University.

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Energy metabolism and muscle fitness

Muscle fitness is an important determinant of health and disease. Exercise training enhances muscle endurance and performance by augmenting the capacity of mitochondria to burn fuels and by increasing the proportion of slow oxidative fibers and blood supply. Conversely, reduced physical activity such as occurs with chronic illness, obesity, and aging results in de-trained muscle (Fig. 1). Our lab focuses on fundamental mechanisms that control muscle energy metabolism in physiological and disease states. We are particularly interested in exploring the regulatory networks involved in the coordinate control of energy metabolic and structural programs that define muscle fitness and their potential for therapeutic development.

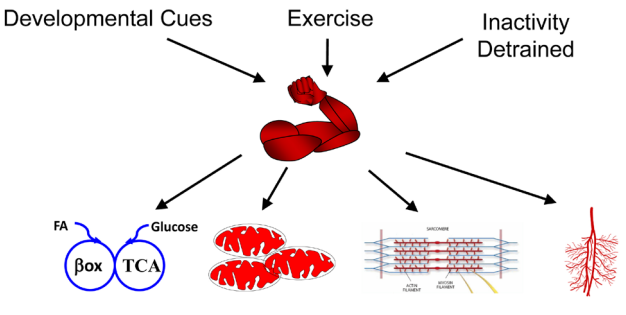

Fig 1. The muscle fitness is determined by developmental as well as physiological inputs. These inputs coordinately control the programs including fuel burning, mitochondrial ATP production, contraction, and angiogenesis.

Muscle-bone cross-talk through the FNIP1-TFEB-IGF2 axis is associated with bone metabolism in human and mouse.

Clinical evidence indicates a close association between muscle dysfunction and bone loss; however, the underlying mechanisms remain unclear. Here, we report that muscle dysfunction–related bone loss in humans with limb-girdle muscular dystrophy is associated with decreased expression of folliculin-interacting protein 1 (FNIP1) in muscle tissue. Supporting this finding, murine gain-and loss-of-function genetic models demonstrated that muscle-specific ablation of FNIP1 caused decreased bone mass, increased osteoclastic activity, and mechanical impairment that could be rescued by myofiber-specific expression of FNIP1. Myofiber-specific FNIP1 deficiency stimulated expression of nuclear translocation of transcription factor EB, thereby activating transcription of insulin-like growth factor 2 (Igf2) at a conserved promoter-binding site and subsequent IGF2 secretion. Muscle-derived IGF2 stimulated osteoclastogenesis through IGF2 receptor signaling. AAV9-mediated overexpression of IGF2 was sufficient to decrease bone volume and impair bone mechanical properties in mice. Further, we found that serum IGF2 concentration was negatively correlated with bone health in humans in the context of osteoporosis. Our findings elucidate a muscle-bone cross-talk mechanism bridging the gap between muscle dysfunction and bone loss. This cross-talk represents a potential target to treat musculoskeletal diseases and osteoporosis. (Fig. 2).

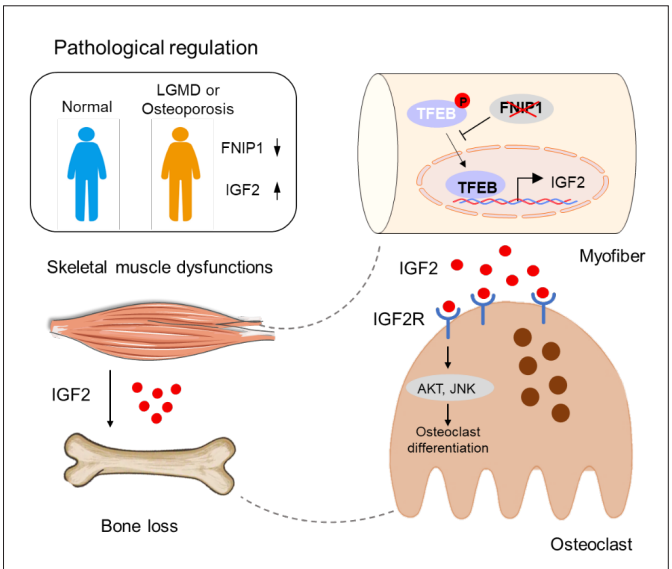

Fig 2. Muscle-bone cross-talk through the FNIP1-TFEB-IGF2 axis is associated with bone metabolism in human and mouse. Myofiber-specific FNIP1 deficiency stimulated expression of nuclear translocation of transcription factor EB, thereby activating transcription of Igf2 at a conserved promoter-binding site and subsequent IGF2 secretion. In addition, muscle-derived IGF2 stimulated osteoclastogenesis through IGF2 receptor signaling. Moreover, serum IGF2 concentration was negatively correlated with bone health in humans in the context of osteoporosis.

AMPK phosphorylation of FNIP1 (S220) controls mitochondrial function and muscle fuel utilization during exercise.

Exercise-induced activation of adenosine monophosphate–activated protein kinase (AMPK) and substrate phosphorylation modulate the metabolic capacity of mitochondria in skeletal muscle. However, the key effector(s) of AMPK and the regulatory mechanisms remain unclear. Here, we showed that AMPK phosphorylation of the folliculin interacting protein 1 (FNIP1) serine-220 (S220) controls mitochondrial function and muscle fuel utilization during exercise. Loss of FNIP1 in skeletal muscle resulted in increased mitochondrial content and augmented metabolic capacity, leading to enhanced exercise endurance in mice. Using skeletal muscle–specific nonphosphorylatable FNIP1 (S220A) and phosphomimic (S220D) transgenic mouse models as well as biochemical analysis in primary skeletal muscle cells, we demonstrated that exercise-induced FNIP1 (S220) phosphorylation by AMPK in muscle regulates mitochondrial electron transfer chain complex assembly, fuel utilization, and exercise performance without affecting mechanistic target of rapamycin complex 1–transcription factor EB signaling. Therefore, FNIP1 is a multifunctional AMPK effector for mitochondrial adaptation to exercise, implicating a mechanism for exercise tolerance in health and disease (Fig. 3).

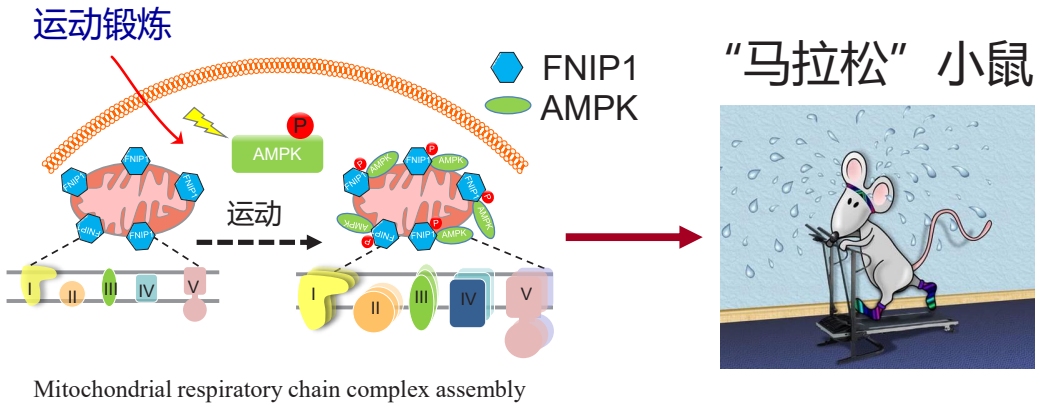

Figure 3. AMPK phosphorylation of FNIP1 (S220) controls mitochondrial function and muscle fuel utilization during exercise. FNIP1 is a multifunctional AMPK effector for mitochondrial adaptation to exercise, implicating a mechanism for exercise tolerance in health and disease.

Selected publications

1. Mao Y#, Jin Z#, Yang J, Xu D, Zhao L, Kiram A, Yin Y, Zhou D, Sun Z, Xiao L, Zhou Z, Yang L, Fu T, Xu Z, Jia Y, Chen X, Niu FN, Li X*, Zhu Z*, Gan Z*. Muscle-bone cross-talk through the FNIP1-TFEB-IGF2 axis is associated with bone metabolism in human and mouse. Sci Transl Med. 16(750): eadk9811.
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9. Xiao L#, Liu J#, Sun Z#, Yin Y, Mao Y, Xu D, Liu L, Xu Z, Guo Q, Ding C, Sun W, Yang L, Zhou Z, Zhou D, Fu T, Zhou W, Zhu Y, Chen XW, Li J, Chen S, Xie X, Gan Z*. AMPK-dependent and -independent coordination of mitochondrial function and muscle fiber type by FNIP1.PLoS Genet.2021; 17(3): e1009488.
10. Liu L#, Ding C#, Fu T, Feng Z, Lee JE, Xiao L, Xu Z, Yin Y, Guo Q, Sun Z, Sun W, Mao Y, Yang L, Zhou Z, Zhou D, Xu L, Zhu Z, Qiu Y, Ge K, Gan Z*. Histone methyltransferase MLL4 controls myofiber identity and muscle performance through MEF2 interaction. J Clin Invest. 2020, 130(9):4710-4725.
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Mechanisms of metabolic disorder

The liver is a key organ in vertebrates, which has a wide range of functions, including detoxification of various metabolites, protein synthesis, and the production of chemicals for digestion. Nonalcoholic fatty liver disease (NAFLD) is a range of condition caused by the hepatic fat accumulation, which is also considered the hepatic manifestation of metabolic syndrome affecting about one-third of the population worldwide. Up to 25% of NAFLD patients develop a progressive inflammatory and damaged liver disease termed non-alcoholic steatohepatitis (NASH) that may progress towards cirrhosis, hepatic carcinoma, and the need for liver transplantation. Yet, the pathogenesis of NAFLD/NASH has not been completely elucidated. However, insulin resistance, inflammatory cytokines, and oxidative stress are thought to be important in the development and/or progression of the disease. Lifestyle modification with exercise and diet has been the first step in NAFLD/NASH treatment.

Our laboratory aims to understand the molecular mechanisms of the development and progression of NAFLD/NASH. Lipidomics, biochemistry, cell biology and transgenics approaches are applied to identify novel components for diagnosis and intervention of NAFLD/NASH progressions.

Insulin stimulates hepatic lipogenesis through mechanisms that are still incompletely understood. We took a proteomic approach to identify novel insulin-responsive proteins in the liver and identified an E3 ligase TRIM24 as a PKB substrate. Upon insulin stimulation, PKB phosphorylates TRIM24 on its Ser1043 and stimulates its shuttling from the nucleus into the cytoplasm. TRIM24 interacts with several critical components of P-bodies in the cytoplasm, promoting their polyubiquitylation, which consequently stabilises Pparγ mRNA. Inactivation of TRIM24 E3-ligase activity or prevention of its Ser1043 phosphorylation via knockin mutations in mice promotes hepatic Pparγ degradation via P-bodies. Consequently, both knockin mutations alleviate hepatosteatosis in mice fed on a high-fat diet. Our results demonstrate the critical role of TRIM24 in linking insulin signalling to P-bodies and have therapeutic implications for the treatment of hepatosteatosis. (Wei W., Chen Q.L., Liu M.J., Sheng Y., …, Wang H.Y.*, Chen S.* 2022 Nat Commun)

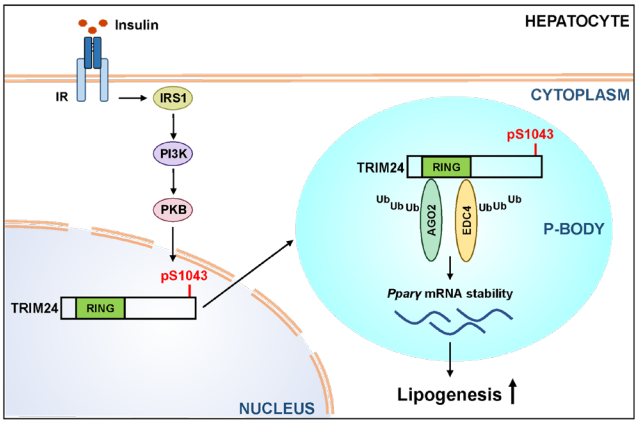

Figure 1 TRIM24 as an insulin-responsive regulator of P-bodies.

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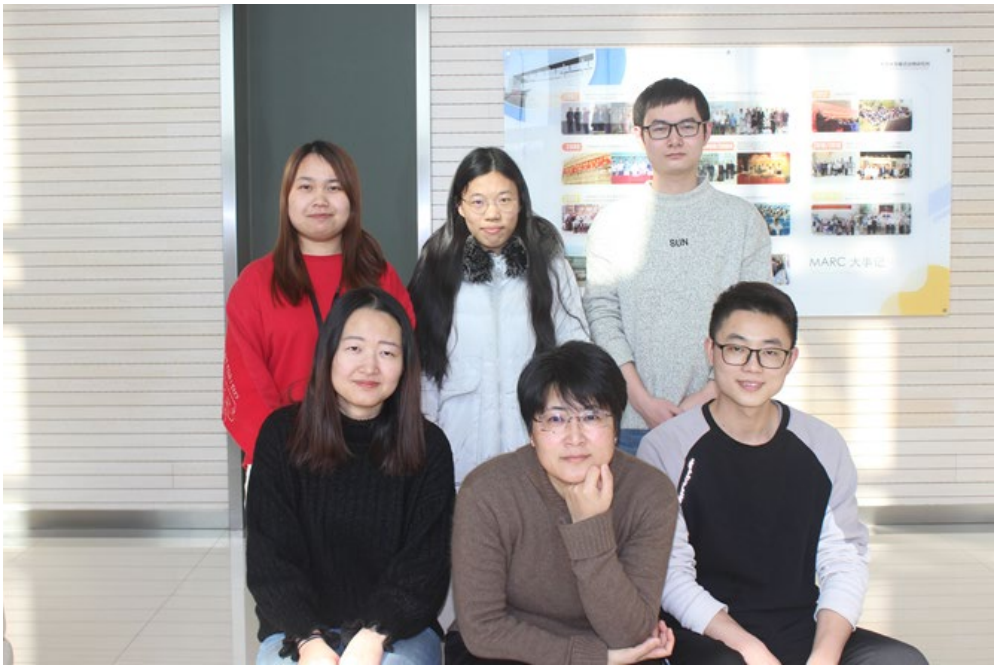
1. Ouyang Q, Chen QL, Ke SY, Ding LF, Yang XY, Rong P, Feng WK, Cao Y, Wang Q, Li M, Su S, Wei W, Liu MJ, Liu J, Zhang X, Li JZ, Wang H-Y and Chen S*. (2023) Rab8a as a mitochondrial receptor for lipid droplets in skeletal muscle. Developmental Cell. 58 (4): 289-305 DOI:https://doi.org/10.1016/j.devcel.2023.01.007
2. Quan C, Zhu SS, Wang RZ, Chen JM, Chen QL, Li M, Su S, Du Q, Liu MJ, Wang H-Y* and Chen S* (2022) Impaired SERCA2a phosphorylation causes diabetic cardiomyopathy through impinging on cardiac contractility and precursor protein processing. Life Metabolism DOI: 10.1093/lifemeta/loac013 (* corresponding authors)
3. Zhu SS, Quan C, Wang RZ, Liang DR, Su S, Rong P, Zhou K, Yang XY, Chen QL, Li M, Du Q, Zhang JZ, Fang L, Wang H-Y* and Chen S* (2022) The RalGAP α 1 RalA signal module protects cardiac function through regulating calcium homeostasis. Nat Commun 13: 4278 DOI: 10.1038/s41467-022-31992-z (* corresponding authors)
4. Wei W, Chen QL, Liu MJ, Sheng Y, OuYang Q, Feng WK, Yang XY, Ding LF, Su S, Zhang JZ, Fang L, Vidal-Puig A, Wang H-Y* and Chen S* (2022) TRIM24 is an insulin-responsive regulator of P-bodies. Nat Commun 13: 3972 DOI: 10.1038/s41467-022-31735-0 (* corresponding authors)
5. Yang XY, Chen QL, Ouyang Q, Rong P, Feng WK, Quan C, Li M, Jiang Q, Liang H, Zhao T-J, Wang H-Y* and Chen S*. Tissue-Specific Splicing and Dietary Interaction of a Mutant As160 Allele Determine Muscle Metabolic Fitness in Rodents. 2021 Diabetes Aug; 70(8): 1826-1842.
6. Chao Q, Qian D, Min L, Wang R, Ouyang Q, Su S, Zhu S, Chen Q, Sheng Y, Chen L, Wang H, Campbell DG, MacKintosh C, Yang ZZ, Ouyang KF, Wang H-Y* and Chen S*. A PKB-SPEG signaling nexus links insulin resistance with diabetic cardiomyopathy by regulating calcium homeostasis. 2020. Nature Comm. volume 11, Article number: 2186
7. Li M, Quan C, Chen S*, Wang H-Y*. The 14-3-3 protein is an essential component of cyclic AMP signaling for regulation of chemotaxis and development in Dictyostelium. https://doi.org/10.1016/j.cellsig.2020.109739
8. Chen Q, Rong P, Xu DJ, Chen L, Xie B, Sheng Y, Li P, Wang H-Y* and Chen S*. (2017) Muscle-specific Rab8a deletion impairs lipid uptake and storage in skeletal muscle and causes hyperlipidemia and hepatosteatosis in mice. Diabetes. 66(9):2387-2399. (*corresponding author)
9. Chen Q, Xie B, Zhu S, Rong P, Sheng Y, Ducommun S, Chen L, Quan C, Li M, Sakamoto K, MacKintosh C, Chen S* and Wang H-Y* (2016) A TBC1D1Ser231Ala knockin mutation partially impairs 5-aminoimidazole-4-carboxamide-1-ß-D-Ribofurano-side- but not exercise-induced muscle glucose uptake in mice. Diabetologia 60(2): 336-345 (*corresponding author)



Group members

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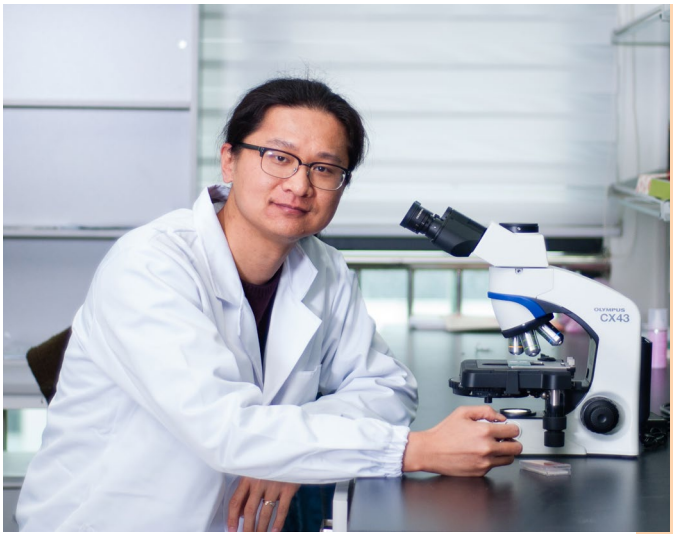

Yan LI Ph.D.

Dr. Li Yan, Ph.D., M.I.T. -Singapore Alliance, 2007-2012; Completed postdoctoral training at Institut Pasteur, France from 2012 to 2016, and worked as an assistant researcher from 2016 to 2018; In 2018, supported by the "Peak Talents Program", he was employed as a professor of Nanjing University, a researcher of the State Key Laboratory of Medical Biotechnology/National Genetic Engineering Mouse Resource Bank, and set up a research group in the Institute of Model Animals; In 2019, I was hired as a doctoral supervisor, and won the chief of the Youth project of the National Key Research and Development Program (former Chief of 973 young people), the "Double Innovation Talent" and "Special Professor" of Jiangsu Province; In 2020, won the Jiangsu Province "double innovation team leading talents; Won the national "Excellent Youth" in 2021; Secretary of the Teaching and Party Group of Model Animal Research Institute in 2022; In 2023, he served as the director of the Institute of Model Animals, and won the "Nanjing University Youth May Fourth Medal" in the same year. His main research results have been published in journals such as Cell, Nature Methods, Nature Cancer, Science Advances, ACS Nano, etc. He has been invited to report at international conferences for many times, and has won a number of international and domestic patents and converted one. He is currently a member of the Scientific Committee of the International Congress of Humanized Mice, a member of the Immune Cell Branch of the Chinese Society of Cell Biology, a member of the Tumor Immune Metabolism Branch of the Chinese Anticancer Association, a member of the Jiangsu Society of Cell and Developmental Biology, and an associate editor of the special issue of Frontiers in Immunology on humanized Mice. Reviewer for journals such as Nature Communications.

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Research direction

I. Human hematopoietic system pedigree development and function

Hematopoietic stem cells transplanted into immunodeficient mice can reconstruct a variety of human immune cell subsets, including T cells and B cells, which is a key tool to replace the human hematopoietic system. However, a variety of human cell subsets, such as erythrocytes and granulocytes, cannot be effectively reconstructed in humanized mice, resulting in the inability to study their corresponding development and function. Therefore, we have developed new mouse strains and techniques to promote the development of these cells in mice, and to explore the similarities and differences in the hematopoietic systems of humans and mice. For example:

1. We reconstructed neutrophils, the largest subgroup of human immune cells, in humanized mice, and combined with clinical samples to study the nature and source of tumor-related immunosuppressive neutrophils, as well as the regulatory effect of neutrophils on bone environmental homeostasis.

2. By supplementing stromal cells, we improved human erythrocyte development in immune system humanized mice, built a humanized mouse model with high level of human erythrocyte reconstruction, and applied it to the study of human erythrocyte related diseases (such as malaria infection, thalassemia, etc.).

3. We found that mother-to-fetal interfacial tissue resident immune cells have special origin, temporal and spatial characteristics and functions.

II. Development and evaluation of drugs and vaccines for infectious diseases and tumors

Since the 20th century, scientists have found that infiltrating lymphocytes in cancer patients' tumors have the function of killing tumors in vitro, and some patients' conditions have been alleviated when they are injected back into cancer patients. Professor Steven Rosenberg, who pioneered this approach, later developed TCR T cell adoptive therapy, which has shown promising results in melanoma patients. However, the use of humanized mice to screen potent TCRS targeting different tumor antigens has not been successful, because the antigen-specific immune response is unusually inefficient. Similarly, humanized mice have a complete human B-cell developmental lineage, but the antigen-specific humoral immune response has been unable to reach a level similar to that of humans. Therefore, the acquisition of human TCR or whole-human antibodies is still dependent on human beings or genetically humanized animals, and the source is very limited. Therefore, we are committed to finding means that can effectively activate the antigen-specific response of humanized mice, while improving the interaction between stromal cells and immune cells in the immune organs of humanized mice, so that humanized mice can become a platform for obtaining whole-human monoclonal antibodies and TCR, and can also be used as an evaluation tool for vaccines and other therapeutic measures. At present, we have achieved breakthroughs in the subject direction are:

1. Through the design and modification of immunogens, the antigen-specific B cell response of humanized mice can be effectively activated to obtain monoclonal antibodies targeting the antigen, and a platform for obtaining whole-human monoclonal antibodies can be established.

2. By optimizing the cytokine environment and the efficiency of antigen presentation, TCR targeting tumor antigen was amplified in humanized mice, and then TCR T cells capable of killing tumor were obtained.

III. Humanized modeling and treatment of tumor/autoimmune diseases

Tumor bearing (PDX or CDX) + immunized humanized mice have been widely used in tumor immunotherapy, especially in immune checkpoint antibody and CAR T cell therapy. Autoimmune diseases, such as systemic lupus erythematosus (SLE), have entered the era of immunotherapy, but the lack of animal models that can simulate clinical disease indications and drug targets has also hindered the development of new drugs. Based on the optimized new humanized mouse model, we can:

1. Explore new tumor immunotherapy methods and detection methods (such as multi-specific antibody immunotherapy, novel oncolytic viruses, living cell factor probes, etc.);

2. The humanized SLE lupus model was successfully established, the clinicopathological features were fully reproduced, and a new targeted treatment scheme was developed.

IV. Next generation humanized mouse model: Immunity +X

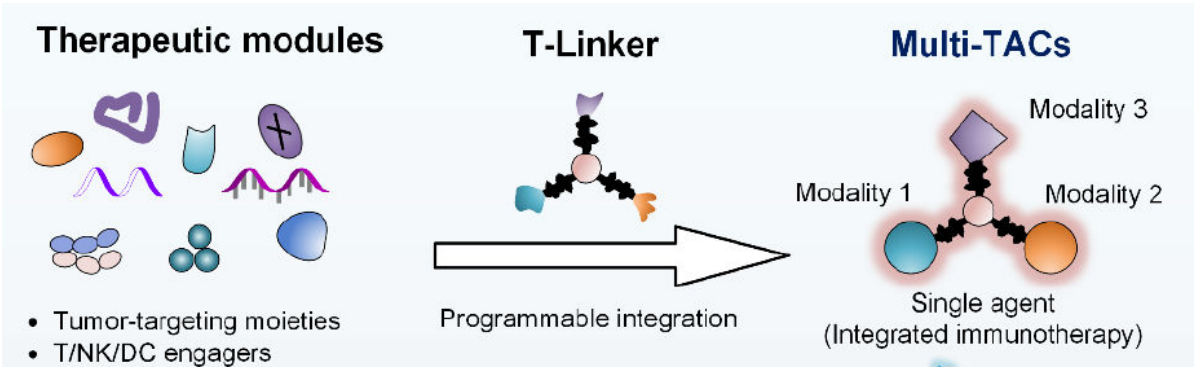
Not only the immune system, but also the study of multiple organs and tissues is limited by traditional mouse models, such as the inability of multiple human viruses or bacteria to infect mouse stromal cells, or even if they can infect, they show pathological features that are inconsistent with the clinic. In addition, gut microbiota plays an important role in immune cell development and function, and mice and humans have significant differences in both microbiota and immune system. Based on this, humanizing the immune system of mice is just the starting

point, and we will continue to embed human organs and flora into mice in order to reduce the use of traditional laboratory animals and truly simulate clinical responses, such as:

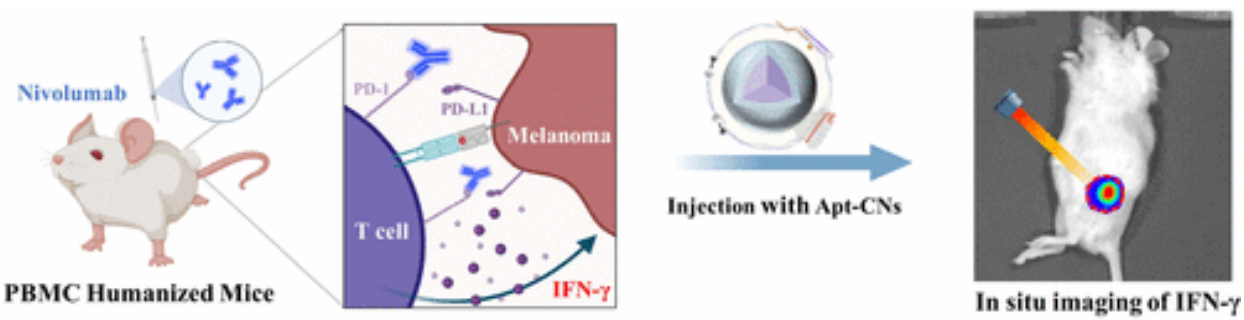
1. Based on immune system humanized mice, we transplanted human liver cells into mice with liver injury to construct immune system/liver double derived mouse model, which can be used as a research platform for pathological research, vaccine and new drug development of liver diseases (such as viral hepatitis).

2. By planting human fetal lung into mice with human immune system, construct mice with double lung/immune system for infection of respiratory pathogens, and further screen antiviral drugs or develop and evaluate vaccines.

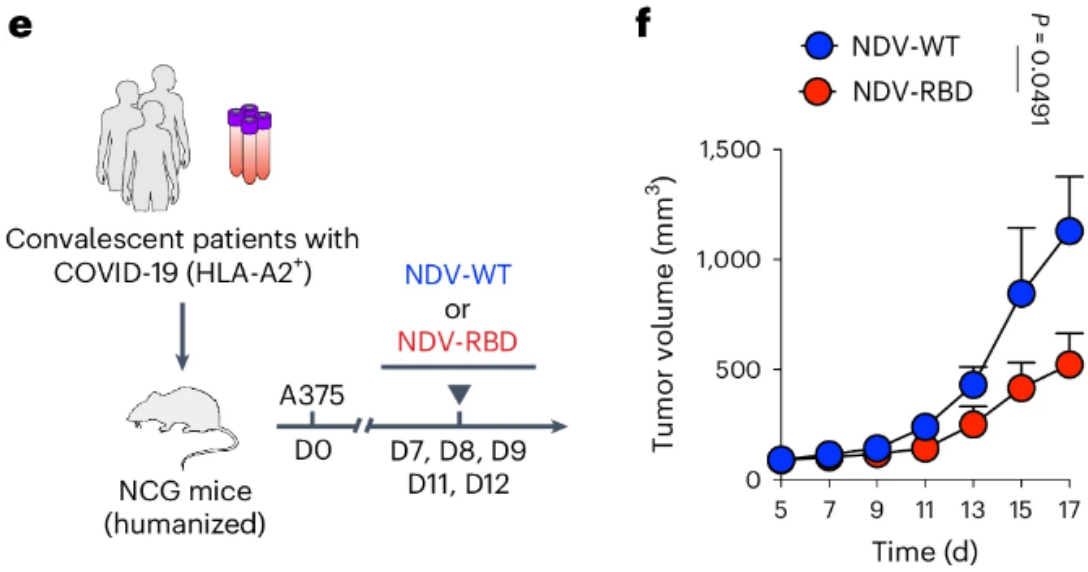
3. To explore the regulation of human immune cell development and function by eliminating and disturbing intestinal bacteria of humanized mice or transplanting human flora.



Development of tri-specific antibodies targeting human immune cells(Cell, 2024)



Development of novel antitumor therapy based on humanized mice(ACS Nano, 2024)



Promote the antitumor effect of bystander T cells in tumors(Nat Cancer, 2024)

Selected Publications

1. Feng Lin, Shenyi Yin, Zijian Zhang, Ying Yu, Haoming Fang, Zhen Liang, Rujie Zhu, Haitao Zhou, Jianjie Li, Kunxia Ca, Weiming Guo, Shan Qin, Yuxuan Zhang, Chenghao Lu, Han Li, Shibo Liu, Heng Zhang, Buqing Ye, Jian Lin*, Yan Li*, Xiaozheng Kang*, Jianzhong Jeff Xi*, Peng R. Chen*. (2024) Multimodal targeting chimeras enable integrated immunotherapy leveraging tumor-immune microenvironment. Cell. DOI: 10.1016/j.cell.2024.10.016
2. Deshan Ren, Zijian Zhang, Xiangkuan Zheng, Chun Lu, Yuxian Song, Shuang Liu, Shuai Ding, Wei Zhang*, Yayi Hou*, Yan Li*. (2024) TLR5 expression marks brain boarder associated macrophages and protects neonatal mice frombacterial meningitis.hLife. doi:10.1016/j.hlife.2024.04.007
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4. Zheng Liu, Xiang Duan, Yangfang Yun, Siqi Li, Zhiyuan Feng, Jiayin Zhan, Ran Liu, Yan Li*, Jingjing Zhang* (2023). A photoactivatable Aptamer-Crisper nanodevice enables precise profiling of interferon-gamma release in humanized mice. ACS Nano, doi: 10.1021/acsnano.3c12499
5. Chunyu Cheng, Yan Li (2023). The liver (Translate Book Chapter). Wiley Blackwell. Deshan Ren, Wei Liu, Shuai Ding, Yan Li*(2022) Protocol for generating human immune system mice and hydrodynamic injection to modulate human hematopoiesis in vivo, STAR protocols, doi: 10.1016/j.xpro.2022.101217
6. Xiufei Chen, Wenjie Zhou, Ren-Hua Song, Shuang Liu, Shu Wang, Yujia Chen, Chao Gao, Chenxi He, Jianxiong Xiao, Lei Zhang, Tianxiang Wang, Peng Liu, Kunlong Duan, Chen Zhang, Jinye Zhang, Yiping Sun, Felix Jackson, Fei Lan, Yun Liu, Yanhui Xu, Justin Jong-Leong Wong, Pu Wang, Hui Yang, Yue Xiong, Tong Chen*, Yan Li*, Dan Ye*. (2022) Tumor suppressor CEBPA interacts with and inhibits DNMT3A activity, Science Advances, doi: 10.1126/sciadv.abl5220

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Zijian Zhang

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Zixian Jiang

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Siqi Li

Xiang Duan

Wei Liu

Miribangu(Dual educate)

Dual educate

Rujie Zhu

Technician

Xiaohong Yu

Xinyang Sun

Zhaoyu Lin, Ph.D.

Zhaoyu Lin received his Ph.D degree in 2012 from Nanjing University under the mentoring of Dr.Gao Xiang. He has been a visiting scholar in Medical School of Washington University in St. Louis for three years. In 2014, he joined the Model Animal Research Center (MARC) of Nanjing University as research associated professor. In 2019, he became associated professor and a principle investigator in MARC.

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Immune and metabolic regulation of physical homeostasis

Immune and metabolism is the key factors to maintain the physical homeostasis. The disruption of immune or metabolic regulation of physical homeostasis will lead to the occurrence of complex diseases, like autoimmune disease, obesity, cancer, cardiovascular disease and Alzheimer's disease. In our laboratory, we are interest in analysis of functions and the underlying molecular mechanisms of the disease related genes in immune or metabolic homeostasis.

We focus on a new discovered immunoregulatory protein family-Gasdermin. Our lab analyzed the roles of Gasdermin family in physical status and autoimmune diseases. Gsdmd and Gsdme are demonstrated to be the executors of pyroptosis, which is a type of pro-inflammatory programmed cell death. We discovered that Gasdermin directly trigger cell death and inflammation in 2015. Our recent works are mainly about the regulation of Gsdmd in pyroptosis (Figure 1). We found that inhibition of ROS reduces the cleavage of Gsdmd in canonical pyroptosis and inhibition of GSDMB reduces the cleavage of GSDMD in non-canonical pyroptosis. We developed several methods to block pyroptosis in autoimmune diseases. Magnesium could block the membrane translocation of Gsdmd-N-terminals and greatly enhance the survival rate of sepsis mice model. We also found that nitrosonisoldipine is a selective inhibitor of inflammatory caspases and protects against pyroptosis and related septic shock. Recently, we found that apoptotic caspase-7 activation inhibits non-canonical pyroptosis by cleaving GSDMB and provide new targets for sepsis therapy.

We are also interesting with the relationship between obesogenic memory and immunity. Weight is very often regained during and after the treatments for obesity. This phenomenon is named obesogenic memory, leading to the failure of weight management and more importantly, of controlling the obesity-associated health problems including diabetes. Therefore, understanding the mechanisms regulating obesogenic memory, is especially beneficial for the patients with obesity. We has demonstrated that among immune cells, CD4+ T cells are the direct carrier, which is necessary and sufficient to induce and maintain obesogenic memory in mice. Recently, we found that obesogenic memory related CD4+ T cells are a subpopulation of central memory T cells with high expression of CD300C, which is a receptor of phosphatidylethanolamine (PE), an essential group of phospholipids in the cell membrane (Figure 2).

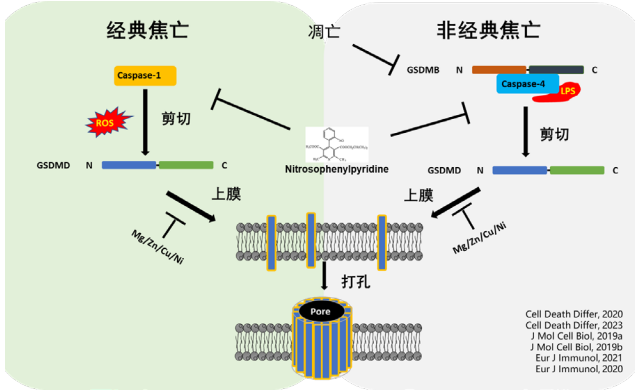

Figure 1. Gsdmd could be the target to block pyroptosis in autoimmune diseases

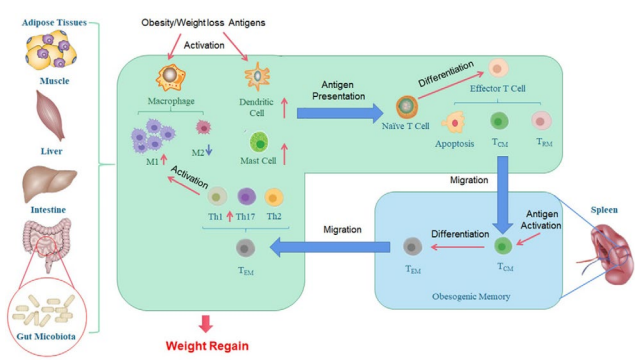

Figure 2. The role of immune cells in obesogenic memory

Selected Publications

1. Pei, J., D. Zou, L. Li, L. Kang, M. Sun, X. Li, Q. Chen, D. Chen, B. Qu, X. Gao*, and Z. Lin*, Senp7 Deficiency Impairs Lipid Droplets Maturation in White Adipose Tissues via Plin4 DeSUMOylation. J Biol Chem, 2024: p. 107319.
2. Liu, Q., M. Li, M. Sun, R. Xin, Y. Wang, Q. Chen, X. Gao*, and Z. Lin*, Depletion of Gsdma1/2/3 alleviates PMA-induced epidermal hyperplasia by inhibiting the EGFR-Stat3/Akt pathway. J Mol Cell Biol, 2024. 16(1).
3. Lin, Z*., Q. Chen, and H.B. Ruan*, To die or not to die: Gasdermins in intestinal health and disease. Semin Immunol, 2024. 71: p. 101865.
4. Li, X., T. Zhang, L. Kang, R. Xin, M. Sun, Q. Chen, J. Pei, Q. Chen, X. Gao*, and Z. Lin*, Apoptotic caspase-7 activation inhibits non-canonical pyroptosis by GSDMB cleavage. Cell Death Differ, 2023. 30(9): p. 2120-2134.
5. Zhao, M., K. Ren, X. Xiong, Y. Xin, Y. Zou, J.C. Maynard, A. Kim, A.P. Battist, N. Koneripalli, Y. Wang, Q. Chen, R. Xin, C. Yang, R. Huang, J. Yu, Z. Huang, Z. Zhang, H. Wang, D. Wang, Y. Xiao, O.C. Salgado, N.N. Jarjour, K.A. Hogquist, X.S. Revelo, A.L. Burlingame, X. Gao, J. von Moltke, Z. Lin*, and H.B. Ruan*, Epithelial STAT6 O-GlcNAcylation drives a concerted anti-helminth alarmin response dependent on tuft cell hyperplasia and Gasdermin C. Immunity, 2022. 55(4): p. 623-638.e5.
6. Kang, L., J. Dai, Y. Wang, P. Shi, Y. Zou, J. Pei, Y. Tian, J. Zhang, V.C. Buranasudja, J. Chen*, H. Cai*, X. Gao*, and Z. Lin*, Blocking Caspase-1/Gsdmd and Caspase-3/-8/Gsdme pyroptotic pathways rescues silicosis in mice. PLoS Genet, 2022. 18(12): p. e1010515.
7. Chen, Q., J. Zheng, D. Wang, Q. Liu, L. Kang, X. Gao*, and Z. Lin*, Nitrosonisoldipine is a selective inhibitor of inflammatory caspases and protects against pyroptosis and related septic shock. Eur J Immunol, 2021. 51(5): p. 1234-1245.
8. Zou, D., J. Pei, J. Lan, H. Sang, H. Chen, H. Yuan, D. Wu, Y. Zhang, Y. Wang, D. Wang, Y. Zou, D. Chen, J. Ren*, X. Gao*, and Z. Lin*, A SNP of bacterial blc disturbs gut lysophospholipid homeostasis and induces inflammation through epithelial barrier disruption. EBioMedicine, 2020. 52: p. 102652.
9. Wang, D., J. Zheng, Q. Hu, C. Zhao, Q. Chen, P. Shi, Q. Chen, Y. Zou, D. Zou, Q. Liu, J. Pei, X. Wu, X. Gao*, J. Ren*, and Z. Lin*, Magnesium protects against sepsis by blocking gasdermin D N-terminal-induced pyroptosis. Cell Death Differ, 2020. 27(2): p. 466-481.
10. Sun, M., S. Zheng, X. Gao*, and Z. Lin*, The role of immune cells in obesogenic memory. Cell Mol Immunol, 2020.
11. Wang, Y., P. Shi, Q. Chen, Z. Huang, D. Zou, J. Zhang, X. Gao*, and Z. Lin*, Mitochondrial ROS promote macrophage pyroptosis by inducing GSDMD oxidation. J Mol Cell Biol, 2019. 11(12): p. 1069-1082.

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Mingqi Zhao

Technicians

Jiafeng Zou
Jiaxiang Zou

Qiaoli Chen, Ph.D.

Dr. Qiaoli Chen received her Ph.D. degree from Nanjing University in 2017. From 2018 to 2023, she contributed her expertise as an associate researcher at the Model Animal Research Center (MARC) of Nanjing University. In 2023, Dr. Chen embarked on a new chapter in her career by establishing her own research group as a principal investigator and assistant professor in Metabolic Physiology. she was honored with the title of "Double Creation Doctor" by Jiangsu Province in 2009. Currently, Dr. Chen holds the position of Director of the Technical Center at the Model Animal Research Institute. Furthermore, Dr. Chen serves as the Youth Director of the Metabolic Biology Society and a member of both the Chinese Physical Society and the Jiangsu Society of Aging and Immunology.

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Signal transduction in pathology and treatment of metabolic syndrome

Dr. Qiaoli Chen's group is focus on the study of signal transduction mechanisms in the pathology and therapeutic process of metabolic syndrome. She conducted research on the metabolism and systemic metabolic homeostasis molecular mechanism of insulin sensitive organs, including kidney, liver and skeletal muscle. The goal of her laboratory is to provide theoretical basis and new pharmaceutical targets for the prevention, diagnosis and treatment of metabolic diseases such as type 2 diabetes, obesity and non-alcoholic fatty liver. Dr. Chen's research results have been published in international mainstream journals such as Science Advances, Diabetes, Developmental Cell, Nature Communications, PNAS, and Cell Discovery.

Selected Publications

1. Shu Su#, Chao Quan#, Qiaoli Chen#, Ruizhen Wang, Qian Du, Sangsang Zhu, Min Li, Xinyu Yang, Ping Rong, Jiang Chen, Yingyu Bai, Wen Zheng, Weikuan Feng, Minjun Liu, Bingxian Xie, Kunfu Ouyang, Yun Stone Shi, Feng Lan, Xiuqin Zhang, Ruiping Xiao, Xiongwen Chen, Hong-Yu Wang* & Shuai Chen*, AS160 is a lipid-responsive regulator of cardiac Ca2+ homeostasis by controlling lysophosphatidylinositol metabolism and signaling, Nature Communications, 2024, 15:9602
2. Qian Ouyang#, Qiaoli Chen#, Shunyuan Ke, Longfei Ding, Xinyu Yang, Ping Rong, Weikuan Feng, Ye Cao, Qi Wang, Min Li, Shu Su, Wen Wei, Minjun Liu, Jin Liu, Xu Zhang, John Zhong Li, Hong-Yu Wang * and Shuai Chen*， Rab8a as a mitochondrial receptor for lipid droplets in skeletal muscle, Developmental Cell,2023,58(4):289-305
3. Wen Wei#, Qiaoli Chen#, Minjun Liu#, Yang Sheng#, Qian OuYang, Shu Su, Lei Fang, Antonio Vidal-Puig, Hong Yu Wang* and Shuai Chen*, TRIM24 is an insulin-responsive regulator of P-bodies, Nature Communications, 2022,13(1): p. 3972.
4. Kun Zhou#, Qiaoli Chen#, Jiamou Chen, Derong Liang, Weikuan Feng, Minjun Liu,Qi Wang, Ruizhen Wang, Qian Ouyang, Chao Quan* and Shuai Chen*, Spatiotemporal regulation of insulin signaling by liquid-liquid phase separation, Cell Discovery , 2022, 8(1): p. 64.
5. Xinyu Yang#, Qiaoli Chen#, Qian Ouyang, Ping Rong, Weikuan Feng, Chao Quan, Min Li, Qing Jiang, Hui Liang, Tong-Jin Zhao*, Hong Yu Wang* and Shuai Chen*, Tissue-specific splicing and dietary interaction of a mutant As160 allele determine muscle metabolic fitness in rodents, Diabetes, 2021,70(8):1826-1842
6. Qiaoli Chen#, Ping Rong#, Sangsang Zhu#, Xinyu Yang, Qian OuYang Hong Yu Wang, Shuai Chen* Targeting RalGAP α 1 in skeletal muscle to simultaneously improve postprandial glucose and lipid control, Science Advances 5, eaav4116, 2019
7. Qiaoli Chen#, Ping Rong#, Dijin Xu, Sangsang Zhu, Liang Chen, Bingxian Xie, Qian Du, Chao Quan, Yang Sheng, Tongjin Zhao, Peng Li, Hong Yu Wang*, Shuai Chen*, Rab8a deficiency in skeletal muscle causes hyperlipidemia and hepatosteatosis via impairment of muscle lipid uptake and storage. Diabetes, 2017, 66(9): 2387-2399
8. Qiaoli Chen#, Bingxian Xie#, Sangsang Zhu, Ping Rong, Yang Sheng, Serge Ducommun, Liang Chen, Chao Quan, Min Li, Kei Sakamoto, Carol MacKintosh, Shuai Chen* and Hong Yu Wang*, A TBC1D1Ser231Ala knockin mutation partially impairs 5-aminoimidazole- 4-carboxamide-1-ß-D-ribofuranoside- but not exercise-induced muscle glucose uptake in mice. Diabetologia, 2017, 60(2): 336-345
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Tingting Fu, Ph.D.

Dr. Tingting Fu completed her Ph.D. at Nanjing University in 2019. Following that, she served as an associate researcher at the Model Animal Research Center (MARC) of Nanjing University from 2019 to 2023. In 2024, Dr. Fu was appointed as an associate professor at MARC. In 2020, she was selected for the "Double Creation Doctor" by Jiangsu Province.

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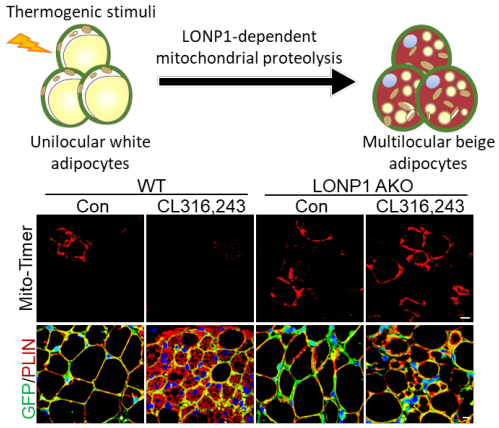
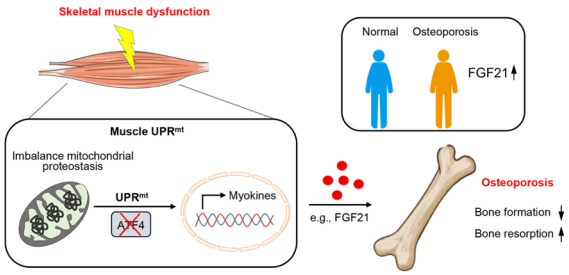
Mitochondrial quality control and Energy metabolism

Mitochondria are the essential organelles to generate energy and maintain the homeostasis of metabolic microenvironment. Dr. Fu's research focus on mitochondrial physiological relevance and molecular working mechanisms of mitochondrial quality control. Mitochondrial proteases serve as the first-line quality control by selective targeting and removal of damaged or dysfunctional mitochondrial protein to maintain proper function of mitochondria. Dr. Fu's group found that skeletal muscle LONP1-regulated mitochondrial protein homeostasis control muscle mass and function (Nat Commun., 2022). Dr. Fu's recent work found that LONP1 links proteolytic surveillance to mitochondrial metabolic rewiring and directs cell identity conversion during adipocyte thermogenic remodelling (Nat Cell Biol., 2023). These findings highlight the importance of the LONP1–succinate axis in maintaining WAT beiging ability, and suggest that targeting the natural decline of LONP1-dependent succinate regulation may be a viable strategy for reinstating white-to-beige adipocyte conversion capacity during ageing. Dr. Fu's also emphasized the pivotal role of skeletal muscle mitochondrial proteostasis in responding to alterations in loading conditions and in coordinating UPRmt to modulate bone metabolism (Reasearch, 2023).



Proteolytic rewiring of mitochondria by LONP1 directs cell identity switching of adipocytes



Imbalanced skeletal muscle mitochondrial proteostasis causes bone loss

Selected Publications

1. Fu T*, Sun W*, Xue J*, Zhou Z*, Wang W, Guo Q, Chen X, Zhou D, Xu Z, Liu L, Xiao L, Mao Y, Yang L, Yin Y, Zhang X， Wan Q， Lu B, Chen Y, Zhu M, Scherer PE, Fang L, Piao H, Shao M#, Gan Z#. Proteolytic rewiring of mitochondria byLONP1 directs cell identity switching of adipocytes. Nature Cell Biology. 2023; Jun;25(6):848-864.
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4. Jin Z*, Mao Y*, Guo Q*, Yin Y, Kiram A, Zhou D, Yang J, Zhou Z, Xue J, Feng Z, Liu Z, Qiu Y, Fu T#, Gan Z#, Zhu Z#. Imbalanced Skeletal Muscle Mitochondrial Proteostasis Causes Bone Loss. Research (Wash D C). 2024 Aug 30;7:0465.
5. Fu T*, Xu Z*, Liu L, Guo Q, Wu H, Liang X, Zhou D, Xiao L, Liu L, Liu Y, Zhu M, Chen Q#, Gan Z#. Mitophagy Directs Muscle-Adipose Crosstalk to Alleviate Dietary Obesity. Cell Reports. 2018; 23:1357–1372.

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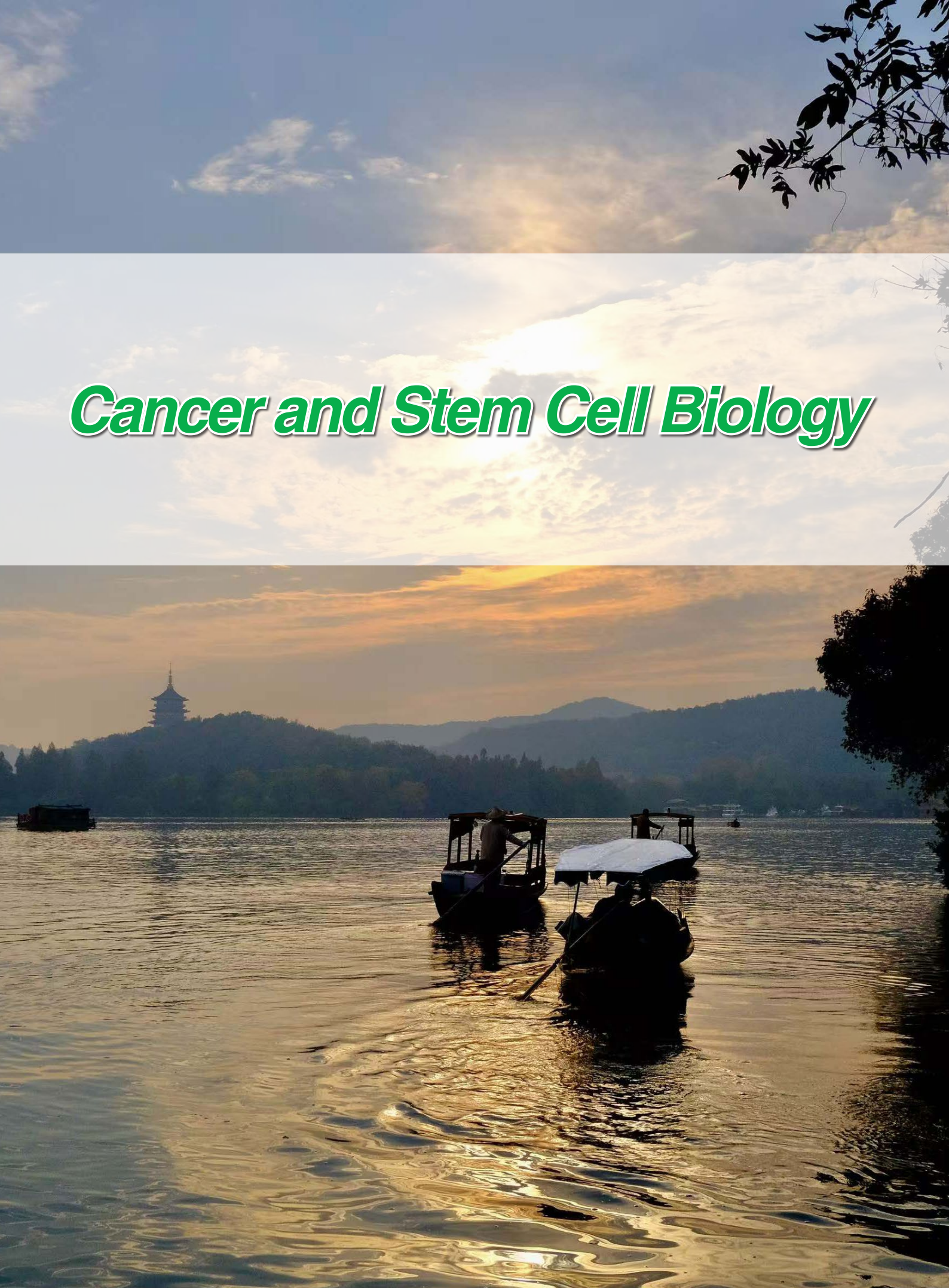

Cancer and Stem Cell Biology

Geng Liu, Ph.D.

Geng Liu received his B.S. degree in Biochemistry from Wuhan University, China and his Ph.D. degree in Gene & Development from University of Texas Graduate School of Biomedical Sciences at Houston in 1999. After his postdoctoral training at University of Texas M.D. Anderson Cancer Center, Dr. Geng Liu joined the Model Animal Research Center of Nanjing University as a principal investigator and professor of Genetics in 2006.

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Probing and Understanding Cellular Metabolism and Stress Response

Integral to their functions, various cell behaviors are dictated by extrinsic and intrinsic stimuli through a network of signaling mechanisms. Our laboratory is interested in studying the determinants of cell behaviors and their close connections with stress responses and cellular metabolism in the contexts of tissue homeostasis as well as cancer. We investigated how stress response as mediated by the p53 signaling pathway regulated cell behaviors including cell proliferation, cell competition, inflammation, and Epithelial-Mesenchymal transition. On the other hand, cellular metabolisms are not only required for the execution of proper cell functions but also serve as a signaling module in adapting the cells to certain behaviors. In addition, cell metabolisms are intrinsically connected to cellular redox state and stress response. Therefore, dissecting the intricate interplay between cell behaviors, stress responses and metabolism, facilitated with the establishment and utilization of probes and reporters may allow us to fully understand the complex cell behaviors in many fundamental processes including development, ageing and tumorigenesis.

p53 stress response pathway influences cell behaviors in distinctive manners

p53 is extremely important for stress response and tumor suppression as exemplified by its mutations found in over 50% of human cancers. p53 protein is undetectable in normal tissues. With the BAC transgenic p53 reporter mice, we revealed a regulatory mechanism controlling p53 expression and activity selectively in the proliferating cellular compartments during mouse development, postnatal growth, tissue homeostasis, regeneration and tumorigenesis (Chen, et al., 2015). The close monitoring of cellular proliferation state by p53 also serves as a base to generate the first genetic tool for proliferation tracing in studying the cardiomyocyte proliferation during heart regeneration (Xiao, et al., 2017). On the other hand, in collaboration with Dr. Jianghuai Liu's laboratory, the successful identification and marking of p53 deficient cells also offers a unique and highly specific strategy for the future development of targeted cancer prevention and therapy (Wang, et al., 2022).

In the presence of stress, p53 is activated to exert its role in influencing the cell fate. Various degree of stresses results in different level of p53 activation. Instead of directing the classic pathways of cell cycle arrest, senescence or apoptosis, we demonstrated that low dose X-ray induced mild p53 activation affected the EMT process during valvuloseptal morphogenesis of cardiac development and resulted in congenital heart defects in mice (Zhang, et al., 2012). p53 also play a crucial role in macrophage polarization in the tumor microenvironment to affect tumorigenesis in a non-cell autonomous manner (He, et al., 2015). Our recent study found that mild p53 activation in cells renders them less competitive in multi-cellular context during mouse embryogenesis, possibly contributing to the control of tissue fitness (Zhang, et al, 2017). These results indicate that p53 signaling pathway critically and delicately influence cell behaviors and functions in distinctive manners.

Probing, manipulating and understanding cellular metabolic states and their maintenance in vivo

To study the influence of cellular metabolism on cell behaviors and function in a multitude of in vivo contexts, we established mouse models in imaging and probing the metabolic heterogeneity within the tissues, in which we reveal highly stringent quality control mechanisms for an active mitochondrial state (Fig.1, Xie et al., 2022). Extending from the in vivo observations, we focused on further elucidating the regulatory network of mitochondrial oxidative metabolism and redox homeostasis using various approaches including drug screening and expression profiling.

In addition, we have established a series of mouse models involved in promoting specific metabolic pathways in a controlled manner. Our results showed that cellular metabolisms could be manipulated in vivo and may have great impact on either cell behavior or systemic homeostasis (Xiang et al., 2021). Aiming to discover new strategies to boost cancer immune therapy, we found that specific manipulation and alteration of T cell metabolism could potently stimulate the anti-tumor immune response, revealing interesting insights for the intrinsic regulatory roles of the specific metabolic route on T cell differentiation and function. We believe these attempts will greatly impact on our abilities in the understanding and fighting against a variety of diseases, especially those linked to cancer and ageing, in the perspectives of cellular metabolism and stress response.

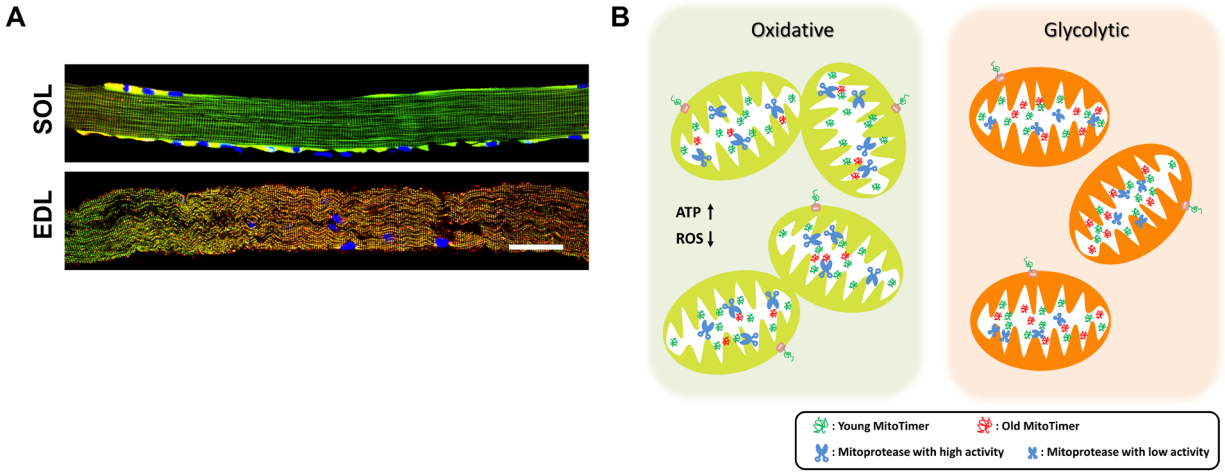

Figure 1. MitoTimer fluorescence reveals an active mitochondrial state tightly coupled with mitoproteolysis in the mouse oxidative skeletal muscle fibers

(A) Representative MitoTimer fluorescence images of freshly isolated fibers in mouse soleus (oxidative) and EDL (glycolytic) muscles following doxycycline induction from 1 month to 3 months of age. Scale bar, 50μm. Note the green predominant fluorescence as well as the lack of red puncta (indicating mitophagy) in the soleus fiber. (B) A schematic summarizes the results that the energy coupled mitoproteolytic activity dictates MitoTimer fluorescence spectrum and marks an active and well-maintained mitochondrial state.

Selected Publications

1. Xie YY#, Zhang YN#, Sun AN#, Peng YM, Hou WK, Xiang C, Zhang GX, Lai BB, Hou XS, Zheng FF, Wang F and Liu G*. The coupling of mitoproteolysis and oxidative phosphorylation enables tracking of an active mitochondrial state through MitoTimer fluorescence. Redox Biology 2022, 56,102447.
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5. Xiao Q, Zhang GX, Wang HJ, Chen L, Lu SS, Pan DJ, Liu G*, Yang ZZ*. A p53 based genetic tracing system to follow postnatal cardiomyocyte expansion in heart regeneration. Development. 2017, 144(4):580-589.
6. He XY, Xiang C, Zhang CX,Xie YY, Chen L, Zhang GX, Liu G*. p53 in myeloid lineage modulates an inflammatory microenvironment limiting initiation and invasion of intestinal tumors. Cell Rep. 2015, 13(5):888-97.
7. Chen L, Zhang GX, He XY, Zhang CX, Xie YY, Liu G*. BAC transgenic mice provide evidence that p53 expression is highly regulated in vivo. Cell Death Dis. 2015, 6: e1878.
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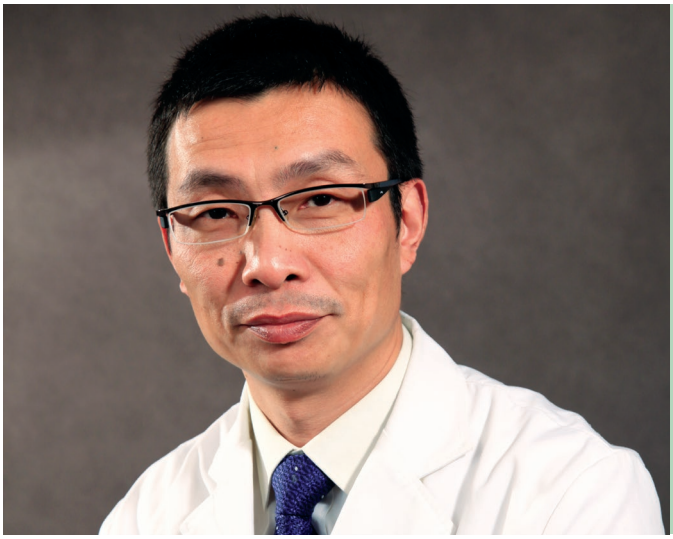

Qing Jiang Ph.D., M.D.

The head of the department of Sports Medicine and Adult Reconstructive Surgery, Nanjing Drum Tower Hospital/ The vice president of school of medicine, Nanjing University.

Won the National Science Fund for Distinguished Young Scholars in 2011. Established human gene bank of bone and joint disease. Published hundreds of SCI articles, included Nat Med, Nat Gene, Sci Transl Med, PNAS, Cell Metab, etc. The first domestic scholars who hold the post of committee member of the OARSI; vice chair of China branch of ICRS; Chairman orthopaedic branch of Jiangsu medical association.

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Etiology and treatment of skeletal diseases

Motor system diseases such as abnormally elevated osteocyte-derived sclerostin, achilles tendinopathy (AT) and osteoarthritis (OA) et al. significantly reduce the quality of life for patients. And tissue engineering scaffolds have presented effective value in bone and cartilage repair. However, the precise mechanism and treatment remains unclear. Further study is still a challenge.

Herein, we speculate that abnormally elevated osteocyte-derived sclerostin may contribute to cognitive impairment by inhibiting Wnt–β-catenin signalling in neurons during ageing and AD pathogenesis. And we revealed that abnormally elevated sclerostin levels accelerate cognitive impairment by increasing Aβ production through β-catenin–β-secretase 1 (BACE1) signalling during AD progression. Cognitive decline was accompanied by deregulation of Wnt–β-catenin signalling in the brains of 22-month-old male mice but not in those of 12-month-old male mice, and sclerostin levels in the brain were significantly increased in 22-month-old male mice compared to 12-month-old male mice (Fig. 1). Peripheral sclerostin could pass through the BBB into the brain during ageing (Fig. 1). Thus, all of the above results prove that Scl-Ab can suppress the production of Aβ and the formation of amyloid plaques to alleviate memory impairment and synaptic deficits in AD mice with high serum sclerostin levels (Shi, 2024). We also provide novel insights into the involvement of FLS-derived exosomes in OA pathogenesis, suggesting that inf-exo-induced macrophage dysfunction represents an attractive target for OA therapy (Liu, 2024). revealed that WTAPdependent RNA m6 A modification contributed to Wnt/β-catenin pathway activation and OA progression through posttranscriptional regulation of FRZB mRNA (An, 2024). Cartilage-on-achip platform provides a desired in vitro model for osteoarthritis, which is of great significance in disease research and drug development (Liu, 2024). we developed poly (lactic-co-glycolic acid) (PLGA) microspheres loaded with nano-magnesium oxide modified with stearic acid (SA), MgO&SA@ PLGA, for intra-articular injection (Zheng, 2024). We also identified the protective role of the circadian clock against oxidative stress and inflammation in the Achilles (Zhang, 2024). The multifunctional Dopa-gel enhanced immunomodulatory and angiogenic properties (Wang, 2024). Thus, we providing potentially effective therapeutic strategies for motor system diseases treatment.

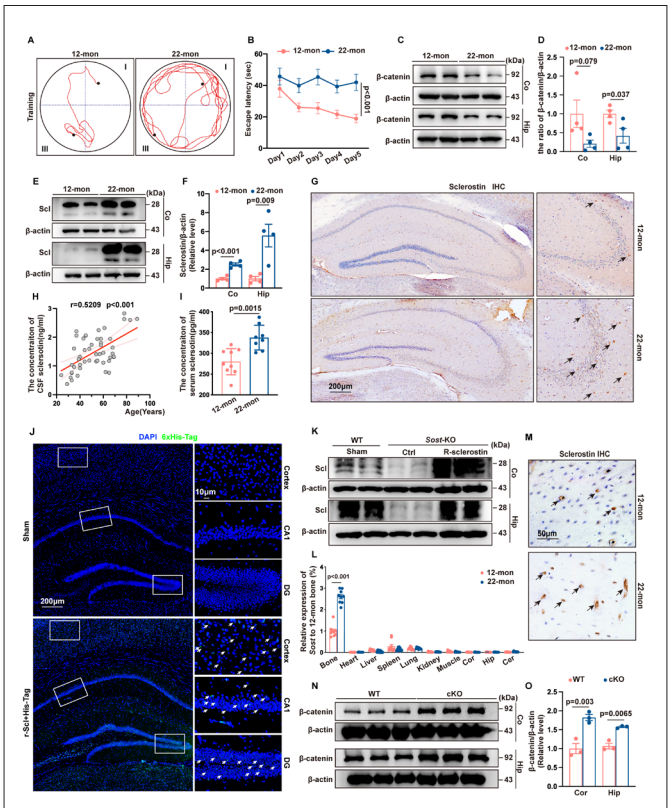

Figure 1. Osteocyte-derived sclerostin mediates canonical Wnt signalling deregulation in the brain during ageing.

Selected publications

1. Shi T, Shen S, Shi Y, Wang Q, Zhang G, Lin J, Chen J, Bai F, Zhang L, Wang Y, Gong W, Shao X, Chen G, Yan W, Chen X, Ma Y, Zheng L, Qin J, Lu K, Liu N, Xu Y, Shi YS, Jiang Q*, Guo B*. Osteocyte-derived sclerostin impairs cognitive function during ageing and Alzheimer's disease progression. Nat Metab. 2024 Mar;6(3):531-549. (IF: 20.852)
2. Liu B, Xian Y, Chen X, Shi Y, Dong J, Yang L, An X, Shen T, Wu W, Ma Y, He Y, Gong W, Peng R, Lin J, Liu N, Guo B*, Jiang Q*. Inflammatory Fibroblast-Like Synoviocyte-Derived Exosomes Aggravate Osteoarthritis via Enhancing Macrophage Glycolysis. Adv Sci (Weinh). 2024 Apr;11(14):e2307338. (IF: 15.168)
3. An X, Wang R, Lv Z, Wu W, Sun Z, Wu R, Yan W, Jiang Q, Xu X. WTAP-mediated m6A modification of FRZB triggers the inflammatory response via the Wnt signaling pathway in osteoarthritis. Exp Mol Med. 2024 Feb;56(1):156-167. (IF: 12.899)
4. Liu H, Wu X, Liu R, Wang W, Zhang D, Jiang Q. Cartilage-on-a-chip with magneto-mechanical transformation for osteoarthritis recruitment. Bioact Mater. 2023 Nov 8;33:61-68. (IF: 18.964,)
5. Zhang Y, Wu Y, Wang Y, Lu J, Lu Y, Wang P, Li L, Yan W, Cai H, Hannah Leigh W, Zhang L, Bai W, Jiang Q, Xu X. Achilles tendinopathy treatment via circadian rhythm regulation. J Adv Res. 2024 Oct 21:S2090-1232(24)00477-6. (IF: 10.776)
6. Zheng L, Zhao S, Li Y, Xu J, Yan W, Guo B, Xu J, Jiang L, Zhang Y, Wei H, Jiang Q. Engineered MgO nanoparticles for cartilage-bone synergistic therapy. Sci Adv. 2024 Mar 8;10(10):eadk6084. (IF: 13.659)
7. Wang P, Qian L, Liang H, Huang J, Jin J, Xie C, Xue B, Lai J, Zhang Y, Jiang L, Li L, Jiang Q. Polyvinyl Alcohol/Acrylamide Hydrogel with Enhanced Mechanical Properties Promotes Full-Thickness Skin Defect Healing by Regulating Immunomodulation and Angiogenesis Through Paracrine Secretion. Engineering. 2024, 37:138-151. (IF: 10.1)
8. Wang P, Wang Q, Wu D, Zhang Y, Kang S, Wang X, Gu J, Wu H, Xu Z, Jiang Q. Enhancing osteogenic bioactivities of coaxial electrospinning nano-scaffolds through incorporating iron oxide nanoparticles and icaritin for bone regeneration. Nano Research, 2024. (IF: 9.9)

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Genetic rewiring of immune regulation

In recent years, our laboratory has been devoted to development of new genetic tools (based on the principle of synthetic biology and genome editing) to accurately reprogram cell functions. With our past research backgrounds in tumor immunology, we are very excited about the prospect of applying such new tools to development of cancer immunotherapy. Our investigations shall also hold potential for broad applications in medicine and agriculture.

Some ongoing projects in the lab are described in the following section:

1. Writing-enabled genome editing tools:

We and collaborators have recently developed a more efficient version of PE (xrPE) (Fig. 1A, Zhang G et al, 2022). Furthermore, our collaborative team has also integrated the PE-specialized editing mechanism with Cas9's dsDNA nuclease activity, to establish a highly active uPEn platform. Attributed to the adoption of a regulatory protein module, the uPEn showed marked improvements in "copying" accuracies (Fig. 1B, C, Li X et al., 2023). In comparison to other state-of-the-art platforms, the uPEn features superior efficiencies for accurate edits, despite also causing certain levels of undesirable indels (Fig. 1D, E). Therefore, the uPEn represents a non-canonical, yet readily applicable platform to install small-sized genetic elements, especially when the efficiencies are considered a priority. We are actively experimenting the tool in animal zygotes to install previously-difficult genetic modifications (Fig. 1F, manuscript in revision). We envision that these new tools have laid a solid foundation for future applications to rewire genetic circuits in cells/organisms (Fig. 1G).

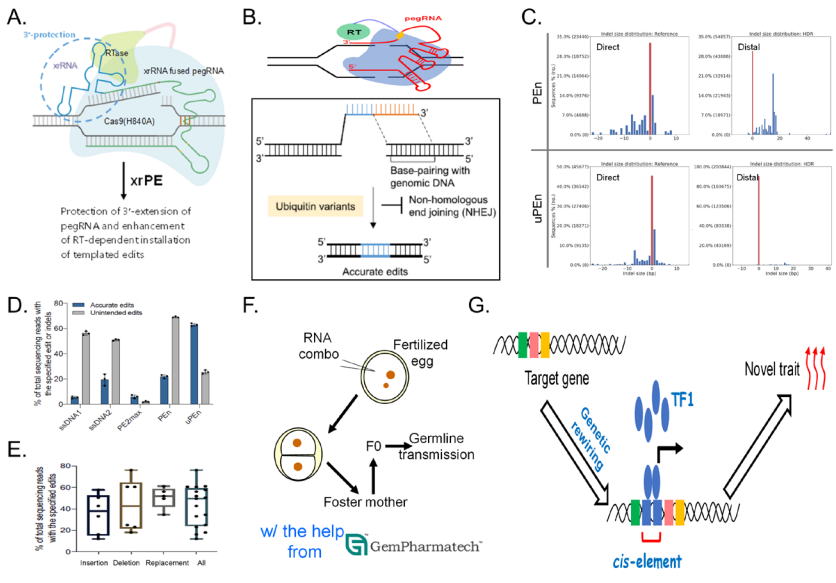

Figure 1: Writing-enabled genome editing tools.

(A) The xrPE platform is further applied to precisely install primary and reverse mutations in cells. (B-E) The uPEn platform is based on the previous PEn tool that integrates DSB induction and the "copying" mechanisms to allow genetic knock-ins. The uPEn further adopts a protein regulator of DSB repair that drives more accurate installation of reverse-transcribed edits into the target site. For knock-in efficiencies, uPEn compares quite favorably to canonical PE, PEn, and the CRISPR/HDR approach. (F) We have applied the uPEn tool to knocking in regulatory element in animal zygotes. (G) These advanced "writing-enabled" genome editing tools provide exciting opportunities to purposeful modifications of genetic circuits in cells and organisms.

2.Improvement of base editors:

Base editors (BEs) are a recent generation of genome editing tools that couple a cytidine or adenosine deaminase activity to a catalytically impaired Cas9 moiety (nCas9) to enable specific base conversions at the targeted genomic loci. Given their strong application potential, BEs are under active developments toward greater levels of efficiency and safety. Here, a previously overlooked nCas9-centric strategy is explored for enhancement of BE (Fig. 2, Zhang G et al, 2024). Based on a cytosine BE (CBE), 20 point mutations associated with nCas9-target interaction are tested. Subsequently, from the initial positive X-to-arginine hits, combinatorial modifications are applied to establish further enhanced CBE variants (1.1~1.3). Parallel nCas9 modifications in other versions of CBEs including A3A-Y130F-BE4max, YEE-BE4max, CGBE and split-AncBE4max, as well as in the context of two adenine BEs (ABE), likewise enhance their respective activities. The same strategy also substantially improves the efficiencies of high-fidelity nCas9/BEs (Fig. 2, left). Further evidence confirms that stabilization of nCas9-substrate interactions underlies the enhanced BE activities. In support of their translational potential, the engineered CBE and ABE variants respectively enable 82% and 25% higher rates of editing than the controls in primary human T cells (Fig. 2, right). Our study thus demonstrates a highly adaptable strategy for enhancing BE, and for optimizing other forms of Cas9-derived tools.

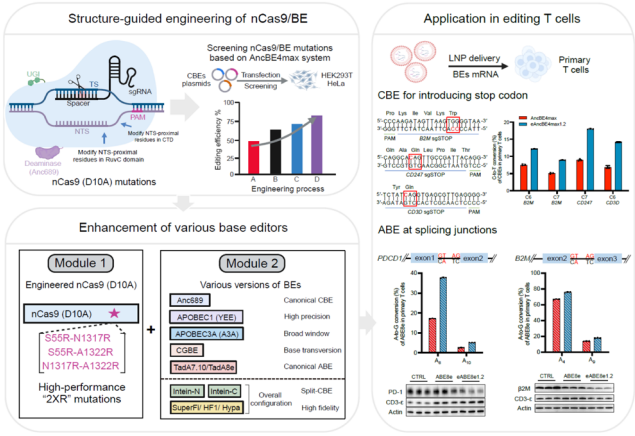

Figure 2: Improvement of base editors.

Our recent study explored a previously overlooked nCas9-centric strategy for enhancement of base editors (BE). Structure-guided protein engineering established nCas9 variants that can commonly enhance a collection of BE tools. In support of their translational potential, the engineered CBE and ABE variants respectively enabled 82% and 25% higher rates of editing than the controls in primary human T cells.

Selected publications: (*corresponding author)

1. Zhang G , Song Z , Huang S , Wang Y , Sun J, Qiao L, Li G, Feng Y, Han W, Tang J, Chen Y, Huang X, Liu F*, Wang X* and Liu J*. nCas9 Engineering for Improved Target Interaction Presents an Effective Strategy to Enhance Base Editing. Adv Sci 2024, 11(31):e2405426.
2. Song Z , Zhang G , Huang S , Liu Y, Li G, Zhou X, Sun J, Gao P, Chen Y, Huang X, Liu J* and Wang X*. PE-STOP: A versatile tool for installing nonsense substitutions amenable for precise reversion. J Biol Chem 2023, 299(8):104942.
3. Li X , Zhang G , Huang S , Liu Y, Tang J, Zhong M, Wang X, Sun W, Yao Y, Ji Q, Wang X, Liu J*, Zhu S*, Huang X*. Development of a versatile nuclease prime editor with upgraded precision. Nat Commun 2023, 14(1):305.
4. Meng Q, Sun H* and Liu J*. Precise somatic genome editing for treatment of inborn errors of immunity. Front Immunol 2022, 13:960348.
5. Zhang G , Liu Y , Huang S , Qu S, Cheng D, Yao Y, Ji Q, Wang X*, Huang X* and Liu J*. Enhancement of prime editing via xrRNA motif-joined pegRNA. Nat Commun 2022, 13(1):1856.
6. Wang Y , Zhang G , Meng Q , Huang S, Guo P, Leng Q, Liu G*, Huang X* and Liu J*. Precise tumor immune rewiring via synthetic CRISPRa circuits gated by concurrent gain/loss of transcription factors. Nat Commun 2022, 13(1):1454.

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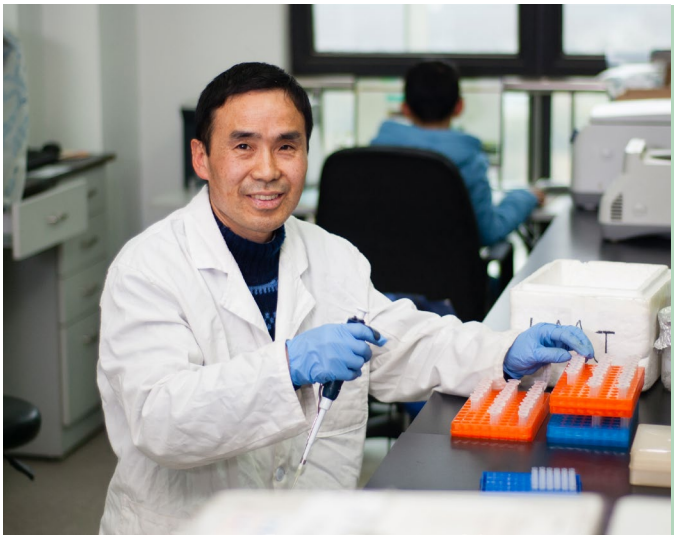

Jinzhong Qin , Ph.D.

Jinzhong Qin received his Ph.D. from Cleveland State University (Ohio, USA) in 2004 after completing a research project at Department of Immunology, Cleveland Clinic Foundation. His research at Cleveland Clinic was focused on the regulation of Innate Immune signaling pathways. From 2005 to 2008, Jinzhong did his postdoctoral fellowship at the Massachusetts General Hospital Cancer Center, Harvard Medical School in Boston, USA, and he was promoted to Assistant in Genetics within the same Institution in 2008. Using murine genetics, he described an essential role of L3mbtl2-containing atypical Polycomb Repressive Complex 1 (PRC1) in embryonic stem cells (ESCs) proliferation and early embryonic development. He joined the Faculty of Model Animal Research Center (MARC), Nanjing University in 2013. He is now a Professor of genetics and developmental biology and a Principal Investigator in MARC.

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Roles of the polycomb group proteins in stem cells & early development

1. A functional crosstalk between the H3K9 methylation writers and their reader HP1 in safeguarding embryonic stem cell identity

Histone H3 lysine 9 (H3K9) methylation, as a hallmark of heterochromatin, has a central role in cell lineage and fate determination. Although evidence of a cooperation between H3K9 methylation writers and their readers has started to emerge, their actual interplay remains elusive. Here, we show that loss of H3K9 methylation readers, the Hp1 family, causes reduced expression of H3K9 methyltransferases, and that this subsequently leads to the exit of embryonic stem cells (ESCs) from pluripotency and a reciprocal gain of lineage-specific characteristics. Importantly, the phenotypes of Hp1-null ESCs can be rescued by ectopic expression of Setdb1, Nanog, and Oct4. Furthermore, Setdb1 ablation results in loss of ESC identity, which is accompanied by a reduction in the expression of Hp1 genes. Together, our data support a model in which the safeguarding of ESC identity involves the cooperation between the H3K9 methylation writers and their readers.

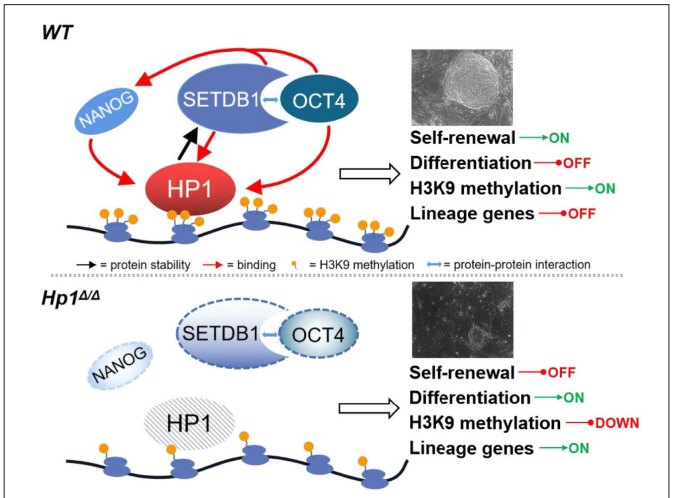

Figure 1. Schematic representing of the role of HP1 family in the maintenance of ESC pluripotency. HP1 and SETDB1 is integrated with the major pluripotent transcription factors OCT4 and NANOG to safeguard ESC identity.

2. Functional redundancy among Polycomb complexes in maintaining the pluripotent state of embryonic stem cells

Polycomb group proteins assemble into multi-protein complexes, known as Polycomb repressive complexes 1 and 2 (PRC1 and PRC2), that guide cell fate decisions during embryonic development. PRC1 forms an array of biochemically distinct canonical PRC1 (cPRC1) or non-canonical PRC1 (ncPRC1) complexes characterized by the mutually exclusive presence of PCGF (PCGF1-PCGF6) paralog subunit; however, whether each one of these subcomplexes fulfills a distinct role remains largely controversial. Here, by performing a CRISPR-based loss-of-function screen in embryonic stem cells (ESCs), we uncovered a previously unappreciated functional redundancy among PRC1 subcomplexes. Disruption of ncPRC1, but not cPRC1, displayed severe defects in ESC pluripotency. Remarkably, coablation of non-canonical and canonical PRC1 in ESCs resulted in exacerbation of the phenotype observed in the non-canonical PRC1-null ESCs, highlighting the importance of functional redundancy among PRC1 subcomplexes. Together, our studies demonstrate that PRC1 subcomplexes act redundantly to silence lineage-specific genes and ensure robust maintenance of ESC identity.

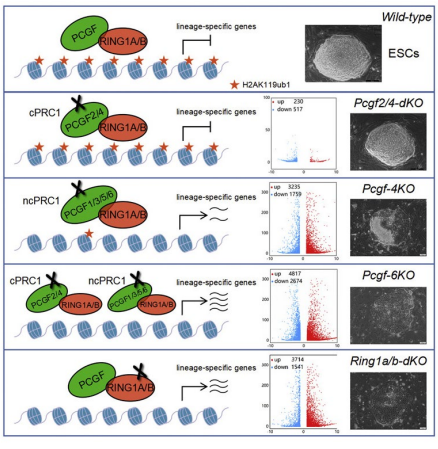

Figure 2. Canonical PRC1 and non-canonical PRC1 act redundantly to suppress lineage-specific genes and preserve ESC identity.

Selected publications:

1. Dong L., Liao H., Zhao L., Wang J., Wang C., Wang B., Sun Y., Xu L., Xia Y., Ling S*., Lou X*., Qin J*. (2023) A functional crosstalk between the H3K9 methylation writers and their reader HP1 in safeguarding embryonic stem cell identity. Stem Cell Reports. 18(9):1775-1792.
2. Zhu Y., Dong L., Wang C., Hao K., Wang J., Zhao L., Xu L., Xia Y*., Jiang Q*., and Qin J*. (2022) Functional redundancy among Polycomb complexes in maintaining the pluripotent state of embryonic stem cells.Stem Cell Reports. 17(5):1198-1214.
3. Wang C., Hao K., Dong L., Wang J., Zhao L., Xu L., Xia Y*., Jiang Q*., and Qin J*. (2022) The MuvB complex safeguards embryonic stem cell identity through regulation of the cell cycle machinery. J Biol Chem. 298(3):101701.
4. Qin J*., Wang C., Zhu Y., Su T., Dong L., Huang Y., Hao K. (2021) Mga safeguards embryonic stem cells from acquiring extraembryonic endoderm fates. Sci Adv. 7(4): eabe5689.
5. Huang Y., Su T., Wang C., Dong L., Liu S., Zhu Y., Hao K., Xia Y*., Jiang Q*., and Qin J*. (2021) Rbbp4 suppresses premature differentiation of embryonic stem cells. Stem Cell Reports. S2213-6711(21)00039-4.
6. Zhao W., Liu M., Ji H., Zhu Y., Wang C., Huang Y., Ma X., Xing G., Xia Y*., Jiang Q*., and Qin J*. (2018) The polycomb group protein Yaf2 regulates the pluripotency of embryonic stem cells in a phosphorylation-dependent manner. J Biol Chem. 293(33):12793-12804.
7. Huang Y., Zhao W., Wang C., Zhu Y., Liu M., Tong H., Xia Y*., Jiang Q*., and Qin J*. (2018) Combinatorial Control of Recruitment of a Variant PRC1.6 Complex in Embryonic Stem Cells. Cell reports. 22, 3032 -3043.
8. Zhao W., Huang Y., Zhang J., Liu M., Ji H., Wang C., Cao N., Li C., Xia Y*., Jiang Q*., and Qin J*. (2017) Polycomb group RING finger proteins 3/5 activate transcription via an interaction with the pluripotency factor Tex10 in embryonic stem cells. J Biol Chem. 292, 21527 -21537.

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Pingping Shen received her Ph.D. degree at Nanjing University in 2003. From 2002 to 2003, she worked at University of California at San Diego as a visiting professor. In 2004, she was appointed as a professor in Nanjing University. Research in Pingping Shen's Lab is mainly focused on two fields: (1) the development of novel immunotherapeutic techniques for disease treatment. (2) the functional regulation of macrophages, stem cells in chronic inflammatory diseases such as cancer, metabolic disturbance.

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Inflammatory diseases and cell therapy techniques

PPARγ T166 dephosphorylation-mediated lipid synthesis sustains the reparative function of macrophages during tissue repair

In this study, wound macrophage atlas revealed that fatty acid synthesis (FAS) was a feature of reparative macrophages in 9 tissue injury models. This metabolic reprogramming was precisely regulated by PPARγ threonine 166 (T166) dephosphorylation. In injured tissues, repair signaling led to decreased macrophage PPARγ T166 phosphorylation, which resulted in a partially active PPARγ transcriptional program comprised of increased binding activity to the regulator regions of lipid synthesis-associated genes, thereby increased lipogenesis. The accumulated lipids served as signaling molecules, triggering STAT3-mediated growth factor expression, and supporting the synthesis of phospholipids for the expansion of the endoplasmic reticulum (ER), which was required for protein secretion. Genetic or pharmacological inhibition of PPARγ T166 phosphorylation promoted the reparative function of macrophages and facilitated tissue regeneration. These results provide an additional rationale for the efficacy of FAS activation in the treatment of tissue injury.

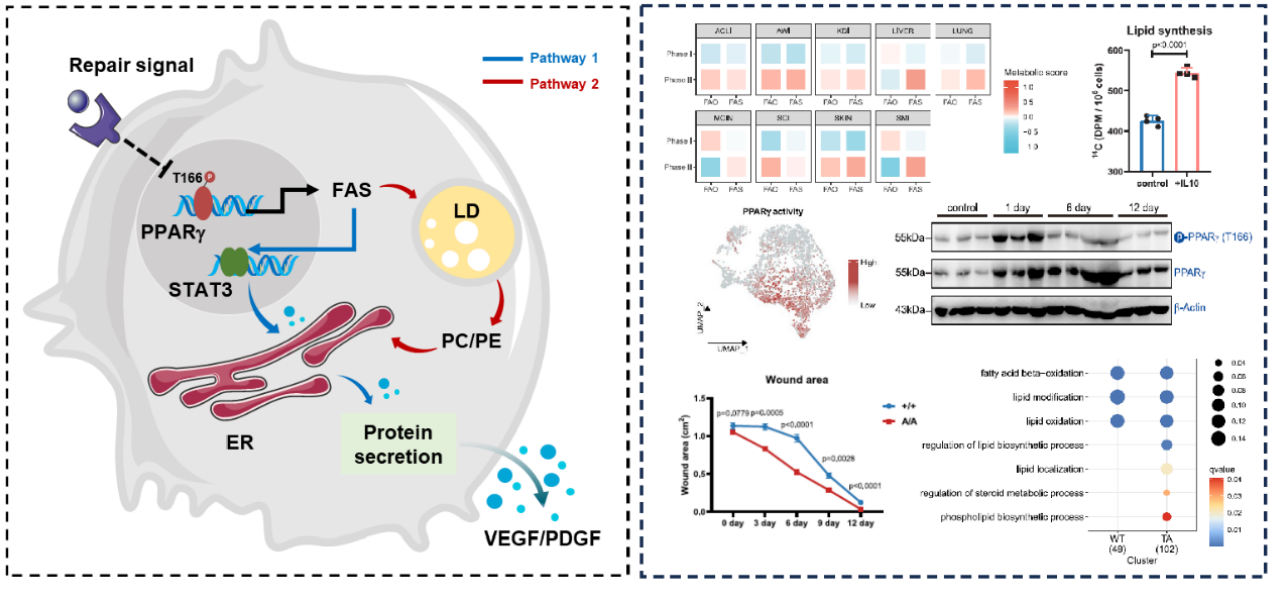

Fig. PPARγ T166 dephosphorylation regulates lipid synthesis in reparative macrophages.

Selected publications

1. Zuo SM, Wang YX, Bao HJ, Zhang ZH, Yang NF, Jia M, Zhang Q, Jian AN, Ji R, Zhang LD, Lu Y, Huang YH, Shen PP*. Lipid synthesis, triggered by PPAR γ T166 dephosphorylation, sustains reparative function of macrophages during tissue repair. Nat. Commun. 2024; 15:7269.
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3. Yang NF, Wang YX, Tian Q, Wang QP, Lu Y, Sun LC, Wang SJ, Bei YC, Ji JG, Zhou H, Yang W, Yao PJ, Zhu WY, Sun LY, Huang ZF, Li XK*, Shen PP*. Blockage of PPAR γ T166 phosphorylation enhances the inducibility of beige adipocytes and improves metabolic dysfunctions. Cell Death Differ. 2023; 30:766-778.
4. Dong XH, Fan JQ, Xie WX, Wu X, Wei J, He ZL, Wang WX, Wang XT, Shen PP*, Bei YC*. Efficacy evaluation of chimeric antigen receptor-modified human peritoneal macrophages in the treatment of gastric cancer. Br J Cancer. 2023; 129 (3):551-562.
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7. Zuo SM, Sun LC, Wang YX, Chen B, Wang JY, Ge XY, Lu Y, Yang NF*, Shen PP*. Establishment of a novel mesenchymal stem cell-based regimen for chronic myeloid leukemia differentiation therapy. Cell Death Dis. 2021; 12: 208.
8. Bei YC, Cheng N, Chen T, Shu YX, Yang Y, Yang NF, Zhou XY, Liu BR, Wei J, Liu Q, Zheng W, Zhang WL, Su HF, Zhu WG, Ji JG, Shen PP*. CDK5 inhibition abrogates TNBC stem cell property and enhances anti-PD-1 therapy. Adv Sci (Weinh). 2020; 7: 2001417.

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Yohei Niikura, Ph.D.

Yohei obtained his PhD in Chemistry at the University of Florence, Italy in 2000 and then conducted his postdoctoral research at Switzerland (Friedrich Miescher Institute), Japan (National Center for Geriatrics and Gerontology), and US (St. Jude Children's Research Hospital; Nationwide Children's Hospital; Greehey Children's Cancer Research Institute). He joined the MARC of Nanjing University as a Principal Investigator and Research Professor in September of 2018. His current research interest is molecular mechanism of cell division in cancer and brain development.

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Mitotic regulators in cancer and brain development

Our lab is interested in the molecular mechanism involved in both cell division and human diseases, currently focusing on cancer and brain development using human cells and animal models (zebrafish and mouse).

During cell division, proper chromosomes segregation must be achieved otherwise it can result in unequal distribution of chromosomes to daughter cells. Spindle microtubules must attach to a single region of each chromosome, termed the "centromere" in most eukaryotes. The kinetochore is a complex of proteins that is located at the centromere. Defects in the centromere-kinetochore function as well as the spindle check point function, lead to aneuploidy, cancer, and abnormal brain development, and are often associated with a poor prognosis. Therefore, it is highly important to study the temporal-special regulation and the structure of centromere and kinetochore protein(s) to understand chromosome instability (CIN) in cancer and brain development.

Depletion of TSG101 showed synthetic dosage lethality (SDL) in MAD2-overexpressing cells

The spindle assembly checkpoint (SAC) is a surveillance mechanism and its activation is a fundamental step that ensures faithful chromosome segregation stability. Mitotic arrest deficiency 2 (MAD2), a pivotal component of the SAC, and its overexpression also resulted in many types of cancer. However, research into the treatment of MAD2-overexpressing cancer and the cell death mechanism of these cells is still under development. Our lab found that depletion of TSG101 showed lethality in MAD2-overexpressing human cells in a p53-independent but AIFM1- and caspase-dependent manner, proposing that the TSG101 can be a potential therapeutic target in MAD2-overexpressing tumors. For convenience and simplicity, the following sentence refers to this cell death as MOID (MAD2-Overexpressing Interphase cell Death).

We further detected that TSG101 and the components in AIF-PML-DAXX axis are closely inter-dependent in protein stability, and they also regulate mitochondria in survival interphase (Figure 1, left). We found that loss of C-terminal phosphorylations of TSG101 and a closed C-MAD2-overexpression contribute to induce MOID.

We also observed the colocalization of MAD2 with PML NBs, and the series of our results propose at least 2 steps of MOID induction process: (1) priming with PML deSUMOylation in which O-MAD2 is converted to C-MAD2 and binding of C-MAD2-AIFM1 occurs, (2) releasing of PML-DAXX from PML NBs with MAD2 SUMOyaltion/multimerization (Figure 1, right). Our results using HA-tagged and/or untagged TSG101 WT vs. Y390F replaced with ca. 85% endogenous TSG101 also suggest that TSG101 localizes at PML NBs in interphase, and TSG101 Y390 phosphorylation is presumably required for localization of TSG101 to PML NBs in survival cells.

Furthermore, overexpressed O-MAD2 primarily binds to phosphorylated TSG101, while C-MAD2 favors non-phosphorylated TSG101. A part of MAD2 colocalizes with PML at PML NBs, and the PML release from PML NBs through PML deSUMOylation contributes to induce MOID. Because overexpression of phosphorylation-deficient mutant (e.g., Y390F) does not rescue the MOID, we also speculate that phosphorylated TSG101 may block the priming conversion of O-MAD2 to C-MAD2 for the MOID induction (Figure 1, (1) "Priming") interacting with O-MAD2. It could be plausible to describe that TSG101 release from overexpressed C-MAD2 could not be necessary for MOID induction, rather loss of Y390 phosphorylation combined with overexpressed C-MAD2 could be required for MOID induction (Figure 1, right). How TSG101 contributes to the conversion between O-MAD2 and C-MAD2 and how it is localized and functions in PML NBs and the cell cycle is an interesting future research direction.

Figure Legends

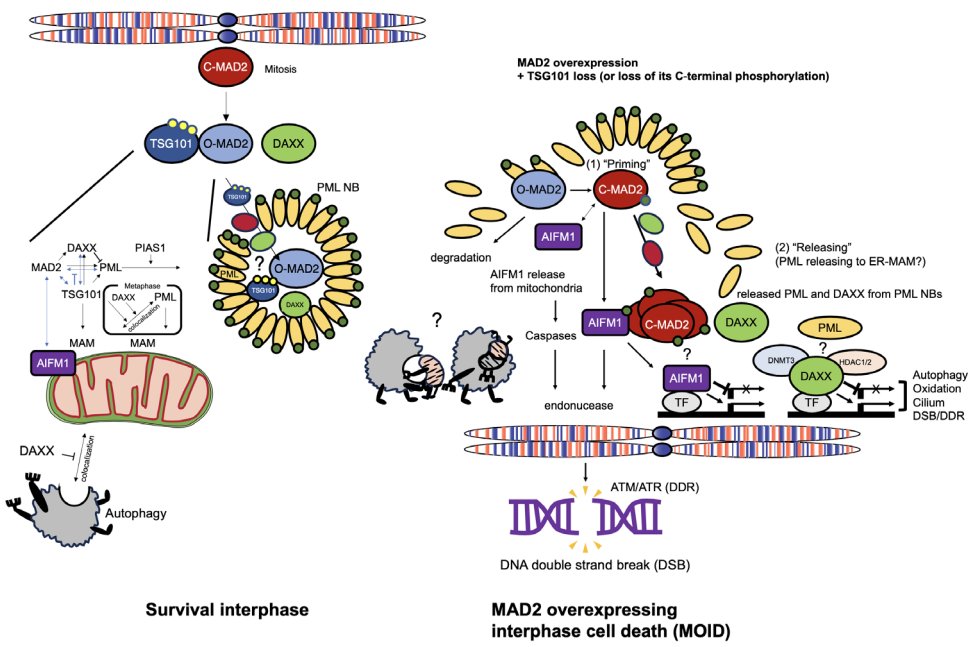

Figure 1. A hypothetical model depicting that PML-MAD2 interaction at PML NBs and formation of PML NBs regulates MOID.

(Left) In survival interphase, PML, DAXX, MAD2, and TSG101 maintain a close dependence and contribute mutually to protein stability sustaining inter-organelle integrity. Note that previous reports suggested that PML can be auto-SUMOylated and/or SUMOylated by PIAS1 SUMO E3 ligase. O-MAD2-specific binding of TSG101 and TSG101 function inside PMN NB are hypothetical. Black arrows indicate activatory or inhibitory direction based on our results of immunofluorescence and protein stability assay or other reports. Black double-head arrows indicate colocalization based on our immunofluorescence results. Blue arrows indicate inhibitory or interactive relationships based on our immunoprecipitation and/or in vivo SUMOylation assays.

(Right) The series of our results propose at least 2 steps of MOID induction process: (1) "Priming" and (2) "Releasing". Mechanisms and roles of MAD2 SUMOylation/multimerization and autophagy are open questions. Transcriptional roles of AIFM1 and PML-DAXX collaboration are unknown.

Selected publications (*Co-corresponding author)

1. Xi Y, Xu R, Chen S, Fang J, Duan X, Zhang Y, Zhong G, He Z, Guo Y, Li X, Tao W, Li Y, Li Y, Fang L, *Niikura Y. TSG101 depletion dysregulates mitochondria and PML NBs, triggering MAD2-overexpressing interphase cell death (MOID) through AIFM1-PML-DAXX pathway. Cell Death and Disease. 2024. doi: 10.1038/s41419-024-07229-w.
2. Kitagawa R, Niikura Y, Becker A, Houghton PJ, Kitagawa K. EWSR1 maintains centromere identity. Cell Rep. 2023;42(6):112568.
3. *#Niikura Y, #Kitagawa K. E3 Ligase for CENP-A (Part 2). In: Catala A, editor. London, UK: IntechOpen [one book chapter]; 2022.3.6. (# Equal contribution)
4. *#Niikura Y, #Kitagawa K. E3 Ligase for CENP-A (Part 1). In: Catala A, editor. London, UK: IntechOpen [one book chapter]; 2022.1.24. (# Equal contribution)
5. *#Niikura Y, #Fang L, #Kitagawa R, Li P, Xi Y, You J, Gao Y, Kitagawa K*. Mass Spectrometry Analysis to Identify Ubiquitylation of EYFP-tagged CENP-A (EYFP-CENP-A). J. Vis. Exp. 2020(160). Epub 2020/07/01. doi: 10.3791/61138. PubMed PMID: 32597847. (# Equal contribution)
6. *#Niikura Y, #Kitagawa R, Fang L, *Kitagawa K. CENP-A Ubiquitylation Is Indispensable to Cell Viability. Dev Cell. 2019;50(6):683-9 e6. Epub 2019/09/25. doi: 10.1016/j.devcel.2019.07.015. PubMed PMID: 31550462; PMCID: PMC6761987. (# Equal contribution)

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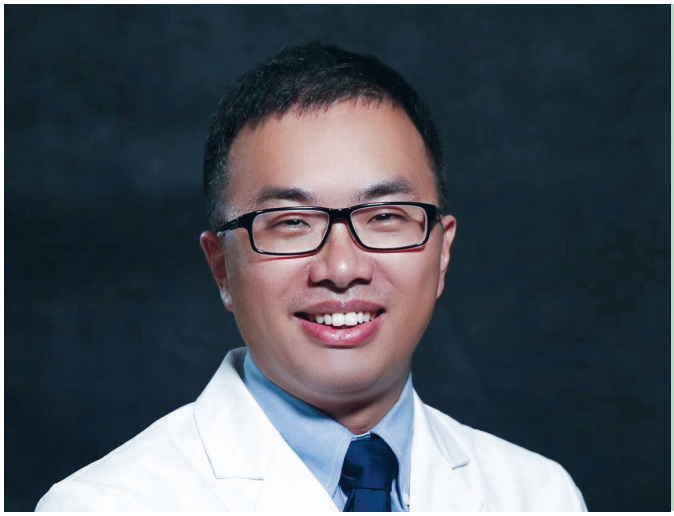

Dongquan Shi Ph.D., M.D.

Prof. Shi graduated from Medical School, Nanjing University (MD, PhD). He received training at Drum Tower Hospital, Nanjing University, University of Pittsburgh and RIKEN Center for Integrative Medical Science in Tokyo. Now he is an experienced surgeon of Sports Medicine and Adult Reconstrution Department. Prof. Shi serves on several societies. Prof. Shi led the research team to study the genetics of bone, joint diseases, and regenerative medicine, and published 162 SCI articles. In 2016, Prof. Shi won the National Natural Science Foundation of China Youth Fund.

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Molecular classification and fibro cartilage hyalinization of osteoarthritis

Osteoarthritis(OA) are common disease that resulting serious physical and mental burden of patients. Our group focuses on fundamental mechanisms and intervention of osteoarthritis as well as cartilage regeneration.

1.Molecular classification of knee osteoarthritis

Knee osteoarthritis (KOA) is a molecular disorder characterized by the interplay of numerous molecules. According to the temporal alteration of representative molecules, we propose a novel molecular classification of KOA. This molecular classification allows for the prediction of high-risk KOA individuals, the diagnosis of early KOA patients and the selection of homogenous patients who may benefit most from the appropriate therapeutic agents.

2.Knee osteoarthritis mechanism and intervention

2.1 The role of CD73, the rate-limiting enzyme of extracellular adenosine synthesis, in osteoarthritis

We found that the expression of CD73 was upregulated in OA, and the variants of SNP rs2229523 (base A to G) on NT5E were significantly higher in OA population, and CD73 could alleviate OA by maintaining anabolism and suppressing catabolism of chondrocytes extracellular matrix. This work showed that CD73 might be one of the biological therapeutic targets of OA, which would provide a reference for future novel treatment strategy of OA.

2.2 Attenuate Osteoarthritis Progression by Targeting TRPV1

Transient receptor potential vanilloid family member 1 (TRPV1) has been revealed as a therapeutic target of osteoarthritis,the clinical application for capsaicin as the TRPV1 agonist is largely limited by its chronic toxicity,To address this issue, we developed a bifunctional controllable magnetothermal switch (MNPs-TRPV1) and a Citrate-stabilized gold nanorods (Cit-AuNRs@Anti-TRPV1) to targeting TRPV1 for the alleviation of OA progression.

2.3 Research progress of drug delivery in the early treatment of osteoarthritis

A collagen hybridizing peptide (CHP) is a synthetic peptide that binds the denatured collagen triple helix. We constructed an albumin nanoparticle (An) conjugated with CHP, loaded with a chondrogenesis-promoting small molecule drug, kartogenin (KGN), robustly attenuated OA progression. Our study showcases that targeting the degenerated cartilage by collagen hybridization can remarkably promote the efficacy of small molecule drugs.

3. Fibrocartilage hyalinization

The therapy of articular cartilage injures remains a challenge. The poor intrinsic characteristic of fibrocartilage leads to degeneration and progression of cartilage disease. Herein, we proposed a novel strategy in cartilage repair focusing on the modification of existing fibrocartilage to hyaline cartilage in situ, namely fibrocartilage hyalinization. In our study, we confirmed the feasibility of modifying the fibrocartilage to hyaline cartilage in situ, which provided a novel strategy in cartilage regeneration.

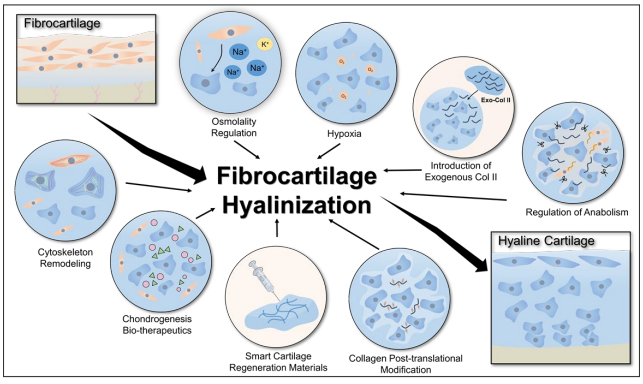

Figure 1. Schematic illustrations of the strategies for fibrocartilage hyalinization

Selected publications (*Co-corresponding author)

1. Guo H, Lv Z, Wang M, Li W, Xie Y, Liu Z, Chen F, Jiang R, Liu Y, Wu R, Li J, Sun Z, Tan G, Shi D*. CD73 alleviates osteoarthritis by maintaining anabolism and suppressing catabolism of chondrocytes extracellular matrix. J Orthop Translat. 2024 Oct 5;49:96-106.
2. Li W, Lv Z, Wang P, Xie Y, Sun W, Guo H, Jin X, Liu Y, Jiang R, Fei Y, Tan G, Jiang H, Wang X, Liu Z, Wang Z, Xu N, Gong W, Wu R, Shi D*. Near Infrared Responsive Gold Nanorods Attenuate Osteoarthritis Progression by Targeting TRPV1. Adv Sci (Weinh). 2024 Apr;11(16):e2307683.
3. Fei Y, Li X, Lv Z, Liu Z, Xie Y, Chen J, Li W, Liu X, Guo H, Liu H, Zhang Z, Wang X, Fan J, Hu C, Jin X, Jiang R, Xu N, Xia J, Li Y*, Shi D*. Promoting chondrogenesis by targeted delivery to the degenerating cartilage in early treatment of osteoarthritis. Bioact Mater. 2024 Aug 15;40:624-633.
4. Lv Z, Wang P, Li W, Xie Y, Sun W, Jin X, Jiang R, Fei Y, Liu Y, Shi T, Guo H, Sun Z, Lin J, Wang X, Tan G, Wu Y, Bao N*, Shi D*. Bifunctional TRPV1 Targeted Magnetothermal Switch to Attenuate Osteoarthritis Progression. Research (Wash D C). 2024 Feb 16;7:0316.
5. Sun Z, Muhammad F, Qiao C, Gong W, Wang Z, Liu Y, Yu X, Dong J, Lv J, Cheng X, Lu Z, Lin C, Lv Z, Sun W, Yuan T, Meng J, Wu R, Shi D*, Wei H*, Bao N*. Templated Synthesis of Hollow RuO2 Nanospheres for Alleviating Metal Wear Particle-Induced Osteoclast Activation and Bone Loss. Small. 2024 Dec 2:e2406210.

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NJU-MARC Laboratory Animal Center

The Laboratory Animal Center of MARC is a public comprehensive service platform integrating teaching, scientific research and technical services. The center has nearly 2,000 m^2 of SPF-grade experimental animal facility, equipped with more than 6,000 individual ventilated cages (IVC), and has obtained the SPF rats and mice use permit issued by Jiangsu Provincial Department of Science and Technology (SYXK(Su) 2021-0034), providing qualified and standardized experimental animal resources and animal experiment facilities and places for many laboratories inside and outside the school.

At present, the center has 14 professional and technical staff, mainly responsible for the operation of the facility, animal feeding, scientific research projects, and the ethical welfare review of experimental animals. The center is equipped with advanced and complete experimental instruments, including metabolic cage, small animal live component analyzer, high-resolution live multi-mode imaging platform, ECG detector, fundus gap imaging system, treadmill and other large instruments.

The center strictly abides by national standards and regulations, respects animal ethical welfare and attaches great importance to ethical review. The center has established and improved various rules and regulations and standard operating procedures, conducted regular training for scientific research and experimental personnel, and strictly managed experimental animals and related facilities to ensure the normal and safe operation of the entire center.

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Ding Yingnan	Veterinarian
Fan Junluan	Animal Keeper Supervisor
Yang Kefeng	Animal Keeper
Xu Dong	Animal Keeper
Wang Chuanhong	Animal Keeper
Hou Min	Animal Keeper
Zhou Anqin	Animal Keeper
Li Feiyan	Animal Keeper
Zhao Dingfu	Animal Keeper
Wu Zixing	Animal Keeper
Zhuo Zaijun	Engineering Department
Li Lin	Engineering Department
Wu Jinyin	Engineering Department

The Laboratory Animal Center offers mouse breeding services, with the requirement that the mice are SPF level. The specific services and fees are as follows:

- Mouse cage fee: 9 yuan/cage/day
- Tail cutting and caging: 10 yuan/each/time; if the total cost is less than 200 yuan, a minimum charge of 200 yuan applies
- PCR identification: Regular PCR: 40 yuan/tail; Nested PCR: 70 yuan/tail
- Checking for vaginal plugs: 12 yuan/each/time; if the total cost is less than 200 yuan, a minimum charge of 200 yuan applies
- Weighing: 5 yuan/each/time; if the total cost is less than 50 yuan, a minimum charge of 50 yuan applies
- Ear tagging: 5 yuan/each/time; if the total cost is less than 50 yuan, a minimum charge of 50 yuan applies
- High-fat diets feeding fee: 7 yuan/mouse/day (cage fee not included, includes management fee); if the total cost is less than 200 yuan, a minimum charge of 200 yuan applies
- High-fat diets feeding management fee: 2 yuan/mouse/day (customer provides diets, cage fee not included); if the total cost is less than 200 yuan, a minimum charge of 200 yuan applies
- Blood glucose measurement: 12 yuan/each/time, fasting blood glucose measurement: 16 yuan/each (with sawdust pad); if the total cost is less than 100 yuan, a minimum charge of 100 yuan applies








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Brief Introduction of NJU-MARC Core Facilities

After 7 years in operation, the Core Facilities of MARC have begun to take shape. The Core Facilities is a comprehensive service platform, which is fully open to services inside and outside the school. The center has provided external services to a total of 43 enterprises and institutions, and has provided more than 3,000 hours of external services every year. We have more than 30 sets of world-class equipment with a total value of 40 million, and provide over 142000 hours service within or outside MARC research community.

So far, we have set up Microscopy and Imaging Core, Flow Cytometry Core, Proteomics and Metabolomics Core, Macromolecular Core, and Experimental Animal Core, providing a diverse range of resources and services, including high resolution imaging, flow cytometry, protein and gene expression profiling, and metabolic analysis. The featured instruments are listed below and more resources could be found on our website. https://marc.nju.edu.cn/platform/.

Qiaoli Chen -Director of MARC Core

Danlu Shi -Engineer of MARC Core

Microscopy and Imaging Core

► Services

- Live cell imaging
- Optical sectioning of thick biological samples
- 3D reconstruction of images
- 3-D mosaic imaging
- Multi-area time-laps and spectral scanning
- Super-resolution imaging

► Equipment

- Zeiss LSM880 with Airyscan
- Leica TCS II sp5 confocal
- GE Healthcare DeltaVision Imaging System
- GE Healthcare DeltaVision OMX 3D-SIM
- Olympus SLIDEVIEW VS200
- Simple & Smart SS-MCS6 Microscopic Confocal Scanning System

Proteomics and Metabolomics Core

► Services

- Quantitative analysis of small molecules
- Identification of unknown metabolites
- Able to analyze various kinds of samples
- Metabolomics study
- Live cell energy metabolism
- Cardiac, lipid, renal, diabetes and liver profiles.

► Equipment

- Agilent 6550 iFunnel Q-TOF LC/MS System
- Agilent Seahorse Xfe24 Extracellular Flux Analyzer
- Sysmex BX-3010 chemistry analyser
- BioTek synergy H1 plate reader

High-resolution in vivo imaging

► Services

- Cardiovascular research
- Oncology study
- Drug metabolism study
- ……

► Equipment

- FUJIFILM Vevo® 3100 LAZR-X system
- FUJIFILM Vevo® 770
- Vilber Newton 7.0 FT-500

Flow Cytometry Core

► Services

- Cell sorting
- Able to analyze multiple fluorescent probes simultaneously

► Equipment

- BD LSRFortessa™ Flow Cytometer
- BD FACSCalibur Flow Cytometer
- BD FACSAria™ III Cell Sorter

Real time qPCR

► Services

- Gene expression detection

► Equipment

- ABI StepOne Plus
- Roche LightCycler 96

Single-cell sequencing library preparation systems

► Services

- Single cell 3' whole transcriptome amplification
- Analyze the TCR and BCR sequence information
- Assay for Transposase-Accessible Chromatin with high-throughput Sequencing (ATAC-Seq)

► Equipment

- The MobiNova-100® single-cell sequencing library preparation system
- BD Rhapsody® single-cell sequencing library preparation system
- MGI DNBelab C-TaiM 4

Others

► Equipment

- Beckman OPTIMA XPN-100 centrifuge
- BOTETF GL - 21R
- DAKEWE HP300 fully enclosed intelligent tissue dehydrator

New equipment

► Simple & Smart SS-MCS6 Microscopic Confocal Scanning System

- Multi-dimensional image acquisition is completed under full software control, realizing multi-channel XY, XYZ, XYT, XYZT, MP multi-dimensional imaging.
- In Vivo Observation: The confocal microscope SS-MCS6 can be used to track the changes over time in the structures and physiological processes within living cells under natural conditions or after being stimulated by certain factors, obtaining accurate and intuitive dynamic change data and providing direct experimental data for analyzing the physiological and biochemical reactions within cells.
- Continuous Section Scanning and Image Reconstruction: Different layers in the sample can be continuously scanned layer by layer to obtain the images of each layer, and the spacing between layers can reach 0.1 micrometer or even smaller.
- Multiple Labeling Technique: Information about different structures within cells can be obtained in a single experimental observation, and the location and interconnection methods of different structural components can be studied.
- Obtaining Quantitative Information: While performing fluorescence localization within cells, quantitative analysis can also be carried out on it to obtain the fluorescence intensity values distributed in different parts of the sample in two-dimensional or three-dimensional space as well as the changes in fluorescence intensity under various treatment conditions.

► Sysmex BX-3010 chemistry analyser

- Measurement Principle: Colorimetry and Immunoturbidimetric
- Throughput: 404 Tests/Hour
- Sample Volume: minimum 1.5 μL
- Reaction Volume: minimum 100 μL
- Sensors: Liquid-Level and Clot Sensor detectors
- Host Interface: Bi-directional
- Water Consumption: 5L/Hour
- Test Items Service Contents: Blood glucose (Glu), alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (AKP), creatinine (CREA), triglyceride (TG), total cholesterol (Chol), high - density lipoprotein cholesterol (HDL), low - density lipoprotein cholesterol (LDL), calcium (Ca), phosphorus (P), iron (iron), urea nitrogen (BUN), total bilirubin (TBIL), cerebrospinal fluid and urine total protein (CSF/UTP)

► Single-cell sequencing library preparation systems

- The MGI DNBelab C-TaiM 4 is a portable droplet generator designed to encapsulate single cells into droplets for 1-4 samples in one run. It is meticulously crafted to facilitate high-throughput single-cell RNA and ATAC in any setting.
- It seamlessly integrates advanced technologies, including dual-bead cell capture, a microfluidic droplet generator, and state-of-the-art computing modules. These robust features empower researchers to execute intricate genomic analyses in any location at any time.

► Large - capacity High - speed Refrigerated Centrifuge BOTETF GL - 21R

- Maximum speed: 14000r/min, maximum relative centrifugal force: 30070×g;
- Temperature control range: - 20℃ ~ 40℃ ±1℃;
- Rotors: 6 pieces of 250ml angle rotors (P8),
- 12 pieces of 50ml conical - bottom angle rotors (P6)
- It can centrifuge and purify samples quickly and effectively. It is compatible with a variety of different angle rotors to meet the experimental requirements of various samples.

► DAKEWE HP300 fully enclosed intelligent tissue dehydrator

- The DAKEWE HP300 fully enclosed intelligent tissue dehydrator adopts a fully enclosed design and precisely completes the dehydration process under a fully enclosed state.
- Instrument Application: The automatic tissue dehydrator is used for fixing, dehydrating, clearing and paraffin-embedding treatment of tissue samples.

National Resource Center for Mutant Mice

The National Resource Center for Mutant Mice (NRCMM) is one of the 31 national-level germplasm resource banks certified by the Ministry of Science and Technology in China. It provides services related to the preservation and supply of mouse resources, the creation of disease models, training of experimental animal talents, and international exchanges.

At present, a cooperative and co-construction relationship has been established with GemPharmatech LLC., Animal Center of Yunnan University and Animal Experimental Center of the Institute of Biophysics, Chinese Academy of Sciences.

By the end of 2024, the resource database has 39,601 rat and mouse models. 827 strains of national science and technology program were collected in the current year. It is the largest resource pool of mouse strains in the world. The NRCMM serves more than 2,000 universities, hospitals, biotechnology companies, CRO enterprises and pharmaceutical enterprises worldwide; meanwhile, the total number of SCI articles published based on NRCMM animal model reache 3,454, and the total impact factor become 34,063. The research fields include tumor, autoimmunity, metabolism and nerve.

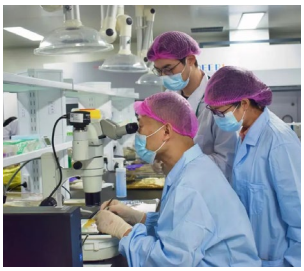
In 2024, NRCMM continues carrying out the "Key Model for Research Project" (abbreviation: KMR Project) and the independent R&D project. As of now, we have assisted more than 200 scientists to carry out cutting-edge scientific research, with a support fund of more than 16 million yuan. More than 300 innovative mouse models have been researched and developed in total. We have published 41 SCI papers with 540.67 points of impact factors. Including Neuron cover articles, cell, Adv Materials, Journal of Hepatology, Immunity, Nat Cancer, ACS nano, Bioact Mater, Adv Science, Nat Comm, Brain, etc.

In the same year, NRCMM successfully held the "Sino-German Academic Exchange Meeting on Metabolic Disorder and Immunity", while the top experts in the fields of metabolism and immunity from China and Germany participated. In the conference they discussed the latest research progress and future development direction of metabolic disorder and immunity;

As a tradition, the 4th National Laboratory Animal Resource Development Seminar was held in Foshan, that more than 10 authoritative experts shared the latest industry developments . meanwhile, hundreds of scholars and practitioners from related fields joined exchange ideas. The Seminar was broadcast at real time on many network platforms, attracting thousands of audiences, Which showed great impact on the laboratory animal industry.

In 2024, NRCMM organized one session of embryo manipulation technique training annually, and this year marks the seventh session. More than 30 experimental animal technicians participated in the course, which included theoretical and practical operations. Over the course of four days, the trainees gained solid theoretical basis and practical operation technology.

In the future, NRCMM will continue providing high quality mouse resources and services, which will help the innovation and development of life science and pharmaceutical research and development.



Event in 2024

Laboratory Open Day

As a well-known biomedical research institution both domestically and internationally, MARC has held a special science popularization brand activity "Laboratory Open Day" in response to the call of the Chinese Society for Cell Biology for ten consecutive years, attracting nearly 1,000 primary and secondary school students and their families to the "first scene" of biological research.

On June 1th, MARC held the "2024 Laboratory Open Day" event with the theme of "Exploring Life's Mysteries - A Day as a Little Animal Researcher". More than 100 local primary and secondary school students and their parents from Nanjing, totaling more than 200 people, were invited to enter the center together to get up close and observe these "Lonely Heroes", aka. model animals, who have made great contributions to human health research.

Publications in 2024

1.	Lin F, Yin S, Zhang Z, Yu Y, Fang H, Liang Z, et al. Multimodal targeting chimeras enable integrated immunotherapy leveraging tumor-immune microenvironment. Cell. 2024.
2.	Chen XY, Zhao J, Yue S, Li ZY, Duan X, Lin Y, et al. An oncolytic virus delivering tumor-irrelevant bystander T cell epitopes induces anti-tumor immunity and potentiates cancer immunotherapy. Nat Cancer. 2024;5(7).
3.	Shi TS, Shen SY, Shi Y, Wang QJ, Zhang GQ, Lin JQ, et al. Osteocyte-derived sclerostin impairs cognitive function during ageing and Alzheimer's disease progression. Nat Metab. 2024;6(3).
4.	Yang GL, Jia M, Li GZ, Zang YY, Chen YY, Wang YY, et al. TMEM63B channel is the osmosensor required for thirst drive of interoceptive neurons. Cell Discov. 2024;10(1).
5.	Zhang GQ, Song ZG, Huang SS, Wang YF, Sun JY, Qiao L, et al. nCas9 Engineering for Improved Target Interaction Presents an Effective Strategy to Enhance Base Editing. Adv Sci. 2024;11(31).
6.	Mao Y, Jin Z, Yang J, Xu DQ, Zhao L, Kiram A, et al. Muscle-bone cross-talk through the FNIP1-TFEB-IGF2 axis is associated with bone metabolism in human and mouse. Sci Transl Med. 2024;16(750).
7.	Su S, Quan C, Chen Q, Wang R, Du Q, Zhu S, et al. AS160 is a lipid-responsive regulator of cardiac Ca(2^{+}) homeostasis by controlling lysophosphatidylinositol metabolism and signaling. Nat Commun. 2024;15(1):9602.
8.	Liu Z, Duan X, Yun YF, Li SQ, Feng ZY, Zhan JY, et al. Photoactivatable Aptamer-CRISPR Nanodevice Enables Precise Profiling of Interferon-Gamma Release in Humanized Mice. Acs Nano. 2024;18(4):3826-38.
9.	Liu Q, Zhang LQ, Chen Z, He YH, Huang YH, Qiu C, et al. Metabolic Profiling of Cochlear Organoids Identifies α-Ketoglutarate and NAD as Limiting Factors for Hair Cell Reprogramming. Adv Sci. 2024;11(34).
10.	Xiao LW, Yin YJ, Sun ZC, Liu J, Jia YH, Yang LK, et al. AMPK phosphorylation of FNIP1 (S220) controls mitochondrial function and muscle fuel utilization during exercise. Sci Adv. 2024;10(6).
11.	Jiang DY, Zhao J, Zheng J, Zhao YM, Le MN, Qin DN, et al. LOX-mediated ECM mechanical stress induces Piezo1 activation in hypoxic-ischemic brain damage and identification of novel inhibitor of LOX. Redox Biol. 2024;76.
12.	Teng XY, Hu P, Zhang CM, Zhang QX, Yang GL, Zang YY, et al. OPALIN is an LGI1 receptor promoting oligodendrocyte differentiation. P Natl Acad Sci USA. 2024;121(32).
13.	Lin ZY, Chen QY, Ruan HB. To die or not to die: Gasdermins in intestinal health and disease. Semin Immunol. 2024;71.
14.	Wang H, Chen J. Cell migration: Collective cell migration is intrinsically stressful. Curr Biol. 2024;34(7):R275-R8.
15.	Wang Q, Rong P, Zhang W, Yang XY, Chen L, Cao Y, et al. TBC1D1 is an energy-responsive polarization regulator of macrophages via governing ROS production in obesity. Sci China Life Sci. 2024.
16.	Rong P, Mu YQ, Wang MQ, Chen L, Liu FT, Jin YX, Feng WK, Zhou K, Liang H, Wang HY, Chen S. Targeting IGF1 to alleviate obesity through regulating energy expenditure and fat deposition. SCIENCE CHINA Life Sciences. 2024.
17.	Xi Y, Xu R, Chen SN, Fang JZ, Duan X, Zhang YD, et al. TSG101 depletion dysregulates mitochondria and PML NBs, triggering MAD2-overexpressing interphase cell death (MOID) through AIFM1-PML-DAXX pathway. Cell Death Dis. 2024;15(11).
18.	Yang R, Li DD, Li XX, Yang XX, Gao HM, Zhang F. Dihydroquercetin alleviates dopamine neuron loss via regulating TREM2 activation. Int J Biol Macromol. 2024;269.

19.	Cao Y. Lack of basic rationale in epithelial-mesenchymal transition and its related concepts. Cell Biosci. 2024;14(1).
20.	Huang YH, Zhang LQ, Sun YC, Liu Q, Chen J, Qian XY, et al. A human-specific cytotoxic neopeptide generated by the deafness gene. J Genet Genomics. 2024;51(11):1215-27.
21.	Liu QY, Li MY, Sun ML, Xin RY, Wang YS, Chen Q, et al. Depletion of Gsdma1/2/3 alleviates PMA-induced epidermal hyperplasia by inhibiting the EGFR-Stat3/Akt pathway. J Mol Cell Biol. 2024;16(1).
22.	Tu JJ, Zang YY, Shi YS, Teng XY. The TMEM63B Channel Facilitates Intestinal Motility and Enhances Proliferation of Intestinal Stem Cells. Cells-Basel. 2024;13(21).
23.	Huang YH, Chen Z, Chen J, Liu JY, Qiu C, Liu Q, et al. Direct reprogramming of fibroblasts into spiral ganglion neurons by defined transcription factors. Cell Proliferat. 2024.
24.	Zhang TY, Zhu YX, Wang XC, Chong DY, Wang HQ, Bu DD, et al. The characterization of protein lactylation in relation to cardiac metabolic reprogramming in neonatal mouse hearts. J Genet Genomics. 2024;51(7):735-48.
25.	Ye C, Zhang TZ, Zang YY, Shi YS, Wan GQ. TMEM63B regulates postnatal development of cochlear sensory epithelia via thyroid hormone signaling. J Genet Genomics. 2024;51(6):673-6.
26.	Shan ZL, Li SN, Gao YX, Jian CH, Ti XX, Zuo H, et al. mtDNA extramitochondrial replication mediates mitochondrial defect effects. Iscience. 2024;27(2).
27.	Zhao MF, Zhang XG, Tang YP, Zhu YX, Nie HY, Bu DD, et al. Ketone bodies promote epididymal white adipose expansion to alleviate liver steatosis in response to a ketogenic diet. J Biol Chem. 2024;300(2).
28.	Pei JW, Zou DY, Li L, Kang LL, Sun ML, Li X, et al. Senp7 deficiency impairs lipid droplets maturation in white adipose tissues Plin4 deSUMOylation. J Biol Chem. 2024;300(6).
29.	Yang YX, Zhang X, Zhao QS, Zhang JZ, Lou X. Compromised COPII vesicle trafficking leads to glycogenic hepatopathy. Dis Model Mech. 2024;17(9).
30.	Qiu C, Zhang LQ, Yong CX, Hu RX, Sun YC, Wang BS, et al. Stub1 promotes degradation of the activated Diaph3: A negative feedback regulatory mechanism of the actin nucleator. J Biol Chem. 2024;300(10).
31.	Yu CR, He YH, Liu Q, Qian XY, Gao X, Yang DY, et al. Thyroid hormone controls the timing of cochlear ribbon synapse maturation. Biochem Bioph Res Co. 2024;704.
32.	Ren D, Zhang Z, Zheng X, Lu C, Song Y, Liu S, et al. TLR5 expression marks brain boarder associated macrophages and protects neonatal mice from bacterial meningitis. hLife. 2024.

Seminar

	Date	Speaker	Title	Unit
1	2024/1/12	Qingfeng Chen Ph.D.	Application of humanized mouse models in human disease research and drug development	A*STAR
2	2024/3/20	Bo Shan Ph.D.	Nonadipogenic Roles for Adipocyte Progenitor Cells	Zhejiang University
3	2024/8/5	Jun Cui Ph.D.	Regulation of Innate Immunity and Inflammation by Selective Autophagy through Multiple PTMs	School of Life Sciences, Sun Yat-sen University
4	2024/8/15	Peng Liu Ph.D.	Genetic Pharmacological Exploration of Cancer-Relevant Dendritic Cell Functions	INSERM
5	2024/12/19	Hongbo Zhang Ph.D.	Formation and aging of human skeletal muscle	Sun Yat-sen Medical University Zhongshan school of Medical

Courses and Lecturers

The MARC, as an institute of the Nanjing University Medical School, is home to more than 200 PhD students. They carry out their dissertation studies under the supervision of MARC group leaders. In addition, MARC group leaders present lectures and laboratory courses at universities in China and worldwide, in addition to Nanjing University. In 2024, the following lecture series and courses were given by MARC staff at Nanjing University (unless indicated otherwise).

Principles, Methods and Techniques in Cell and Molecular Biology

Guoqiang Wan

Hongyu Wang

Zhenji Gan

Basic Concepts and Developments in Genetics

Qing Zhang

Jinzhong Qin

Geng Liu

Cellular and Molecular Mechanism of Development

Jiong Chen

Ying Cao

Basic Concepts and Frontiers in Immunology

Jianghuai Liu

Yan Li

Huiming Gao

Zhaoyu Lin

Medical Physiology

Shuai Chen

Guiquan Chen

Qiaoli Chen

Scientific Reading, Writing and Presentation

Yohei Niikura

Yan Li

Guoqiang Wan

Progress in Life Sciences

All PIs at MARC

PhD Theses

MARC students successfully defended the following PhD theses in 2024

Group Xiang Gao

Minli Sun
Identification of CD300c+ CD4+ T cell subpopulation as a crucial contributor to the obesogenic memory

Qianyue Chen
Zinc stabilizes vimentin structure to suppress gasdermin D N-terminal-induced pyroptosis and prevent septic shock

Jingwen Pei
Senp7 Deficiency Impairs Lipid Droplets Maturation in White Adipose Tissues via Plin4 DeSUMOylation

Group Yan Li

Wei Liu
The role of neutrophils in tumor progression and bone homeostasis

Group Guoqiang Wan

Yuhang Huang
Identification and characterization of a novel deafness gene Cingulin

Linqing Zhang
Mechanism of CRISPRa activating endogenous genes in vivo for potential treating hereditary deafness

Sihao Gong
Identification and functional studies of the downstream target genes of the human DFNA15 deafness gene POU4F3

Group Shuai Chen

Shu Su
AS160 is a lipid-responsive regulator of cardiac Ca2+ homeostasis by controlling lysophosphatidylinositol metabolism and signaling

Kun Zhou
Spatiotemporal regulation of insulin signaling by liquid–liquid phase separation

Group Zhenji Gan

Yan Mao
Investigation into the Pathogenesis of Myogenic Osteopathy Regulated by Musculoskeletal Interactions

Group Jinzhong Qin

Lixia Dong
The role of H3K9 methylation system in maintaining the biological function of embryonic stem cells

Group Chaojun Li

Dandan Bu
The function and mechanistic actions of Early Growth Response-1 (Egr-1) on the balance of muscular anabolism and catabolism

Yangqing Li
The function and mechanism of NQO1 in oxidative stress resistance and promoting glioblastoma stem cell proliferation

Mengfei Zhao
The role of ketone bodies in the development and functional regulation of brown and white adipose tissue

Group Zhongzhou Yang

Wenli Fan
SLC25A1 regulates placental development and guides embryonic heart morphogenesis

Tianyang Zhao
Research on the Mechanism of GPAT4 Regulating Mouse Cardiac Development

Group Minsheng Zhu

Zhihui Jiang
Discovery and pathogenic mechanistic studies of pathogen causing ulcerative colitis

Group Yun Shi

Jingjing Tu
Osmosensitive cation channel TMEM63B regulates insulin secretion in pancreatic β-cells

Group Guiquan Chen

Mengjia Liu
PP2A regulating oligodendrocyte differen-tiation via down-regulation of Sox10

Group Qingshun Zhao

Dongya Jiang
LOX-Mediated ECM Remodeling Induces Piezo1 Activation in Hypoxic-Ischemic Brain Damage and Identification of Novel Inhibitor of LOX

Yuxi Yang
Construction of Regulatory Network and Functional Analysis of Responsive Genes in Zebrafish Epicardial Activation

2024 Summer Camp

As the primary task for MARC is to excel in scientific research and education, graduate students are the most valuable assets of our center. To attract more outstanding students to MARC, we held the 15th Summer Camp on July 9th this summer.

The summer camp was jointly held with the Medical School of Nanjing University, which attracted 61 college students from 29 universities. Dr Yan Li, director of the MARC, introduced the history, research directions and groups of the research center. The 2022 MARC Star winner Lulu Kang and PIs shared their experience and knowledge on scientific research and life at MARC. This year's summer camp activities also included the poster exhibitions from all research teams. The founder of MARC, Professor Xiang Gao, PIs and senior members of the research groups carried out face-to-face academic exchanges with the summer camp participants.

The vision of the Summer Camp is to attract and train excellent students as future leaders in biomedical research involving model animals both at MARC and at other institutes around the globe. Overall, the Summer Camp allowed the participants to experience the vibrant atmosphere of academic research at MARC and stimulate their enthusiasm for biomedical research.

2024 Students Activities

In this season full of vitality and hope, our institute successfully held the student union election and transition activity. This event not only provided a platform for students to showcase themselves but also served as publicity for our institute.

The judging panel for this election consisted of school leaders, teacher representatives, and student representatives. At the election venue, the students were energetic and confident. They presented their advantages and specialties through speeches. The judges comprehensively scored the students based on their speech content, language expression, image and temperament, talent demonstrations, and other aspects, ensuring the fairness, impartiality, and transparency of the selection results. After intense competition, the members were finally selected. These students will shoulder the heavy responsibility of their work, serve their classmates, and contribute their own strength to the development of the school.

Through this activity, we not only selected a group of outstanding student union members but also provided a platform for students to exercise and showcase themselves. At the same time, we also summarized some experiences and lessons, providing useful references for future student work.

To facilitate exchanges and interactions among different laboratories and stimulate critical thinking and creativity, we regularly organize weekly seminars. These seminars bring together professors from diverse experimental backgrounds who not only share their scientific discoveries but also present novel and unique perspectives, engaging in brainstorming sessions with students from various labs. The design of such activities aims to establish an open and inclusive academic platform where ideas between teachers and students collide, sparking wisdom.

The college badminton competition, as an annual sports event, is not only a competitive contest but also a platform to showcase youthful vitality and enhance friendships among students. The competition is usually held in the college's gymnasium and attracts badminton enthusiasts from various majors and grades to actively participate.

At the competition venue, the players wore uniform sports equipment, looking energetic and high-spirited. Every precise smash, clever net shot, and desperate save earned rounds of applause and cheers from the spectators. The competition not only tested the players' badminton skills but also exercised their psychological qualities and team collaboration abilities.

In order to welcome the new academic year, promote communication and integration between new and returning students, our school successfully held a welcome party on December 26th. The purpose of this event was to provide new students with a platform to showcase themselves and integrate into campus life, while also giving returning students the opportunity to relive the joys of campus life and collectively create a warm, harmonious, and positive learning atmosphere. At the same time, we look forward to creating more beautiful memories together with more students at future welcome parties.

Marc Academy

Marc Academy is a newly established teacher-student organization of MARC in 2021. Its purpose is to promote teacher-student exchanges and break the communication barriers of students in various laboratories. At present, Marc College is divided into 4 colleges. The dean of the school is elected spontaneously by students, and competitions between colleges are carried out with the college as a unit. Each college includes students and teachers in each laboratory, and ensures full communication and interaction between teachers and students through activities between each college and within the college. Each activity is sponsored by one of the 4 colleges, and activity funds are obtained through the ranking of each activity to support free activities in the college.

We have held many activities which have received a wide and positive response. Table Tennis Competition held by the MARC Academy showed the athletic demeanor of MARC students. The Fun Games revealed the spirit of solidarity and fraternity for the honor of the school. The First MARC Singer Contest displayed a healthy and civilized cultural atmosphere. Fishing Contest attracted a lot of people whose enthusiasm was relatively high. In particular, Qiaoli Chen, an assistant professor of MARC, also participated in Fishing Contest.

In addition to hosting above competitions, the deans and students of MARC Academy were actively involved in organizing MARC events. In the Summer Camp of 2024, the deans of MARC Academy guided students to visit the environment of MARC. We also called on and participated in the Badminton League hosted by the School of Architecture and Urban Planning of Nanjing University. The deans of MARC Academy also participated in organizing 2023 MARC Welcome Party.

Third National Youth Workshop on Cutting-edge Techniques in Neural Development and Regeneration

The "Third National Youth Workshop on Cutting-edge Techniques in Neural Development and Regeneration" was successfully convened at Longshan Lake Hotel, Nanjing from December 14th to 15th, 2024. The theme of this workshop was "Model Animals and Neuroscience Research", organized by the Neural Development and Regeneration Branch of the Chinese Neuroscience Society, undertaken by the Model Animal Research Center of the Medical School of Nanjing University, and co-organized by the National Resource Center for Mutant Mice and Fine Science Tools. More than 80 experts, young scholars, and students gathered at Longshan Lake Hotel to jointly explore the application and progress of model animals in neuroscience research. Experts in the field of neural development and regeneration successively delivered splendid academic and technical lectures, on model animals including C. elegans, drosophila, zebrafish, axolotl, mice, ferrets and domestic dogs.

In the concluding remarks of the conference, Secretary General He Jie expressed his anticipation that such workshops will continue to be organized in the future. He believes that these events will serve as a valuable platform for learning and communication among researchers in the field of neuroscience. In his closing address, Professor Wan Guoqiang conveyed his gratitude to all participants, particularly highlighting the significance of model animal research. He emphasized that each model animal possesses unique advantages and limitations, and that higher evolutionary status does not necessarily equate to better suitability for research purposes. He emphasized the diversity and applicability that participants should consider when selecting research tools, underscoring the importance of maintaining an open and flexible mindset in scientific research. It not only brought the seminar to a successful conclusion but also laid a robust foundation for future research endeavors and academic collaborations.

南京大学 NANJING UNIVERSITY | MARC 模式动物研究所 Model Animal Research Center

MODEL ANIMAL RESEARCH CENTER OF NANJING UNIVERSITY
MOE KEY LABORATORY OF MODEL ANIMAL FOR DISEASE STUDY
NATIONAL RESOURCE CENTER FOR MUTANT MICE