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

ANNUAL REPORT 2025

Director's Words

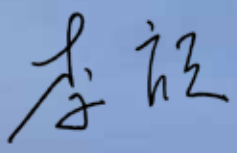
The year 2025 marks a phase of accelerated innovation and expanded impact for the Model Animal Research Center (MARC) at Nanjing University. MARC continues to serve as a leading hub for discovery and scientific excellence in the global biomedical research community.

This year was highlighted by high-impact publications in prestigious journals, including Cancer Cell, Protein & Cell, Cell Research, Nature Communications, Brain, Behavior, and Immunity, Communications Biology, and Advanced Science. These studies, leveraging genetically modified and humanized mouse models developed at MARC, have significantly advanced our understanding of disease mechanisms and therapeutic innovation.

In 2025, MARC further strengthened its commitment to academic exchange by hosting renowned scholars such as Professor Alexander Ploss from Princeton University, Dr. Wei Ying from the University of California, San Diego, and Professor Lijia Ma from Westlake University.

Additionally, MARC launched the MARC Alumni Lecture Series, inviting former trainees to return and engage with faculty and students. These alumni share their scientific expertise, career experiences, and insights into internship and job opportunities, supporting the professional development of current graduate students.

Building on a strong foundation, MARC is poised to shape the future of model organism research. With a continued focus on innovation, collaboration, and education, we are actively exploring new scientific frontiers. By accelerating groundbreaking discoveries and expanding our global network of partnerships, MARC is not only advancing but actively defining the future landscape of biomedical science.



Yan Li
Director

IN FOCUS

Director's Words
Research Highlight in 2024 2
Student of The Year 5

IN DEPTH

Neurobiology

Yun Shi 7
Guiquan Chen 9
Huiming Gao 11
Guoqiang Wan 13

Organogenesis

Jiong Chen 16
Qing Zhang 18
Ying Cao 20
Qingshun Zhao 22
Liang Chi 25
Yongzhen Liu 27
Lei Dong 30

Metabolism and Immunity

Xiang Gao 32
Shuai Chen 34
Chaojun Li 36
Zhenji Gan 38
Hongyu Wang 41
Yan Li 43
Zhaoyu Lin 46
Qiaoli Chen 48

Cancer and Stem Cell Biology

Geng Liu 51
Jianghuai Liu 53
Jinzhong Qin 55
Pingping Shen 57
Yohei Niikura 59
Dongquan Shi 61
NJU-MARC Experimental Animal Center 64
NJU-MARC Core Facilities 66
National Resource Center for Mutant Mice of China 73

IN ADDITION

Event in 2025 74
Publications in 2025 75
Seminar 77
Courses and Lecturers 78
PhD Theses 79
2025 Summer Camp 80
2025 Students Activities 81
Marc Academy 83
China-French Biomedical Industry Cooperation Symposium for Chinese Scientists in France 84
Nanjing University and BGI Group Forge Industry-Academia Partnership in Ceremony and Forum 85

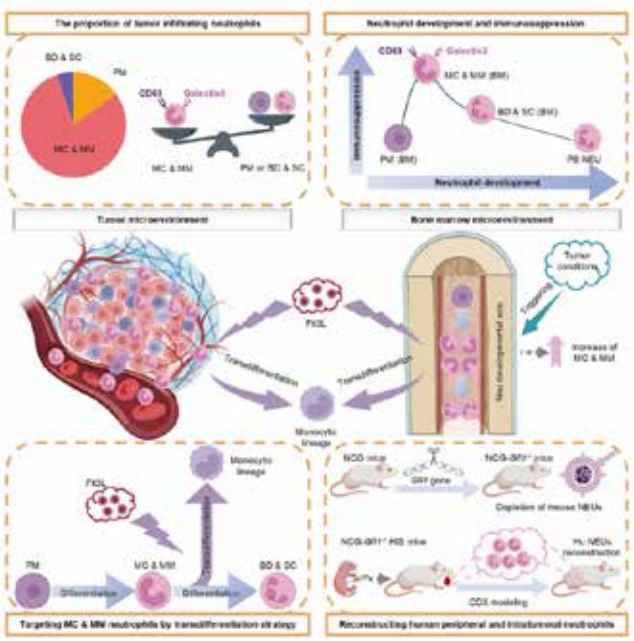
Research Highlight in 2025

Group Yan Li

Human myelocyte and metamyelocyte-stage neutrophils suppress tumor immunity and promote cancer progression

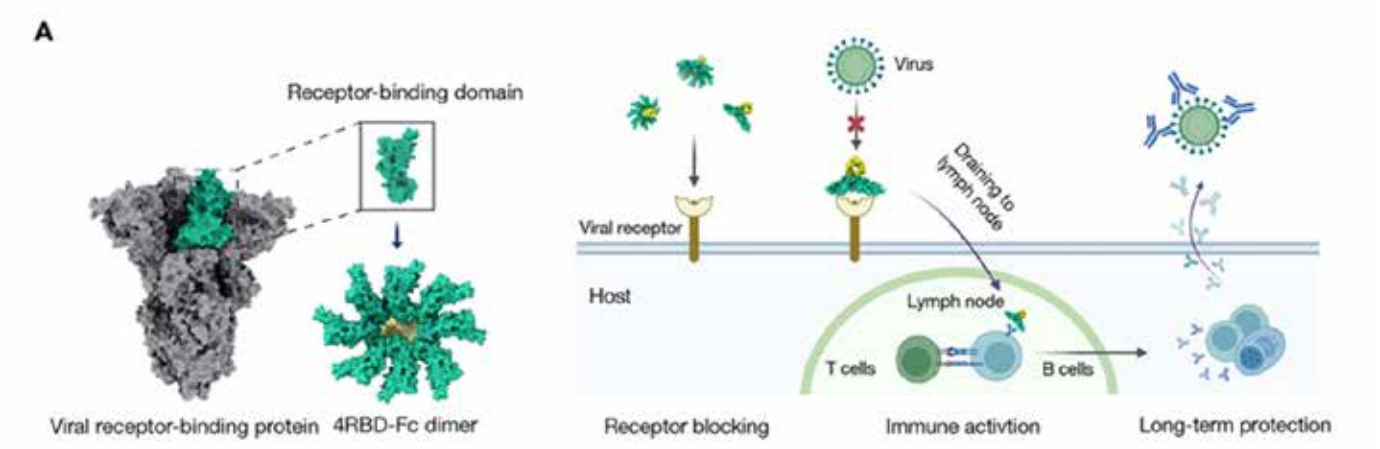
We separated human and mouse neutrophils into three developmental stages, including promyelocyte (PM), myelocyte & metamyelocyte (MC & MM), and band & segmented (BD & SC) neutrophils. Based on this separation, we observed the predominance of human but not mouse MC & MM-stage neutrophils in bone marrow (BM), which exhibit potent immunosuppressive and tumor-promoting properties.

Moreover, through the creation of a NOD/ShiLtJGpt-Prkdc^{em26Cd52}Il2rg^{em26Cd22}/Gpt (NCG)-Gfi1$^{-/-}$ human immune system (HIS) mouse model, which supports efficient reconstitution of human TIN, we found a significant increase of BM MCs & MMs in tumor-bearing mice. By comparing the single-cell RNA sequencing analysis results of human neutrophils from both BM and tumors, we found that CD63 and Galectin-3 distinguish MC & MM from neutrophil populations in cancer patients. Furthermore, we proposed a strategy with Fms-like tyrosine kinase 3 ligand to specifically induce the trans-differentiation of MCs & MMs into monocytic cells, and trigger tumor control in NCG-Gfi1−/− HIS mice. Thus, our findings establish an essential role of human MC & MM-stage neutrophils in promoting cancer progression, and suggest their potential as targets for developing potential biomarkers and immunotherapies for cancer.



Single-dose infusion of engineered viral receptor binding domain confers rapid and durable protection against viral infection

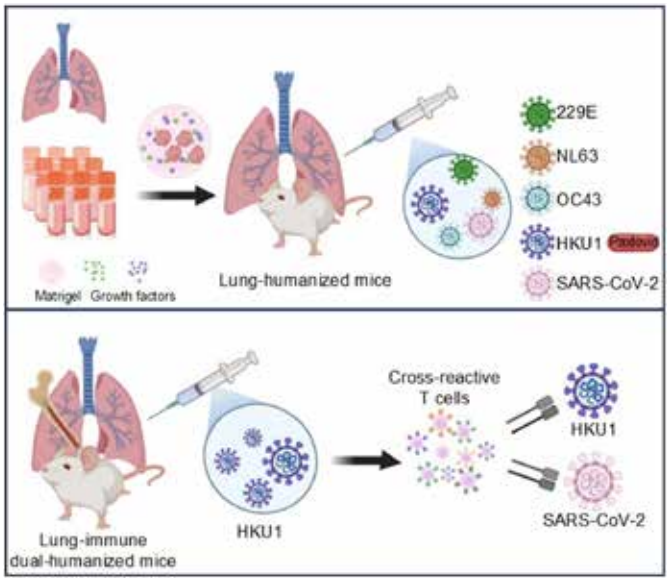
Developing both rapid- and long-acting antiviral drugs for single-dose administration can improve medication adherence and protect people at risk of infection. To provide proof of this concept, here, we designed multimerized form of viral receptor-binding domains (RBDs) to immediately occupy viral receptors to block infection and subsequently induce virus-specific protective immunity. We engineered SARS-CoV-2 RBD, enhancing its affinity to ACE2 and immunogenicity through multimerization and Fc modification. A single administration of 4RBD-Fc not only effectively blocked ACE2-dependent SARS-CoV-2 infections but also elicited robust virus-specific mucosal and systemic immunity in the absence of adjuvants, providing superior early and long-lasting protection compared to adjuvanted vaccines in mice. These findings demonstrate the feasibility and efficacy of engineered viral RBD as immediate-acting and long-lasting single-dose antiviral drugs through rapid receptor blocking and ensuing adaptive immunity induction.



A Lung-Immune Dual-Humanized Mouse Using Cryopreserved Tissue Enables Infection and Immune Profiling of Human Common Cold Coronaviruses

Human common cold coronaviruses (CCCoVs, e.g., 229E, NL63, OC43, HKU1) hold critical yet underexplored significance in understanding coronavirus evolutionary dynamics and immune cross-protection, offering

insights for predicting emerging pathogens and developing pan-coronavirus vaccines. However, research is hindered by the lack of animal models due to strict human-specific tropism and the confounding effects of frequent co-infections from clinical samples, which obscure virus-specific pathogenesis. Although lung-humanized mice have been used in SARS-CoV-2 studies, their application to CCCoVs remains unvalidated and relies on logistically challenging fresh human tissues. This study optimizes a transplantation strategy using cryopreserved human fetal lung tissue, achieving enhanced engraftment efficiency. And the refined model supports robust infection by all four major CCCoVs and demonstrates the therapeutic efficacy of Paxlovid against HKU1. Furthermore, comparative analysis reveals phenotypic distinctions in human immune cells between native mouse lungs and human lung implants in lung-immune dual-humanized mice. The model also enables validation of virus-specific T cell responses and assessment of SARS-CoV-2 cross-reactivity post-HKU1 infection. Overall, this study establishes a scalable platform using cryopreserved tissues for respiratory virus research, overcoming prior limitations in modeling human-specific tropism and dissecting immune-pathogen interactions.

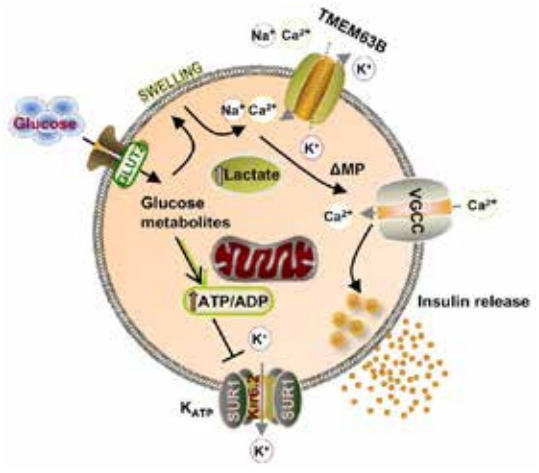


Group Yun Shi

Osmosensor TMEM63B facilitates insulin secretion in pancreatic β-cells

Jing-Jing Tu, Chang Ye, Xiao-Yu Teng, Yan-Yu Zang, Xiao-Ye Sun, Shuai Chen*, Jiang Chen* & Yun Stone Shi*(2025).

Elevated glucose metabolism triggers two primary processes that lead to β-cell depolarization and insulin secretion: the closure of ATP-sensitive K+ channels via ATP-dependent mechanisms and the activation of mechanosensitive channels (MSCs) due to cell swelling. However, the identity of these MSCs remains unclear. In this study, we found that TMEM63B is a stretch-activated cation channel (SAC) crucial for regulating insulin secretion in response to elevated glucose levels. TMEM63B is abundantly expressed in β-cells, and its deletion impairs insulin secretion triggered by high glucose. High glucose levels typically increase Ca2+ influx and firing frequency in β-cells, a response largely eliminated when TMEM63B is deleted. Mechanistically, glucose metabolism induces cell swelling and activates TMEM63B, which, in turn, leads to β-cell depolarization and insulin secretion. In conclusion, our findings demonstrate that TMEM63B is an SAC essential for regulating insulin secretion in response to elevated glucose levels.

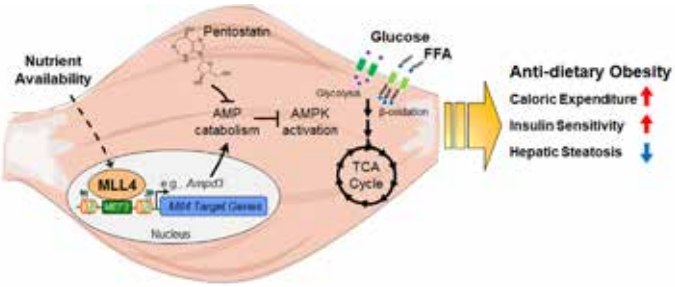


Group Zhenji Gan

Enhancer regulator MLL4 controls skeletal muscle metabolic efficiency by limiting AMPK-mediated fuel catabolism

Likun Yang, Lin Liu, Wen Wang, Chenyun Din, Aneesh K Asokan, Tingze Feng, Danxia Zhou, Zhisheng Xu, Tingting Fu, Qiqi Guo, Zheng Zho, Shaojun Pei, Gonghao Shen, Liwei Xiao, Yujing Yin, Zongchao Sun, Yan Mao, Wanping Sun, Jinjie Li, Jiacheng Xue, Min-Sheng Zhu, Kai Ge, K Sreekumaran Nair, Hai-Long Piao, and Zhenji Gan

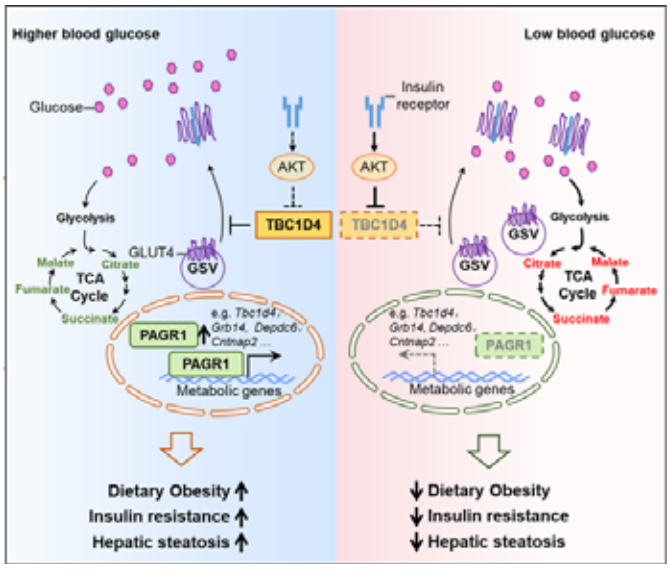
Skeletal muscle is a major organ for maintaining whole-body energy homeostasis, yet the mechanisms underlying its transcriptional and metabolic adaptation to environmental cues remain unclear. Here, we report that histone mono-methyltransferase mixed lineage leukemia 4 (MLL4), a key enhancer regulator, directs muscle metabolic adaptation and systemic metabolism through AMPK signaling. Nutrient availability modulates MLL4 expression, and skeletal muscle-specific ablation of MLL4 in male mice protects against diet-induced obesity and improves glucose homeostasis despite reduced exercise endurance. These effects arise from enhanced fuel catabolism caused by marked activation of AMPK in MLL4-depleted muscles. Mechanistically, MLL4 cooperates with myocyte enhancer factor 2 to induce AMP-metabolizing enzymes cytosolic 5'-nucleotidase 1A and AMP-deaminase 3, which suppress AMPK activity. Pharmacologic inhibition of AMP-metabolizing pathway by Pentostatin activates muscle AMPK, confers resistance to obesity and improves metabolic health. Collectively, our findings identify MLL4 as a pivotal enhancer-based transcriptional regulator that restrains AMPK-mediated fuel catabolism in muscle, revealing a potential therapeutic strategy for obesity-related metabolic disorders.



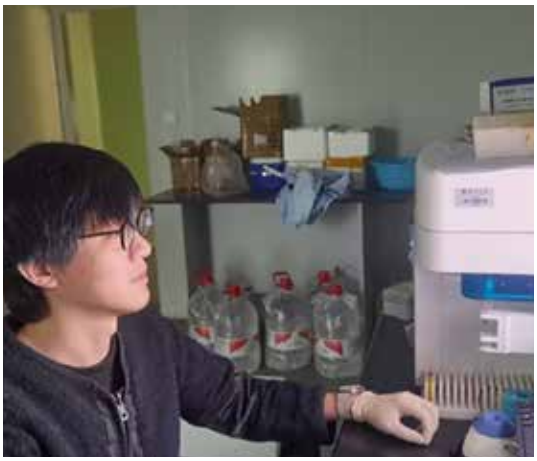
Glucose-Responsive PAGR1-Regulated Skeletal Muscle Gene Program Controls Systemic Glucose Homeostasis and Hepatic Metabolism

Chenyun Ding, Yuhuan Jia, Lin Liu, Wen Wang, Danxia Zhou, Zheng Zhou, Likun Yang, Xinyi Chen, Di Chen, Yan Mao, Liwei Xiao, Cai-Zhi Liu, Zhen-Yu Du, Yujing Yin, Qiqi Guo, Zongchao Sun, Kai Ge, Tingting Fu, Hai-Long Piao, Zhenji Gan

Chronic hyperglycemia, a hallmark of type 2 diabetes (T2D) and related metabolic disorders, exacerbates insulin resistance and impairs muscle glucose utilization, thereby contributing to systemic metabolic dysfunction. As the primary site of postprandial glucose disposal, skeletal muscle is crucial for systemic glucose homeostasis, however, the mechanisms underlying hyperglycemia-induced maladaptation in muscle remain poorly understood. Here, we identify PAGR1 (PAXIP1-associated glutamate-rich protein 1) as a glucose-responsive regulator in skeletal muscle. PAGR1 expression is induced by high glucose and serves as a modulator of systemic glucose homeostasis and hepatic metabolism. Using muscle-specific PAGR1-knockout mice, we show that PAGR1 deficiency enhances insulin signaling, promotes glucose transporter 4 (GLUT4) translocation, and increases muscle glucose uptake and utilization. Mechanistically, PAGR1 directly activates the expression of TBC1D4, a RAB GTPase-activating protein that negatively regulates GLUT4 translocation. Notably, muscle-specific deletion of PAGR1 protects mice from high-fat-diet-induced insulin resistance and hepatic steatosis. Together, these findings establish PAGR1 as a key mediator of skeletal muscle glucose sensing and utilization, highlighting its potential as a therapeutic target for counteracting glucotoxicity and preventing metabolic diseases such as T2D.



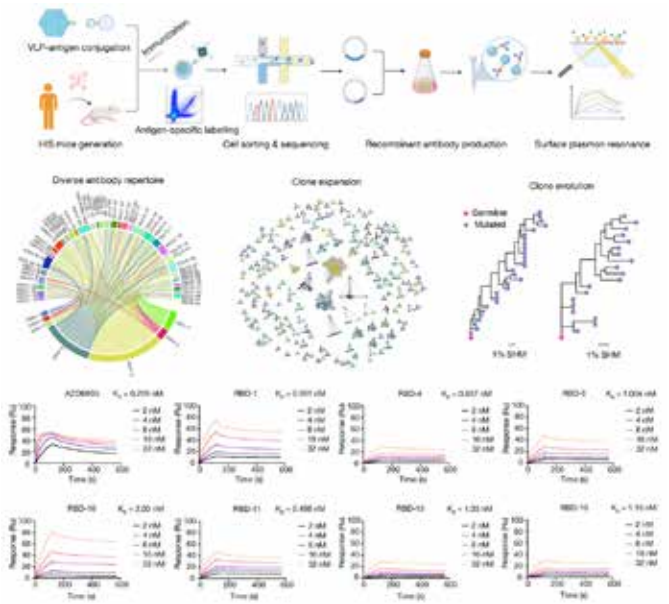
Student of the Year



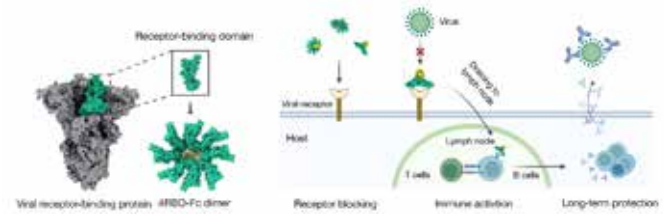
Haiqiao Sun

Haiqiao Sun obtained his Bachelor's degree in Biological Sciences from Jinling College, Nanjing University, in 2019. He then joined Professor Yan Li's laboratory to study B cell immunology. Throughout his academic journey, he received several prestigious awards, including the National Scholarship for Doctoral Students, Model Graduate Student of Nanjing University, the Gold Medal in the 4th Life Sciences GemPharmatech Cup, the 3rd Excellence Award, and achieved an "Excellent" rating in his doctoral mid-term evaluation

Humanized antibodies represent one of the most important classes of biologic therapeutics, yet their development is often time-consuming and costly. To address this challenge, Haiqiao Sun established a technology platform for the direct generation of fully human antibodies using human immune system (HIS) mice. Although HIS mice harbor abundant human B cells, defects in dendritic cell (DC) and T cell functions severely impair T-dependent B cell responses, constituting a major technical bottleneck. To overcome this limitation, he introduced virus-like particles (VLPs) displaying highly repetitive antigenic epitopes on their surface. These VLP antigens directly activate B cells and bypass the requirement for DC–T cell cooperation, thereby enabling robust B cell responses in HIS mice and providing a feasible strategy for downstream screening of antibodies.



In addition, Haiqiao Sun designed a dual-function molecule with combined antiviral drug and vaccine properties, termed 4RBD-Fc. By multimerizing the viral receptor-binding domain (RBD) and fusing it to an Fc domain, 4RBD-Fc can be administered via the respiratory tract to rapidly block viral receptor engagement. Subsequently, the molecule is transported to draining lymph nodes through Fc receptor–mediated pathways, where it elicits RBD-specific immune responses and induces the production of neutralizing antibodies. This strategy integrates the immediate, short-term protection of antiviral drugs with the durable immunity conferred by vaccines, achieving rapid and long-lasting protection with a single administration.



Selected Publications and Patents

1. Haiqiao Sun, et al. Single-dose infusion of engineered viral receptor-binding domain confers rapid and durable protection against viral infection. Communications Biology (2025).
2. Wei Liu, … Haiqiao Sun, et al. Human myelocyte- and metamyelocyte-stage neutrophils suppress tumor immunity and promote cancer progression. Cell Research (2025).
3. Haiqiao Sun, et al. Virus-like particles drive potent antigen-specific B cell responses across human immune system mouse models. Science Immunology (under review).
4. Haiqiao Sun, et al. Optimization of B cell responses in human immune system mice with spleen organoids. Advanced Science (under revision).
5. Yan Li, Haiqiao Sun, Deshan Ren, Xianchi Dong. Antiviral pharmaceutical composition containing multimerized SARS-CoV-2 spike protein fragments. CN202310826181.2A (2023).
6. Yan Li, Haiqiao Sun, He Li, Shuai Ding. A biological system, method, and application for producing fully human monoclonal antibodies. CN202411801044.4 (2025).
7. Yan Li, Haiqiao Sun, He Li. Application of CD40L combined with cytokines in promoting B cell proliferation and differentiation in HIS mice. Patent pending (2025).

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 physiological functions of the ion channel TMEM63B

The Transmembrane protein 63 (TMEM63) family is a mechanosensitive cation channel family that has attracted widespread attention in recent years. It is highly conserved evolutionarily and includes three homologs (TMEM63A, TMEM63B, and TMEM63C) in mammals. Members of this family were initially identified as osmosensitive channels, which can respond to changes in intracellular and extracellular osmolarity, mediate cation influx, and participate in the regulation of various physiological processes. Early studies have shown that TMEM63B, as an osmosensor in inner ear hair cells, is crucial for auditory function, and its loss of function leads to hearing impairment; TMEM63B in SFO neurons was activated by hyperosmotic stress, which leads to depolarization and increased firing rate of these neurons. With in-depth research, the roles of the TMEM63 family in metabolic regulation, nervous system development and other fields have gradually emerged, and the association between related mutations and human diseases has also been successively reported, providing a new perspective for understanding complex physiological and pathological mechanisms.

Precise regulation of insulin secretion in pancreatic β-cells is the core of maintaining blood glucose homeostasis, and its dysfunction can lead to metabolic diseases such as diabetes. The traditional view holds that glucose-induced β-cell depolarization through the closure of ATP-sensitive K channels (KATP channels) is the main pathway for insulin secretion. However, accumulating evidence indicates the existence of KATP-independent regulatory mechanisms, among which mechanosensitive channels (MSCs) activated by cell swelling play an important role. Nevertheless, the specific molecular identity of such channels has long remained unclear, limiting the complete understanding of the insulin secretion regulatory network.

Myelination in the central nervous system (CNS) is the basis for the efficient conduction of neural signals. The process by which oligodendrocytes (OLs) differentiate and mature from oligodendrocyte precursor cells (OPCs) and wrap axons to form myelin sheaths requires strict spatiotemporal regulation. Hypomyelinating leukodystrophy is a group of neurological diseases characterized by myelination defects, clinically manifesting as developmental delay, motor dysfunction, etc., but the pathogenic mechanisms of some subtypes have not been fully elucidated. In recent years, TMEM63A gene mutations have been found to be associated with transient hypomyelination in infancy, but the specific role and molecular mechanism of this gene in oligodendrocyte differentiation remain to be further investigated.

Therefore, our recent study has demonstrated that: 1. TMEM63B is a stretch-activated cation channel (SAC) crucial for regulating insulin secretion in response to elevated glucose levels. 2. the mutation in TMEM63A is the pathogenesis of the hypomyelination in the patient. TMEM63A-mediated Ca2+ influx plays critical roles in the early development of myelin and oligodendrocyte differentiation.

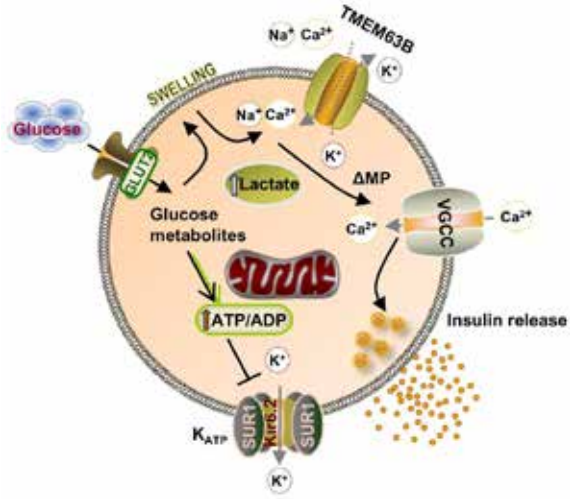

Figure 1. Osmosensor TMEM63B facilitates insulin secretion in pancreatic β-cells. (Science China-Life Sciences, 2025).

TMEM63B is an osmosensor regulating β-cell excitability and insulin secretion. TMEM63B contributes to the plasma membrane depolarization and the increase of intracellular Ca^{2+},both of which are essential for regulating insulin secretion

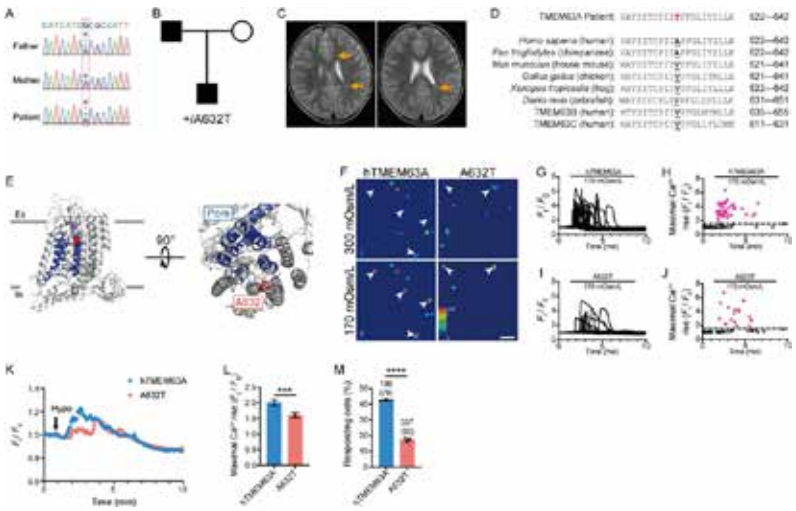

Figure 2. Cation Channel TMEM63A Autonomously Facilitates Oligodendrocyte Differentiation at an Early Stage. (Neuroscience Bulletin, 2025).

The mutation in TMEM63A is the pathogenesis of the hypomyelination in the patient. TMEM63A-mediated Ca2+ influx plays critical roles in the early development of myelin and oligodendrocyte differentiation.

Selected publications

1. Tu JJ, Ye C, Teng XY, Zang YY, Sun XY, Chen S*, Chen J*, Shi YS*. (2025) Osmosensor TMEM63B facilitates insulin secretion in pancreatic β -cells. Sci China Life Sci. 68(6):1714-1726.
2. Wang YY, Wu D, Zhan Y, Li F, Zang YY, Teng XY, Zhang L, Duan GF, Wang H, Xu R, Chen G, Xu Y, Yang JJ*, Yu Y*, Shi YS*. (2025) Cation Channel TMEM63A Autonomously Facilitates Oligodendrocyte Differentiation at an Early Stage. Neurosci Bull. 41(4):615-632.
3. 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.
4. 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.
5. 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.
6. 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.
7. 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.
8. 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.
9. 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.
10. 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.

Group members

Group Leader	Graduate students	Former graduate students			
Yun Shi	Yuhan Ge	Yanjun Li	Jiahui Sun	Yueying Wang	Yanyu Zang
	Shuaifei Lu	Jiang Chen	Shixiao Peng	Guolin Yang	Jingwen Chen
	Xiaofeng Tan	Guifang Duan	Chaohua Jiang	Yangyang Chen	
	Tianzi Zhang	Han Du	Xiaoyu Teng	Jingjing Tu	
	Jing Li	Dan Wu	Qingqing Li	Shiyu Zhan	
		Chang Ye	Wenmin Cai	Guizhou Li	

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 PP2A regulates oligodendrocyte differentiation.

Loss-of-function mutations on phosphatase PP2A subunits are known to cause diseases with hypomyelination and defective motor functions. To investigate the underlying mechanisms, we generated a mutant mouse, in which PP2Acα is inactivated in oligodendrocyte (OL) lineage cells in the central nervous system. We show that, PP2A mutants exhibit deficient oligodendrogenesis and are impaired specifically in a fine motor coordination and balance task (Fig.1). We demonstrate that inactivation of PP2Acα leads to down-regulation of Sox10 in a proteasome-dependent manner (Fig.2). Overall, this study provides insights on mechanisms for PP2A-related brain developmental diseases.

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.

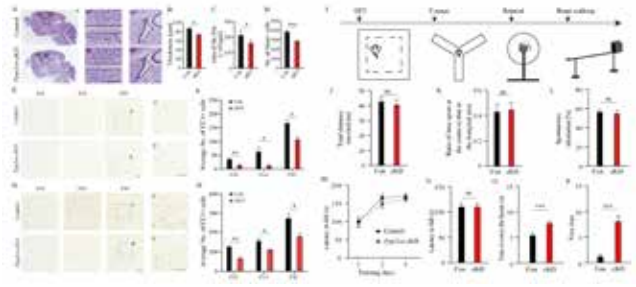

Figure 1. Deficient OL development and impaired fine motor coordination in Ppp2cα cKO mice. (A-D) Characterization of Ppp2cα cKO mice. (E-H) Decreased number of CC1+ cells in the cortex (E,F) and corpus callosum (CC) (G,H) in Ppp2cα cKO mice. (I-P) Behavioral performance in Ppp2cα cKO mice. Unchanged general motor ability (I-N) but impaired fine motor coordination (O,P) in Ppp2cα cKO mice.

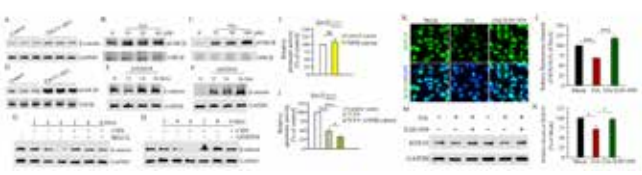

Figure 2. PP2A regulates the expression of Sox10 in a proteasome-dependent manner.

(A) Increased β-catenin levels in Ppp2cα cKO mice (B-D) Increased levels of pGSK3β in OA-treated Oli-neu cells/N2a cells and in Ppp2cα cKO mice. (E,F) Increased β-catenin levels in Oli-neu cells and N2a cells treated with AZD2858. (G,H) Time-dependent degradation of β-catenin in CHX-treated cells. (I,J) Decreased promoter activity of Sox10 in cells expressing TCF4/△N89β-catenin. (K-N) XAV-939 treatment restored SOX10 expression in OA-treated cells.

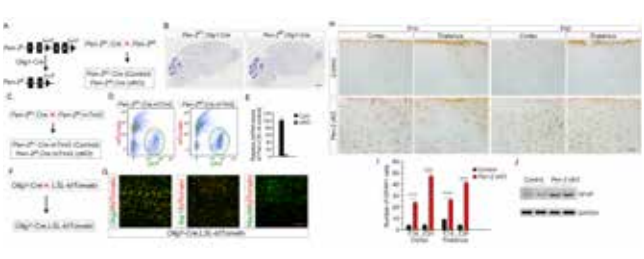

Figure 3. Enhanced generation of astrocytes in OL lineage cellS specific Pen-2 cKO mice. (A-D) Characterization of OL lineage cells specific Pen-2 cKO mice. (F,G) Co-staining of Olig2/tdTomato in Olig1-Cre;LSL-tdTomato mice. (H) IHC on GFAP in Pen-2 cKO mice. (I) Number of GFAP+ cells in Pen-2 cKO mice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

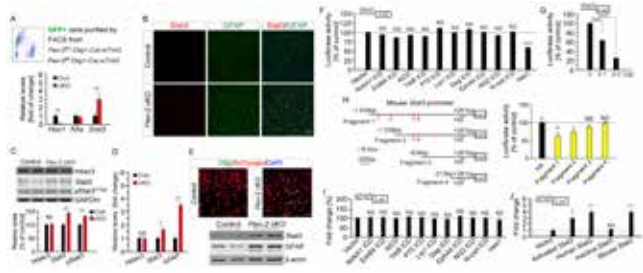

Figure 4. Increased expression of Stat3 in Pen-2 cKO mice. (A) Q-PCR analyses on Hes1, Nfia and Stat3 using Pen-2 cKO RNA samples. (B) IHC of Stat3/GFAP in Pen-2 cKO mice. (C) Western analysis on Hdac3, Stat3 and pStat3 in Pen-2 cKO mice. (D) Q-PCR analyses on Hdac3, Stat3 and GFAP mRNA levels in Pen-2 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. Liu M, Zhang Y, Teng X, Wang R, Liu Y, Hou J, Wang H*, Li Y*, Wang Z* and Chen G*. Phosphatase PP2A is required for CNS myelination via proteasome-dependent regulation of Sox10 expression. Glia, 2025: 70082.
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4. 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.
5. 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.
6. 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.
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8. Hou J, Bi H, Ye Z, Huang W, Zou G, Zou X, Shi Y, Shen Y, Ma Q, Kirchhoff F, Hu Y* and 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.
9. Wang H, Liu M, Zou G, Wang L, Duan W, He X, Ji M, Zou X, Hu Y*, Yang J-J* and 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.
10. Bi H, Zhou C, Zhang Y, Cai X, Ji M, Yang J-J, Chen G* and 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.

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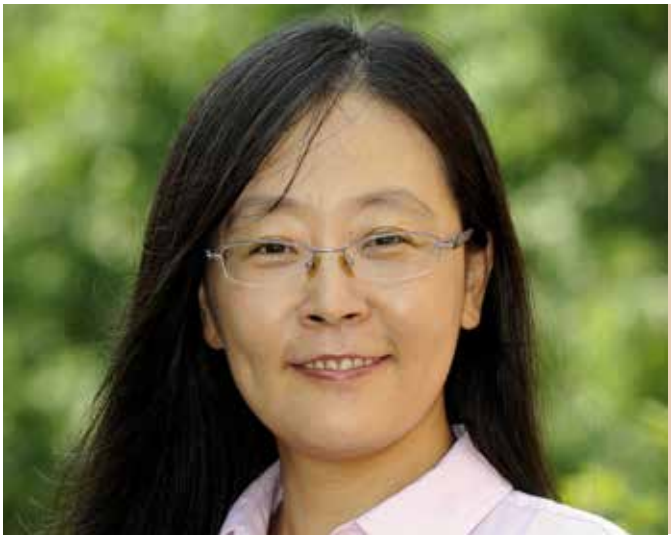

Huiming Gao M.D., Ph.D.

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

Numerous studies indicate that chronic neuroinflammation contributes to the pathogenesis of Alzheimer's disease (AD, the most common neurodegenerative disease) as an initiating or secondary causative factor. This study investigated how an acute and beneficial physiological inflammatory response flipped to a chronic neurodegenerative one thereby critically contributes to AD neurodegeneration. BCL11B, a multifunctional transcription factor, is highly expressed in neurons and T lymphocytes and plays an essential role for their development and differentiation. It participates in immuno-inflammatory response in adulthood. Of special interest is a recent genome-wide linkage analysis of 41 families of late-onset AD reveals an association of BCL11B with AD. Given identified association among BCL11B, inflammation and AD, this study investigated whether and how BCL11B regulated microglia inflammatory response thereby contributing to AD pathogenesis. The results revealed BCL11B expression and its upregulation in microglia in the hippocampus and the cortex of 12-month-old 5×FAD mice (a commonly used AD model). BCL11B expression was also significantly upregulated in primary microglia after inflammatory stimulation for 24 h with lipopolysaccharides (LPS) or Poly (I:C). Inducible BCL11B deletion in primary microglia dampened their inflammatory response to LPS. Moreover, knockout of microglial BCL11B attenuated LPS-elicited death of co-cultured wildtype neurons. Next, tamoxifen was intraperitoneally injected to 4.5-month-old BCL11B $^{flox/+}$; Cx3cr1^{CreER}; 5×FAD heterozygote mice to specifically knockdown BCL11B in microglia in adulthood. Microglial BCL11B knockdown in 5×FAD mice attenuated microglial activation and significantly improved AD-like phenotypes including Aβ accumulation and plaque formation and neuronal damage in the hippocampus and the cortex, as well as spatial learning and memory impairment. Collectively, our results showed microglia BCL11B knockdown improved pathological changes and cognitive impairment in AD mice through suppressing neuroinflammation. This study provides new experimental support for anti-inflammatory therapeutics for AD and suggests that BCL11B may become a potential target for AD treatment.

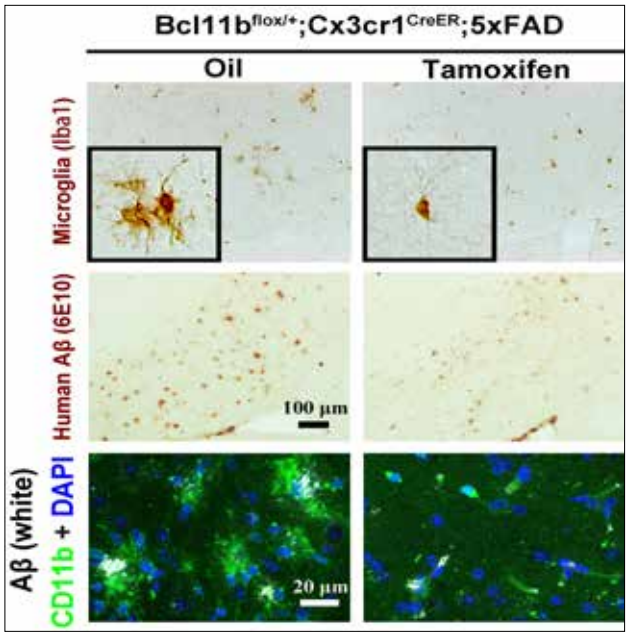

Figure 1. Inducible BCL11B knockdown in microglia in adult AD mice attenuated microglial activation and Aβ plaque formation.

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

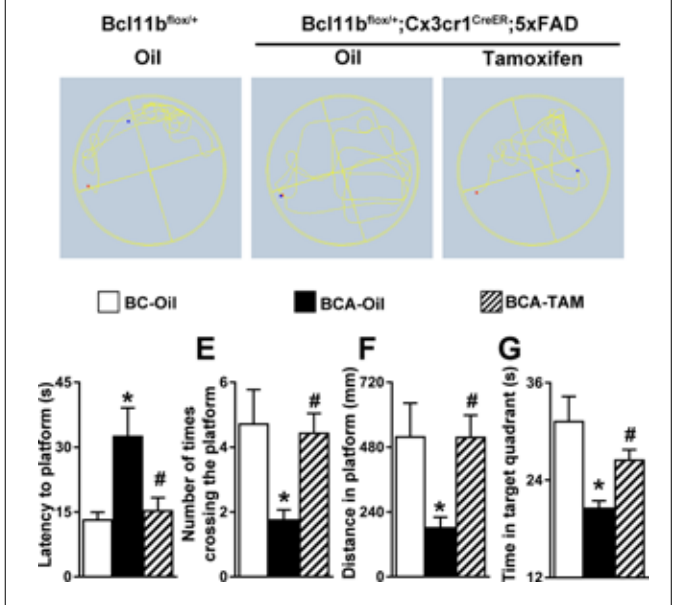

Figure 2. Inducible microglial BCL11B knockdown in adult AD mice improved their cognitive impairment.

Morris water maze test detected spatial learning and memory impairment in AD mice and its improvement by specific BCL11B knockdown in microglia in adult mice. BC-Oil: BCL11B $^{flox/+}$ mice with oil injection; BCA-Oil and BCA-TAM: BCL11B $^{flox/+}$; Cx3cr1^{CreER}; 5×FAD mice with oil or tamoxifen injections respectively.

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
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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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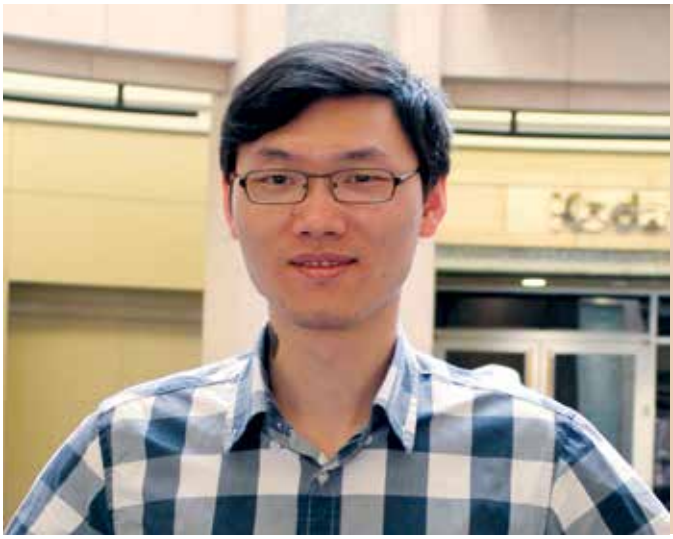

Guoqiang Wan, Ph.D.

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.

In 2025, we identified a number of important genes contributing to hearing functions, including CGN and PLSCR5. Previously, we found that Cingulin (CGN) protein is important to maintain the morphology of cuticular plates of inner ear hair cells and a frameshift mutation in CGN causes autosomal dominant nonsyndromic hearing loss. Here, we found that the mutant CGN proteins form insoluble aggregates which accumulate intracellularly and lead to cell death. Expression of the mutant CGN in the inner ear results in severe hair cell death and hearing loss in mice, resembling the auditory phenotype in human patients. Interestingly, a human-specific residue (V1112) in the neopeptide generated by the frameshift mutation is critical for the aggregation and cytotoxicity of the mutant human CGN. Moreover, the expression of heat shock factor 1 (HSF1) decreased the accumulation of insoluble mutant CGN aggregates and rescued cell death. Thus, we identify mutant-specific toxic polypeptides as a disease-causing mechanism of the deafness mutation in CGN, which can be targeted by the expression of the cell chaperone response regulator HSF1 (Figure 1).

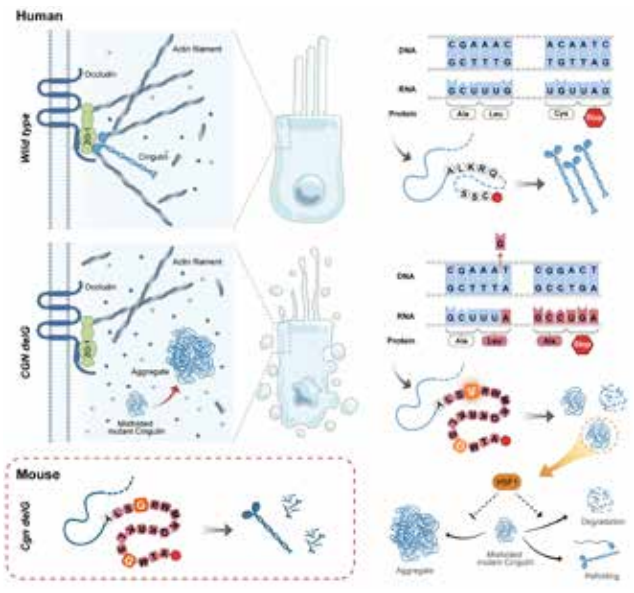

Figure 1. A proposed mechanism for the human-specific cytotoxic neopeptide generated by the deafness gene Cingulin contributing to hearing loss. The wildtype CGN protein predominantly localizes to the apical surfaces of hair cells, which is essential for regulating normal actin assembly and maintaining hair cell cuticular plate and stereocilia morphology. The frameshift mutation in CGN not only reduces the expression of functional CGN protein, but also produces a human-specific cytotoxic neopeptide harboring the key V1112 residue. This neopeptide results in aggregation of the mutant CGN proteins as insoluble cellular deposites, ultimately leading to hair cell death and hearing loss. The expression of HSF1 can reduce insoluble protein aggregates and prevent cell death.

Furthermore, we identify Plscr5 as a novel downstream target of the transcription factor POU4F3, essential for hair cell function and mutation of which causes human DFNA15 deafness. Plscr5 knockout mice exhibit progressive hearing loss due to stereocilia degeneration and hair cell loss. Functional analyses suggest that PLSCR5 contributes to phosphatidylserine (PS) externalization in inner hair cell membranes and is important for outer hair cell and stereocilia maintenance, suggesting complex roles in cellular homeostasis and auditory function. In summary, our findings identify PLSCR5 as an important downstream effector of POU4F3, and indicate that PLSCR5 regulates PS externalization in inner hair cells and is crucial for auditory function (Figure 2).

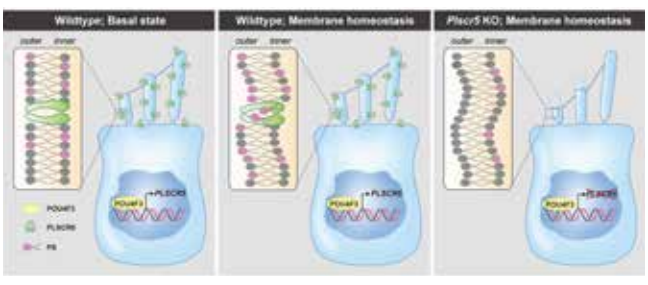

Figure 2. Graphic illustration on the role of PLSCR5 in auditory functions. Plscr5 serves as a critical downstream target of POU4F3, essential for cochlear hair cell function and stereocilia membrane homeostasis. Plscr5 knockout (KO) mice exhibits progressive hearing loss due to stereocilia degeneration and impaired phosphatidylserine (PS) externalization.

Degeneration of the cochlear spiral ganglion neurons (SGNs) is one of the major causes of sensorineural hearing loss, and significantly impacts the outcomes of cochlear implantation. Functional regeneration of SGNs holds great promise for treating sensorineural hearing loss. In our recent study, we systematically screened 33 transcriptional regulators implicated in neuronal and SGN fate. Using gene expression array and principal component analyses, we identified a sequential combination of Ascl1, Pou4f1 and Myt1l (APM) in promoting functional reprogramming of SGNs. The neurons induced by APM expressed mature neuronal and SGN-lineage specific markers, displayed mature SGN-like electrophysiological characteristics, and exhibited single cell transcriptomes resembling the endogenous SGNs. Thus, transcription factors Ascl1, Pou4f1 and Myt1l may serve as novel candidates for direct reprogramming of SGNs and hearing recovery due to SGN damages (Figure 3).

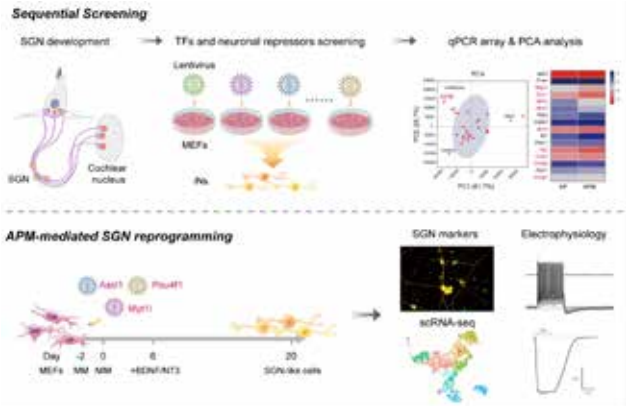

Figure 3. Graphic illustration of SGN reprogramming by Ascl1/Pou4f1/Myt1l. An unbiased sequential screening of the 33 neuronal regulators was performed on MEFs and reprogramming towards SGN fate was evaluated by qPCR array followed by PCA analysis. A combination of Ascl1, Pou4f1 and Myt1l (APM) was identified to promote functional reprogramming of SGNs based on biochemical, electrophysiological and single cell transcriptomic analyses.

Selected publications(* Corresponding author)

1. Zhao, Z.*, Li, A. *, Zhu, Y., Cen, S., Liu, Q., Zhang, Y., Fan, H., Hou, Z., Ma, D.-B., Liu, D., Duan, M.#, Qian, X.#, Chai, R.#, Wan, G.#, Gao, X.# (2025). Blood-Labyrinth Barrier Damage Mediated by Granzyme from Cytotoxic Lymphocytes Results in Hearing Loss in Systemic Lupus Erythematosus. Proceedings of the National Academy of Sciences of the United States of America, 122(33):e2423240122.
2. Chen, Y.*, Cheng, C.*, Li, A.*, Ma, D., Li, S., Wang, H., Gao, S., Liu, D., Song, P., Yu, C.#, Qian, X.#, Wan, G.#, Gao, X.# (2025). Pinoresinol Diglucoside Attenuates Nuclear Receptor Coactivator 4-Mediated Ferritinophagy Associated with Cisplatin-Induced Hearing Loss, Advanced Science, e2408777.
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5. 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.
6. 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.
7. 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.
8. 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.

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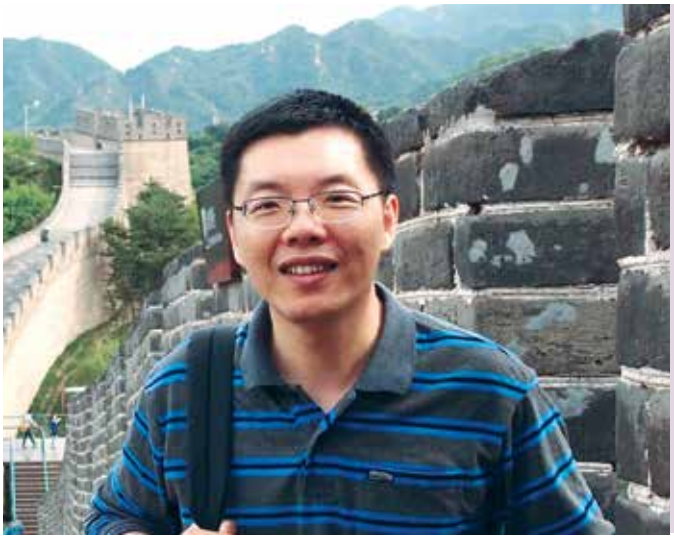
Organogenesis



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 morphogenesis

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 (Kang et al., Dev Cell, 2018) and migratory timing (Wang X et al., Iscience 2020) of a group of cells that will later collectively detach and migrate away from the host tissue? How can the group of cells communicate with each other (Wang H et al., Iscience 2020) and collectively know the front vs. back, top vs. bottom and inside vs. outside during migration (Wang et al., Dev 2018)? Finally, what powers the group to migrate collectively (Qu et al., JGG 2023; Qu et al., Fcell 2022)? A primary focus of my lab has been to address these key questions. We utilized the border cells in Drosophila ovary to study collective migration during development (Figure 1), and they are genetically tractable and amenable to live imaging and optogenetic manipulation.

Mechano-sensing during tissue morphogenesis

A second and more recent focus of my lab is to understand how mechanical cues regulate tissue morphogenesis in the spatial and temporal fashion. During tissue and organ formation, developmental cues regulate tissue morphogenesis in spatial and temporal manners by orchestrating cellular behaviors and tissue dynamics with precise timing and location. It is known that extracellular factors including chemical molecules and mechanical forces can serve as spatial and temporal cues to influence cellular behaviors and tissue mechanics during morphogenesis, through activating specific intracellular signaling pathways. While how extracellular molecules regulate morphogenetic events such as cell migration has been extensively studied, how mechanical forces spatially and temporally regulate the dynamic morphogenetic processes is much less studied and understood. My lab utilized the tissue elongation of stage 9 egg chamber of Drosophila ovary as a model system to addressed this question. We demonstrate in the recently published paper (Dong et al., Current Biology 2025) that growth-induced mechanical pressure from expanding germline cells triggers tissue elongation by activating the TRPM channel in adjacent somatic follicle cells, inducing calcium influx that drives myosin oscillation through the Rho1-Rok and CaM-MLCK pathways, thereby coordinating morphogenesis with spatial and temporal precision.

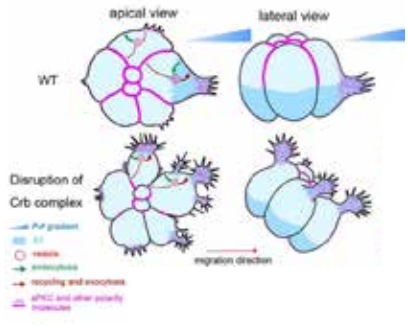

Figure 1. Diagram showing WT and Crb complex-deficient border cells in apical and lateral views. The model proposes how the two pools of aPKC and three distinct cell polarities are established by the Crb and Par complexes and endocytic recycling machinery (from Wang et al., Dev 2018).

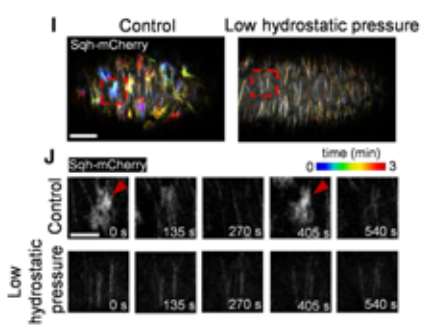

Figure 2. Images showing temporal projections (I) and time-lapsed images (J) of live imaging videos that capture the basal myosin (Sqh-mCherry) oscillation in stage 9 egg chambers under the control or the low hydrostatic pressure conditions (from Dong et al., Current Biology 2025).

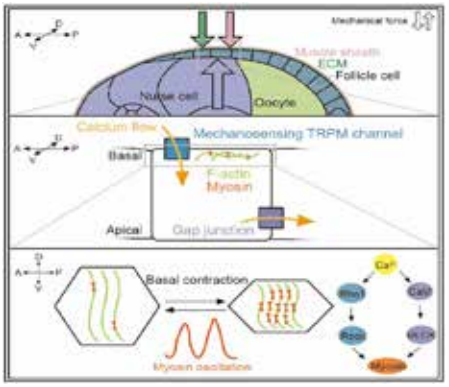

Figure 3. Diagram showing growth-induced mechanical pressure from expanding nurse cells and oocyte triggers tissue elongation by activating the TRPM channel in adjacent somatic follicle cells, inducing calcium influx that drives basal myosin oscillation through the Rho1-Rok and CaM-MLCK pathways (Dong et al., Current Biology 2025).

Selected Publications

1. Dong, Z., Wang, H., Zhang, R., Guo, Z., Zhang, B., Pei, R., Guo, X., Xia, P., Si, G. and Chen, J. * TRPM-mediated mechanoreception regulates myosin oscillation during tissue elongation. Current Biology (2025)
2. Wang, H. and Chen, J.* Cell migration: Collective cell migration is intrinsically stressful. Current Biology, 34(7): R275-R278 (2024)
3. 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)
4. 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)
5. 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)
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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 hedgehog signaling/Mitochondrial homeostasis

1.Parkin mediates the mitochondrial dysfunction through mRpL18

Loss of function of parkin leads to mitochondrial dysfunction, which is closely related to Parkinson's disease. However, the in vivo mechanism is far from clear. One dogma is that impaired Parkin causes dysfunction of mitophagy mediated by Pink1-Parkin axis. The other is that impaired Parkin causes Mfn accumulation which leads to mitochondrial dysfunction. Surprisingly, in Drosophila muscles, the first dogma is not applicable; for the second dogma, our study suggests that Parkin mediates mitochondrial dysfunction through the synergy of both Marf and mitochondrial protein mRpL18 got from our genome-wide screen, whose RNAi rescues parkin RNAi phenotype. Mechanistically, we found that impaired Parkin upregulated both transcription and protein levels of mRpL18 dependent on its E3 ligase activity, causing mRpL18 accumulation outside mitochondria. Consequently, cytosolic-accumulated mRpL18 competitively bound Drp1, leading to the reduction of the binding of Drp1 to its receptor Fis1, which finally inhibited mitochondrial fission and tipped the balance to mitochondrial hyperfusion, thereby affected the mitochondrial function. Taken together, our study suggests that impaired Parkin causes mitochondrial hyperfusion due to two reasons: (1) Parkin defect impairs Pink1-Parkin axis-mediated Marf degradation, which promotes mitochondrial fusion; (2) Parkin defect causes mRpL18 accumulation, which inhibits Drp1/Fis1-mediated mitochondrial fission. These two ways together drive Parkin-mediated mitochondrial hyperfusion. Therefore, knockdown of either marf or mRpL18 can prevent mitochondrial hyperfusion, leading to the rescue of Parkin defect-triggered fly wing phenotypes. Overall, our study unveils a new facet of how Parkin regulates mitochondrial morphology, which provides new insights for the understanding and treatment of Parkinson's disease.

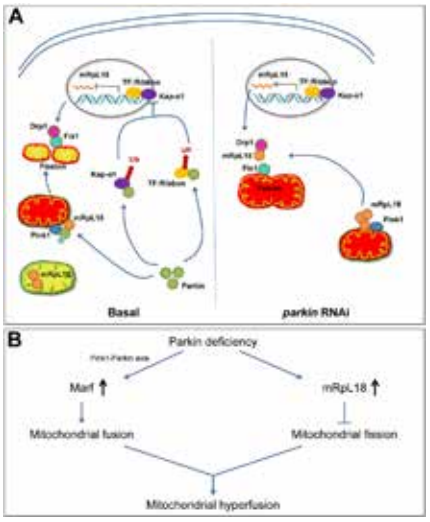

Fig.1 Parkin mediates the mitochondrial dysfunction through mRpL18

A, in kinds of mitochondrial defects, Pink1 accumulates on the mitochondrial outer membrane to recruit and activate Parkin which inhibits the mRpL18 transcription and promotes the protein degradation of cytosolic retained mRpL18 in its E3 ligase activity dependent manner. The reduced mRpL18 leads to more Drp1 binding with its receptor, that promotes mitochondrial fission and prevents mitochondrial hyperfusion. However, in the background of parkin knockdown, cytosolic accumulation of mRpL18 inhibits mitochondrial fission, that results in mitochondrial hyperfusion and finally impairs mitochondrial function. B, loss of parkin can cause mitochondrial hyperfusion due to two reasons: (1) Parkin deficiency impairs Pink1-Parkin axis-mediated Marf degradation, which promotes mitochondrial fusion and (2) Parkin deficiency causes mRpL18 accumulation, which impairs Drp1/Fis1-mediated mitochondrial fission. These two ways function together to drive Parkin-mediated mitochondrial hyperfusion phenotype.

2.Impaired mitochondria-initiated crosstalk with lysosomes reciprocally aggravates mitochondrial defect through LManVI

Mitochondria coordinate with lysosomes to maintain cellular homeomstasis. However, in mitochondrial defect condition, how they communicate is less clear. Here, utilizing dMterf4 RNAi fly model, we find that expression of lysosomal alpha-mannosidase VI (LManVI) is significantly downregulated. Mechanistically, we show that dMterf4 RNAi-triggered mitochondrial defect mediates downregulation of lysosomal LManVI through Med8/Tfb4-E(z)/pho axis, causing impairment of lysosomal function. Reciprocally, downregulation of lysosomal LManVI further decreases many mitochondrial genes expression through downregulation of transcriptional coactivator PGC-1, leading to aggravating the dMterf4 RNAi-mediated mitochondrial defect, suggesting that mitochondrial defect can crosstalk with lysosomes to make mitochondrial status worse in a positive feedback way. Finally, we demarcate that this interaction between mitochondria and lysosomes may be conserved in mammalian cells. Therefore, our findings unveil a communication mechanism between mitochondria and lysosomes in mitochondrial defect case, which provides insights about the treatments of related mitochondrial and lysosomal diseases through modulation of the mitochondria-lysosomes axis.

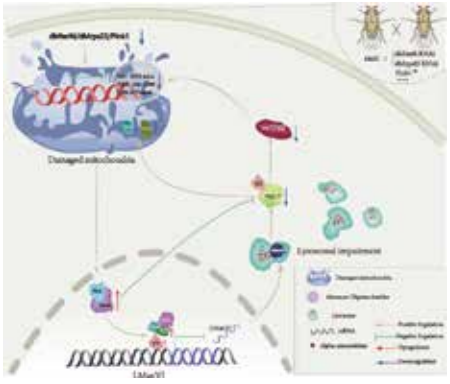

Fig.2 Impaired mitochondria-initiated crosstalk with lysosomes reciprocally aggravates mitochondrial defect through LManVI

Knockdown of dMterf4 results in mitochondrial dysfunction, leading to the upregulation of transcription-related genes Med8 and Tfb4. Med8 and Tfb4 form a complex to upregulate the E(z) and pho, which inhibit LManVI transcription, thus affecting the structure and function of lysosomes. Interestingly, inhibited LManVI decreases the transcription level of PGC-1, which further downregulates the expression of nuclear-encoded mitochondrial genes Tim13, ttm3, mtTFB2 and mitochondria-encoded genes ND1, ND3, ND4, ND5, CoI, CoIII, ATPase6, and Cytb through mitochondrial transcription factors mtTFB2. Ultimately, the downregulation of PGC-1 aggravates the mitochondrial defect phenotypes of dMterf4 RNAi. Therefore, the communication between mitochondria and lysosomes after knockdown of dMterf4 can modulate the phenotypes of impaired mitochondria.

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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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Decoding the relationship between tumorigenicity and immunogenicity of cancer cell

Cancer (tumorigenic) cells exhibit cellular properties such as tumorigenicity, evasion of anti-tumor immunity and cell death, metastasis, etc. Immunogenicity of cancer cells is the key to anti-tumor immunity, and many studies have found different molecular mechanisms that help to boost the sensitivity of cancer cells to antitumor immunity. While tumorigenicity is defined by neural stemness and its regulatory network, whether there is a general rule governing immunogenicity of cancer cells remained unknown. In a latest study, we show that genes conferring tumorigencity and genes conferring immunogenicity are inversely correlated with differentiation status of cells. Cancer cells can be induced to differentiate into different types of cells either by lineage-specific differentiation factors or by blocking cell-intrinsic oncofactors. Induced differentiation reprograms both cellular properties and transcriptomes of cancer cells, leading to suppression of genes conferring tumorigenicity and upregulation of genes conferring immunogenicity, and ultimately, leading to loss of neural stemness, suppression of tumorigenicity and enhancement of immunogenicity in cancer cells after differentiation. Vice versa, dedifferentiation leads to the opposite effect. The results identified the cellular mechanism that tumorigenicity and immunogenicity of cancer cells are inversely connected and determined by differentiation status. Such a mechanism, together with our previous studies, reinforces that cancer cell properties should be understood by understanding neural stemness and the principle of embryonic cell/tissue differentiation, and novel cancer therapies can be developed by employing differentiation effect of cancer cells induced by differentiation factors.

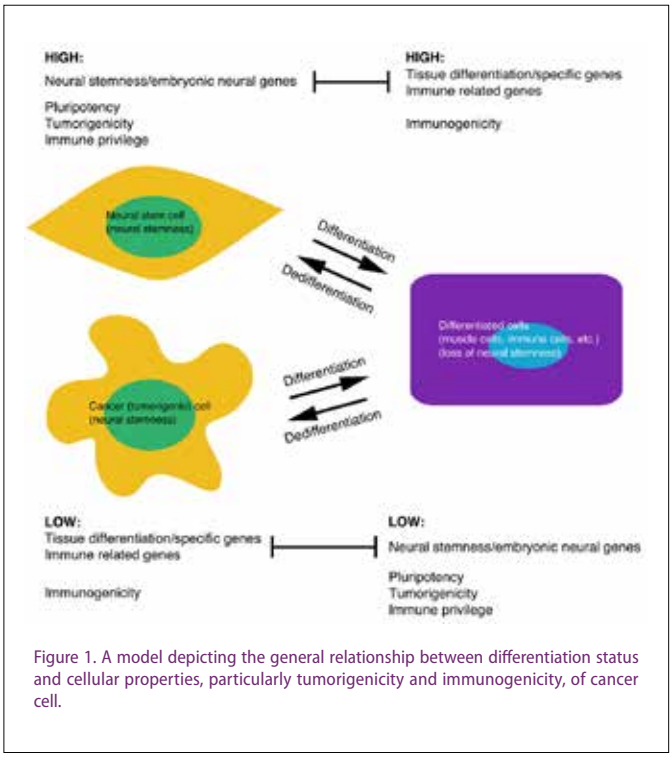

Figure 1. A model depicting the general relationship between differentiation status and cellular properties, particularly tumorigenicity and immunogenicity, of cancer cell.

Selected publications (*Correspondence author)

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5. 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.
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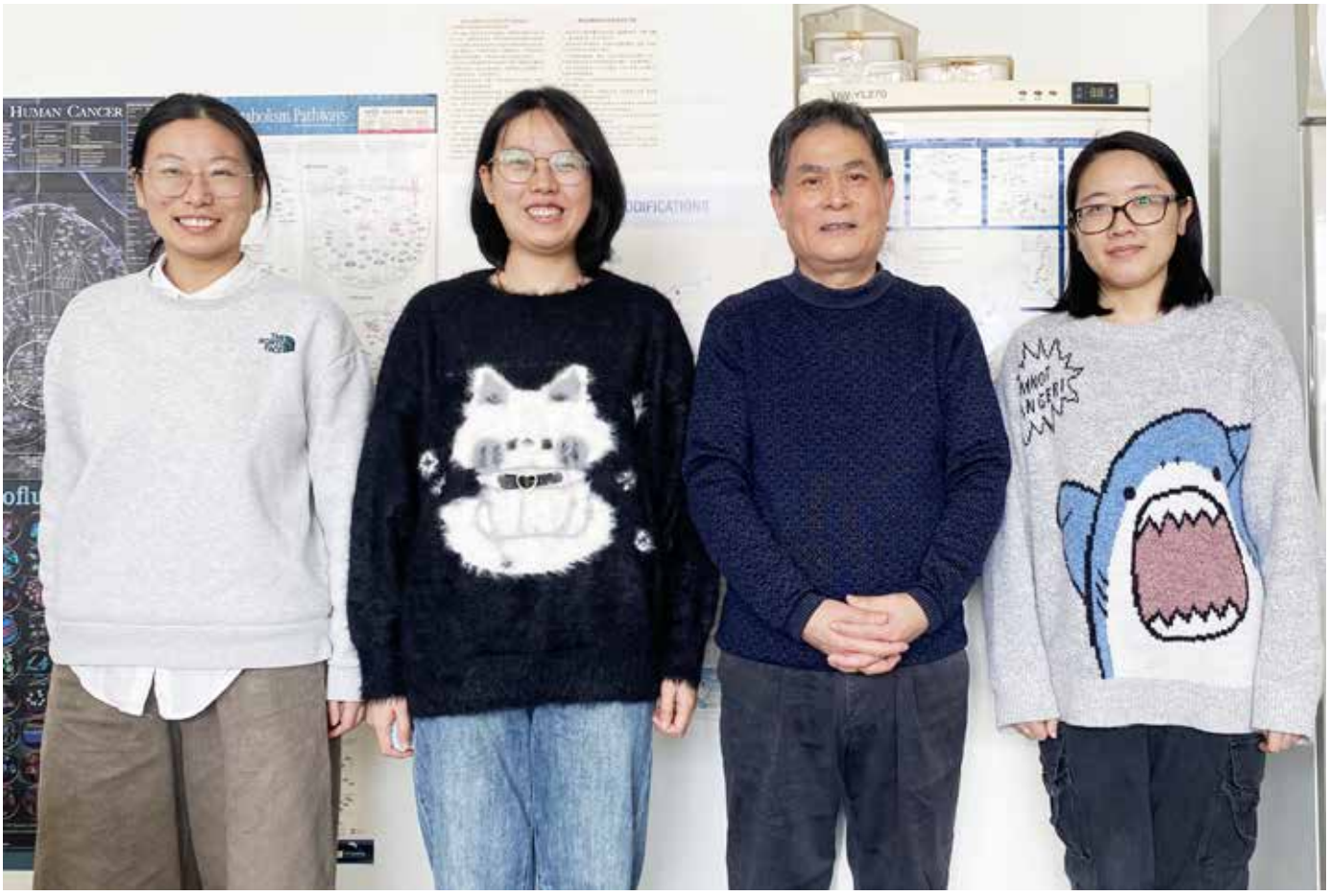

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Zebrafish development

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)·

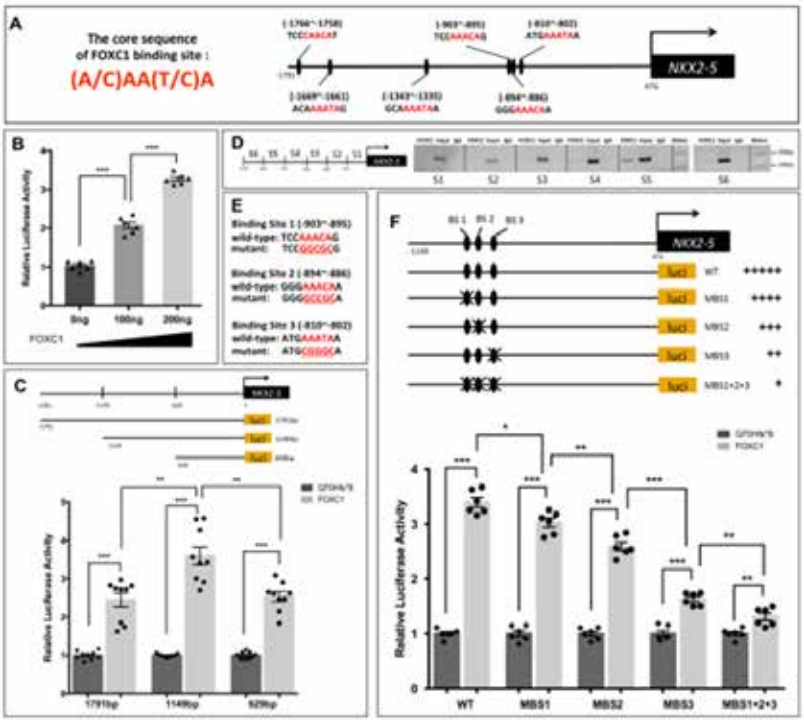

Figure 1. FOXC1 directly regulates the expression of NKX2-5 by binding to its proximal promoter in H9c2 cells.

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.

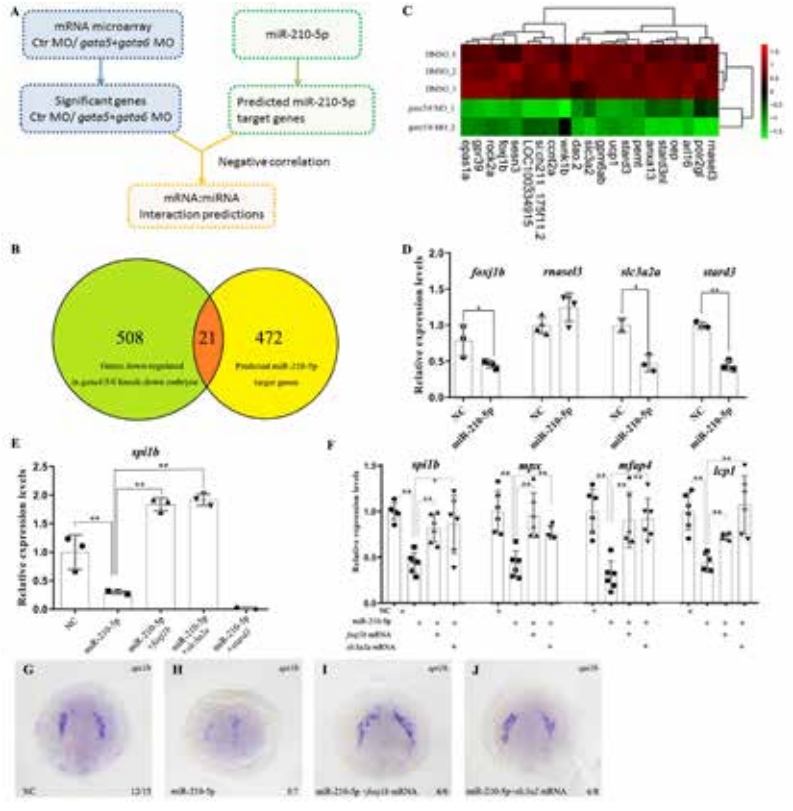

Figure 2. Both foxj1b and slc3a2a work downstream of miR-210-5p to mediate its role in inhibiting zebrafish primitive myelopoiesis.

(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)

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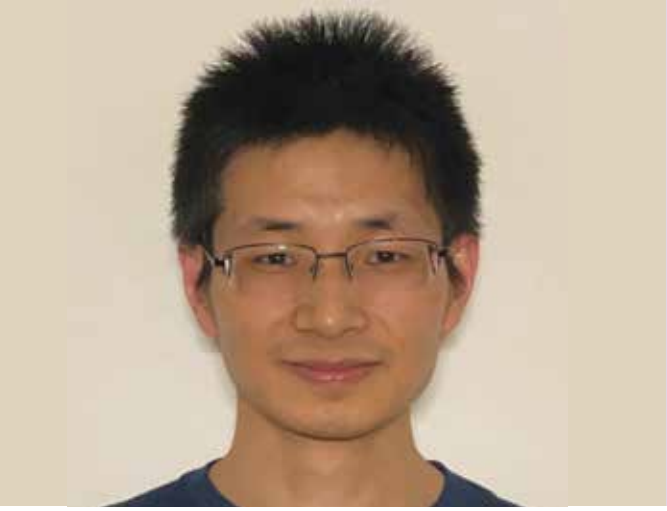

Liang Chi Ph.D.

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.

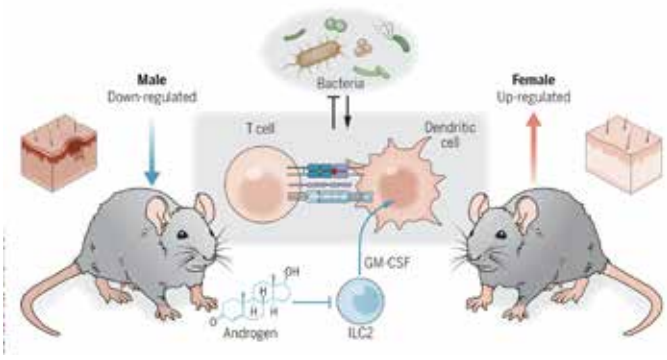
Our lab's long-term goal is to uncover the mechanisms driving sex and individual differences in immune and metabolic systems, with a focus on the roles of microbiota, nutrition, environmental influences, and hormonal regulation. This research aims to pave new pathways for personalized disease prevention 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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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.

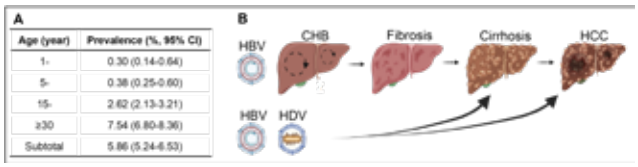

Figure 1. HBV prevalence and pathogenesis. (A) Age-specific HBV prevalence in China in 2020 (Zheng et al. 2024). The HBV infection was characterized by serological HBsAg detection. (B) Compared with chronic HBV infection alone, HBV and HDV dual infection is associated with accelerated liver disease progression.

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).

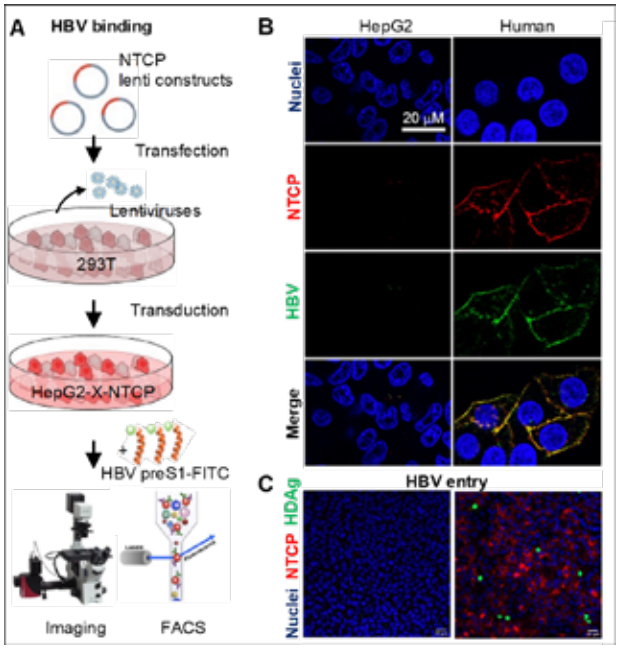

Figure 2. HBV binding and entry detection system. (A) The schematic of how the virus binding was investigated. (B) As a proof-of-concept, HBV binding on HepG2 cells expressing human NTCP was shown by confocal imaging. (C) HBV entry detection system was established by HDV antigen (HDAg) staining. Based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

Selected publications (*Co-corresponding author)

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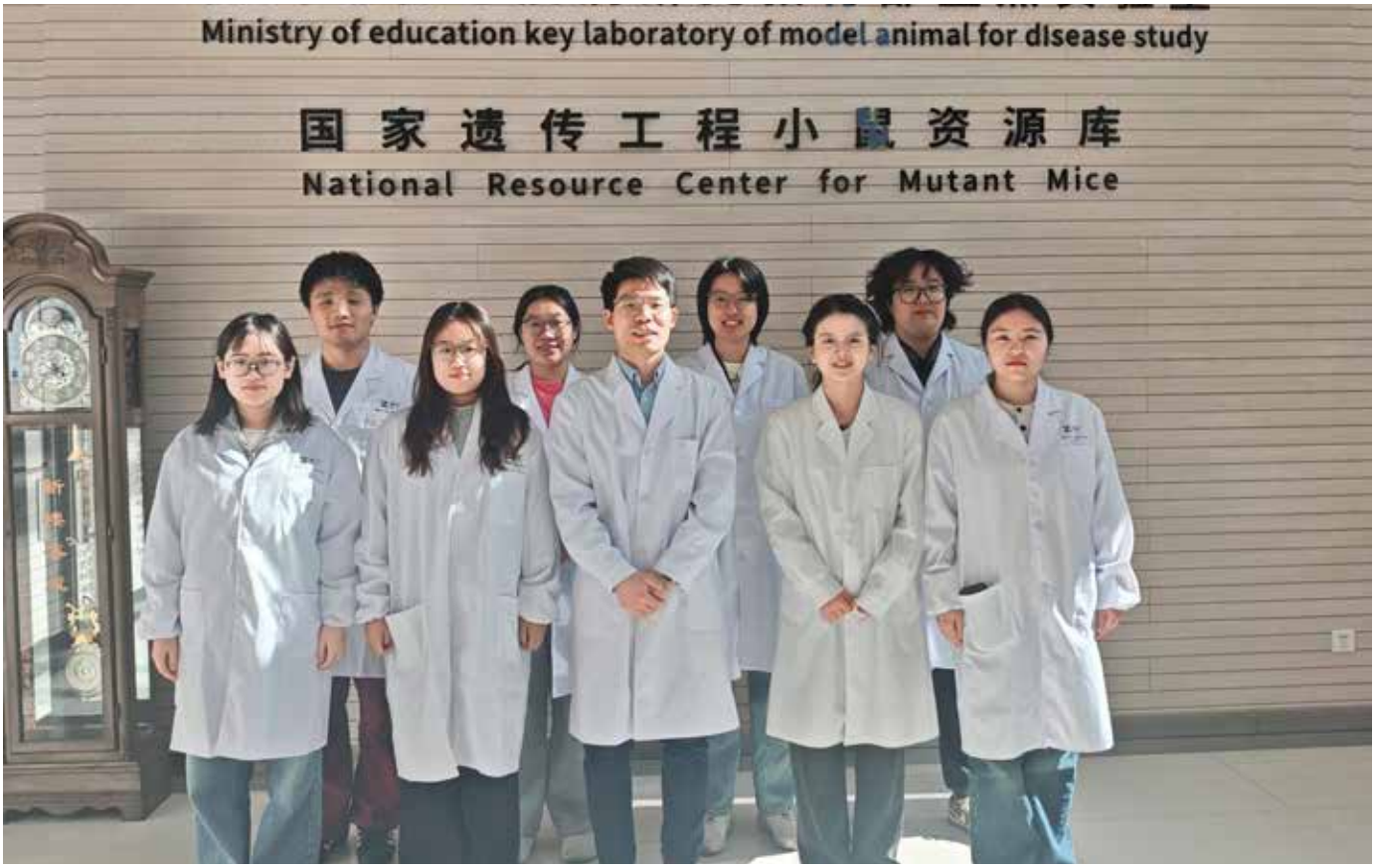
5. Liu Y#, Liu H, Hu Z, Ding Y, Pan XB, Zou J, Xi J, Yu G, Huang H, Luo MT, Guo F, Liu S, Sheng Q, Jia J, Zheng YT, Wang J, Chen X*, Guo J-T*, Wei L*, Lu F*. HBV virions produced under nucleos(t)ide analogue treatment are mainly not infectious due to irreversible DNA chain termination. Hepatology. 2020 Feb; 71(2):463-476.



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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 now is a professor of Pharmaceutics and Biomaterials and a principal investigator at Nanjing University.

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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).

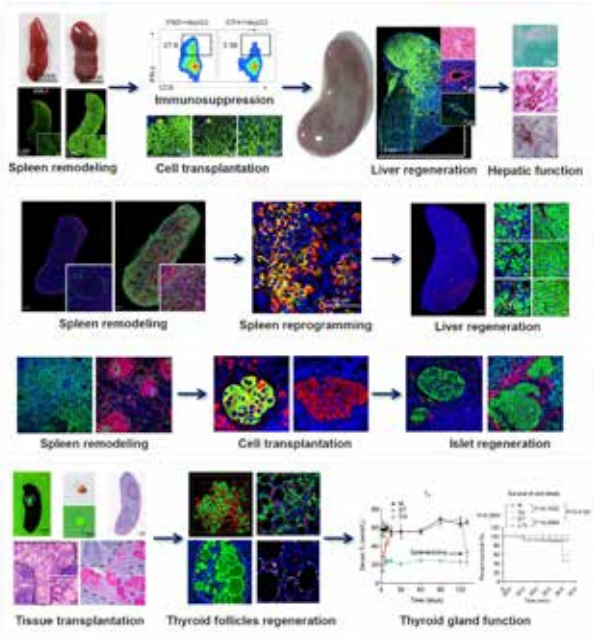

Figure 1. Function reconstruction of complex organs and tissues in the spleen

Building on this foundation, our current work advances the concept of "organ function remodeling" by introducing a nanomaterial-based strategy to reprogram the spleen into a niche highly supportive of islet engraftment and long-term function (Figure 2). Through repeated intrasplenic administration of konjac-glucomannan–modified silica nanoparticles (KSiNPs), we effectively remodeled the native splenic microenvironment, inducing robust extracellular matrix (ECM) deposition and establishing an immunosuppressive milieu. Mechanistically, KSiNPs activated splenic fibroblasts to produce abundant collagens while simultaneously driving macrophage mannose-receptor clustering, promoting M2-type polarization and expanding regulatory T-cell populations. This dual remodeling—structural and immunological—generated an ECM-rich, immune-tolerant niche capable of supporting syngeneic and xenogeneic islets in rodents and even sustaining human islets in nonhuman primates without the need for genetic manipulation or exogenous protein delivery. Notably, transplanted islets within the remodeled spleen achieved rapid revascularization, maintained long-term insulin secretion, and effectively restored normoglycemia in diabetic models, highlighting a translationally promising strategy for metabolic diseases through biomaterial-driven "functional organ remodeling."

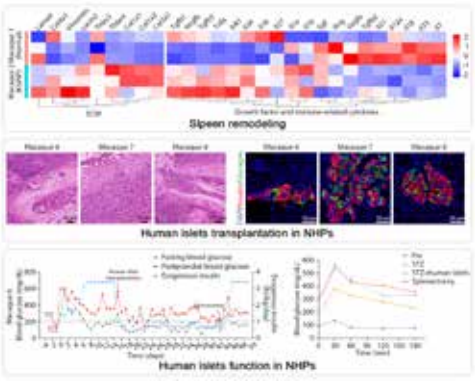

Figure 2. Function of the human islet grafts transplanted into KSiNP-remodeled spleens in NHPs. Repeated ultrasound-guided intrasplenic injections of KSiNPs induced substantial extracellular matrix enrichment and localized immunosuppression, establishing a supportive niche for xenogeneic engraftment. Human islets delivered into this remodeled microenvironment exhibited robust survival, revascularization, and sustained secretion of insulin and C-peptide under reduced immunosuppression. In streptozotocin-induced diabetic NHPs, these islet grafts effectively restored glycemic control, demonstrated physiological glucose responsiveness during tolerance testing, and rapidly reversed to hyperglycemia after splenectomy, confirming spleen-dependent endocrine activity. This figure summarizes the translational feasibility and functional performance of human islets supported by biomaterial-driven splenic remodeling.

Selected publications (*Co-corresponding author)

1. Mi Liu#; Huiming Deng#; Chunyan Liu#; Wang, Lintao#; Liao, Zhongkai; Li, Desheng; Chen, Yan; Li, Jianhui; Dong, Jianhui; Xuyong Sun; Wang; Ling Huang; Lei Dong*; Jian Xiao*; Islet transplantation in immunomodulatory nanoparticle-remodeled spleens, Sci. Transl. Med., 2025, 17(799): eadj9615
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6. Wang Z#, Xie D#, Li J, Zhai Z, Lu Z, Tian X, Niu YM, Zhao Q, Zheng P*, Dong L*, Wang CM*. Molecular force-induced liberation of transforming growth factor-beta remodels the spleen for ectopic liver regeneration. J. Hepatol., 2024, 80(5):753-763.
7. Tian X, Yin Z, Li Z, Wang Z, Xing Z, Liu C, Wang L, Wang C, Zhang J, Dong L. Regeneration of Thyroid Glands in the Spleen Restores Homeostasis in Thyroidectomy Mice. Adv Sci. 2023: e2305913.
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9. Mu R, Zhang Z, Han CW, Niu YM, Xing Z, Liao ZC, Xu JZ, Shao NY, Chen GK, Zhang JF, Dong L*, Wang C*. TAM-educated reparative macrophages promote diabetic wound healing. EMBO Mol Med, 2023, 15 (2), e16671. (Featured: Cover Story)
10. Liu C#, Wang L#, Xu M, Sun Y, Xing Z, Zhang J*, Wang C*, Dong L*. Reprogramming the spleen into a functioning 'liver' in vivo. Gut. 2022; 71(11):2325-2336.
11. Han C, Song J, Hu J, Fu H, Feng Y, Mu R, Xing Z, Wang Z, Wang L, Zhang J*, Wang C*, Dong L*. Smectite promotes probiotic biofilm formation in the gut for cancer immunotherapy. Cell Rep. 2021; 34(6): 108706.
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13. Wang L#, Wang C#, *, Wang Z, Gan J, Liu C, Xia S, Niu Y, Chen D, Zhang J*, Dong L*, Transforming the spleen into a liver-like organ in vivo, Sci. Adv. 2020; 6(24): eaaz9974 .

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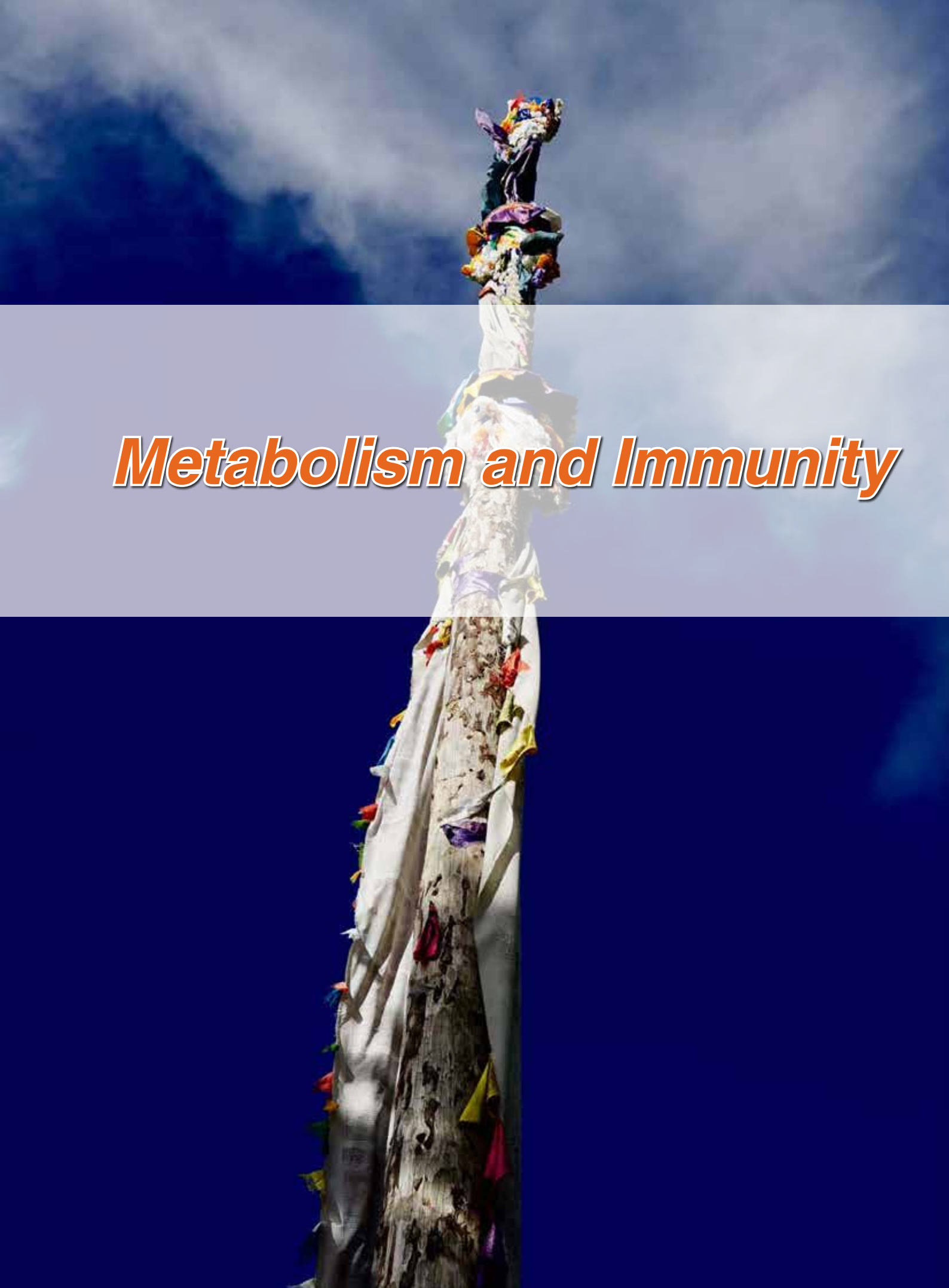
	Yulian Wang	Yali Zhang	Yunfeng Jiang	Lifang Yang	Guangkai An	Wenlu Meng	Xueming Cao	Hao Wei
	Congwei Han	Huijie Fu	Yajie Sun	Zhewei Yang	Zhenjiang Li	Mingzhou Lu	Fashun Wen	
	Yanjun Wang	Xuejiao Tian	Zixuan Kong	Jiayi Yang	Yaxin Tan	Zhixin Wu	Lihui Ma	
	Lin Song	Xiaoyu Yin	Jiayi Li	Xiao Feng	Lin Shi	Yang Wang	Tiandu Bao	



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.

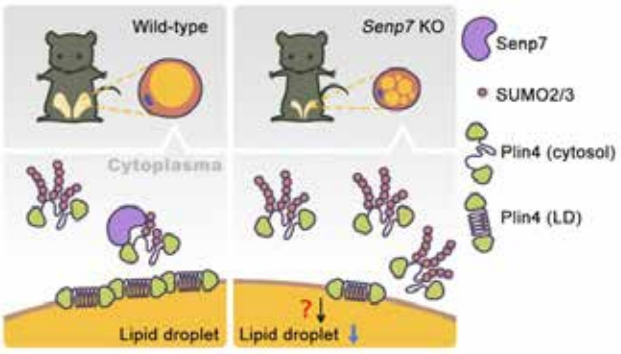

Figure 1. Senp7 deficiency impairs lipid droplets maturation in white adipose tissues via Plin4 deSUMOylation

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.

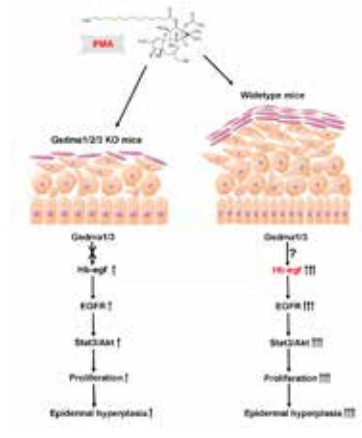

Figure 2. Depletion of Gsdma1/2/3 alleviates PMA-induced epidermal hyperplasia by inhibiting the EGFR-Stat3/Akt pathway

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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).
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4. 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, 2023.
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6. 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.
7. 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.
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Shuai Chen, Ph.D.

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. Moonlighting proteins in regulation of muscle satellite cells in health and disease

Maintenance of skeletal muscle homeostasis and regeneration of injured muscle rely on muscle satellite cells (MuSCs) that are resident muscle stem cells. Dysfunction of MuSCs is linked to diabetic myopathy. The mechanisms vitiating MuSC proliferative activity in diabetes are not well understood. Our recent studies show that AS160, a key cytosolic Rab-GTPase activating protein (RabGAP) in insulin signaling, is a moonlighting protein regulating MuSC proliferation as a transcriptional co-factor. Deletion of AS160, but not its GAP-inactive mutation, impairs MuSC proliferation and consequent muscle regeneration, and exacerbates age-related sarcopenia. Mechanistically, Thr642 phosphorylation of AS160 promotes its translocation into the nucleus where AS160 functions as a co-factor of Signal Transducer and Activator of Transcription 3 (STAT3). AS160 binds to STAT3 to enhance the transcription of myogenic cascades and consequent MuSC proliferation. Disruption of the AS160-STAT3 interaction, or inhibition of AS160-Thr642 phosphorylation, inhibits MuSC proliferation and impairs muscle regeneration. Furthermore, TBC1D1, a RabGAP related to AS160, is required for cytosolic retention of the AS160-STAT3 complex, whose deletion enhances MuSC proliferative activity and improves the repair of muscle damage caused by genetic mutations in muscular dystrophy. Together, these findings reveal a moonlighting function of AS160 as a transcriptional co-factor in the nucleus, and have therapeutic implications for muscle regeneration. (Yang X.Y., …, Wang H.Y.*, Chen S.* Nat Commun 2025a; Yang X.Y., …, Chen S.*, Wang H.Y.* Nat Commun 2025b).

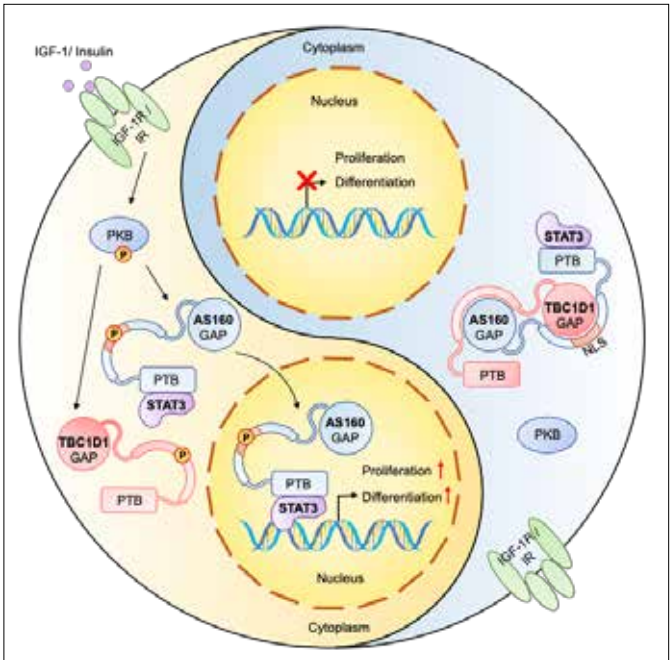

Figure 1 A model for the moonlighting protein AS160 as a transcriptional co-factor regulating MuSCs in skeletal muscle.

Selected Publications(* corresponding author)

1. Yang XY, Cao Y, Zhou YW, Yao Q, Rong P, Wang X, Chen QL, Feng WK, Zhang L, Ai H, Zhu DH, Fang L, Zhao TJ, Ye XH*, Wang HY* and Chen S* (2025a) Nuclear entry of AS160 as a transcriptional regulator of satellite cells for muscle regeneration. Nat Commun 16: 9162 DOI: 10.1038/s41467-025-64220-5.
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7. 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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Chao-Jun Li received his Ph. D in Physiology from Nanjing University in 1994. He did his postdoctoral training at the Hong Kong University of Science and Technology from 1996-1998 and the Medical School of Yale University from 1999-2000. 1994-2008, he was a professor at Nanjing Normal University.2008-2019, he was a professor of Cell Biology and a principal investigator in MARC and the Medical School of Nanjing University, He is now a professor of State Key Laboratory of Reproductive Medicine and Offspring Health of Nanjing Medical University. He was elected as the vice-president of Chinese Society for Cell Biology since 2014.

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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.Adipose GGPPS Stabilizes BCAT2 to Orchestrate BCAA Catabolism and Lipid Mobilization in Fasting-Induced Liver Remodeling (Figure1)

Organisms adapt to fasting by remodeling energy metabolism across tissues, with white adipose tissue (WAT) serving as a key energy reservoir. However, the molecular cues that initiate lipid mobilization during early fasting remain incompletely defined. Here, we identify geranylgeranyl pyrophosphate synthase (GGPPS) as a fasting-responsive regulator that orchestrates lipolysis and branched-chain amino acid (BCAA) metabolism. In mice, 24 hours of fasting marks a metabolic inflection point characterized by hepatic triglyceride accumulation, WAT mass reduction, and a sharp elevation in circulating BCAAs. Proteomic profiling revealed that fasting downregulates GGPPS in both inguinal and epididymal WAT, which in turn destabilizes BCAT2-a key BCAA-catabolizing enzyme-via enhanced K63-linked ubiquitination. Mechanistically, GGPPS scaffolds the deubiquitinase OTUB1 and BCAT2 to stabilize BCAT2 protein level, thereby promoting BCAA catabolism. Elevated BCAAs activate lipolysis in adipocytes and enhance hepatic fatty acid oxidation. Adipose-specific deletion of Ggpps in mice phenocopies fasting responses, including enhanced lipolysis, hepatic lipid accumulation, and systemic BCAA elevation. Conversely, BCAA supplementation promotes adipose lipolysis, protects against diet-induced obesity, and facilitates hepatic oxidative adaptation. Importantly, we found that BCAA supplementation during fasting not only enhanced weight loss efficiency, but also prevented aberrant hepatic lipid accumulation typically induced by prolonged fasting in mice. These findings uncover GGPPS as a central node linking amino acid and lipid metabolism during early fasting and establish a multi-organ metabolic circuit that coordinates the transition from carbohydrate to lipid-based energy utilization.

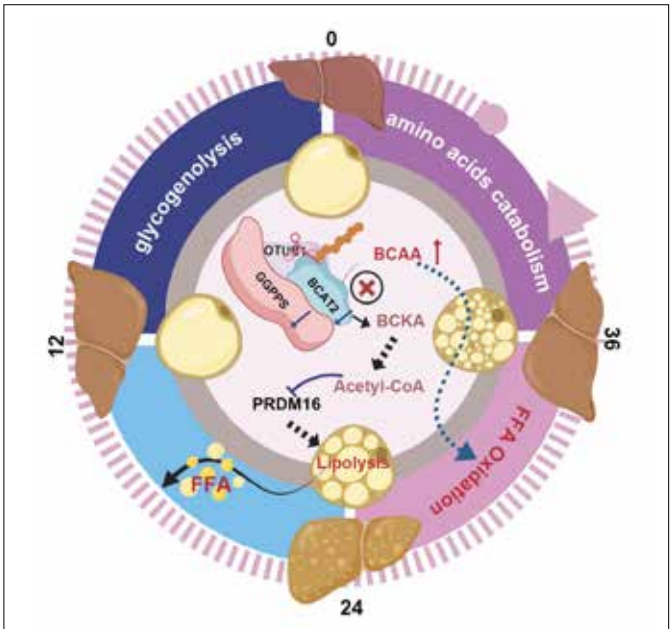

Figure1. Schematic model illustrating how GGPPS downregulation-mediated BCAA accumulation promotes adipose lipolysis and hepatic fatty acid oxidation during fasting.

2. Hepatic Metabolite GGPP Triggers Visceral Adipose Hypertrophy via non-covalent binding with adipocyte ACSL1 in Metabolic Unhealthy Obesity (Figure2)

Obesity can be classified into metabolically healthy obesity (MHO) and metabolically unhealthy obesity (MUO), but the molecular mechanisms remain unclear. We identify geranylgeranyl pyrophosphate (GGPP), a metabolite of the hepatic mevalonate pathway involved in cholesterol biosynthesis, as a critical mediator that distinguishes MUO from MHO. In this study, Long-term feeding of mice with starch oleate significantly upregulated the expression of geranylgeranyl diphosphate synthase (Ggpps), resulting in elevated GGPP levels. Liver-specific deletion of Ggpps reduced GGPP and selectively attenuated adipocyte hypotrophy while specifically enhancing insulin sensitivity in epididymal white adipose tissue (eWAT). Mechanistic studies suggest that GGPP modulates acyl-CoA synthetase long-chain family member 1 (ACSL1) in eWAT through non-covalent binding rather than protein geranylgeranylation, thereby inhibiting its translocation from the endoplasmic reticulum to mitochondria. The retention of ACSL1 in the ER induces eWAT-specific adipose remodeling by promoting triglyceride (TG) synthesis and suppressing lipid oxidation. These findings establish a "liver-adipose" axis mediated by the hepatic metabolite GGPP via its non-covalent interaction with adipocyte ACSL1, highlighting potential therapeutic targets for metabolic dysfunction associated with metabolically unhealthy obesity.

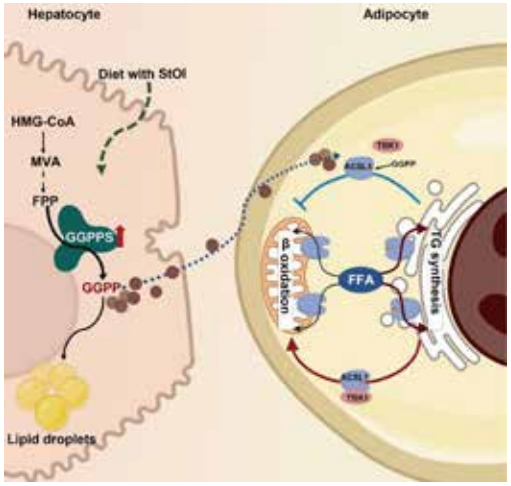

Figure2. Schematic illustration of hepatic GGPP-mediated regulation of adipose metabolism.

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

1. Nie HY, Zhao MF, Wu TY, Zou MJ, Tang YP, Wang XC, Wang NN, Zhou ZY, Bi Y, Zhao Y, Sun XT, Zhang JZ, Fang L, Li CJ. Elevated mevalonolactone from Ruminococcus torques contributes to metabolically unhealthy obesity development. J Biol Chem. 2025 Jun;301(6):110281. doi: 10.1016/j.jbc.2025.110281. Epub 2025 May 22. PMID: 40412522; PMCID: PMC12214271.
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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.

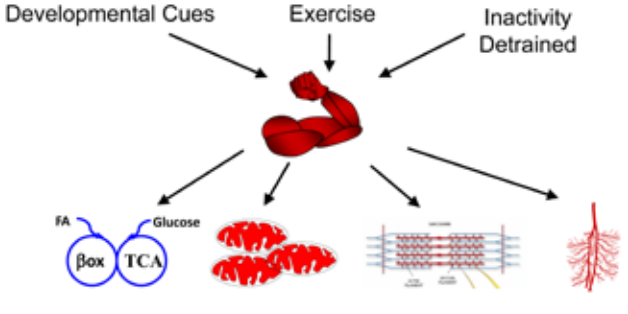

Fig 1. The muscle fitness is determined by developmental as well as physiological inputs. These inputs coordinately control the programs including fuel burning, mitochondrial ATP production, contraction, and angiogenesis.

Enhancer regulator MLL4 controls skeletal muscle metabolic efficiency by limiting AMPK-mediated fuel catabolism.

Skeletal muscle fine-tunes its gene expression patterns and metabolism to adapt to nutrient availability and physiological demands, yet the molecular mechanisms mediating these responses remain poorly understood. Here, we report the enhancer regulator MLL4 as a nutrient-sensitive transcriptional integrator of muscle metabolism. Muscle-specific MLL4 ablation improves systemic glucose homeostasis and confers resistance to diet-induced obesity, despite impairing exercise endurance. Mechanistically, MLL4 cooperates with MEF2 to activate expression of a pair of AMP-metabolizing enzymes NT5C1A and AMPD3, both of which are negative regulators of AMPK. Accordingly, pharmacological inhibition of this pathway with Pentostatin mimics the beneficial metabolic effects, revealing a potential therapeutic strategy for obesity-related disorders (Fig. 2).

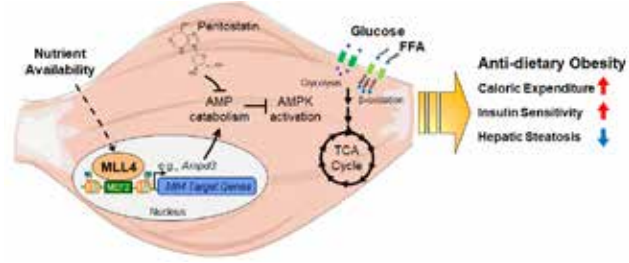

Fig 2. Enhancer regulator MLL4 controls skeletal muscle metabolic efficiency by limiting AMPK-mediated fuel catabolism. MLL4 acts a key regulator of enhancer activation, plays a critical role in directing muscle metabolic transcriptional adaptation that governs metabolic efficiency and systemic metabolism.

Glucose-Responsive PAGR1-Regulated Skeletal Muscle Gene Program Controls Systemic Glucose Homeostasis and Hepatic Metabolism.

Chronic hyperglycemia, a hallmark of type 2 diabetes (T2D), exacerbates insulin resistance and impairs skeletal muscle glucose utilization. However, the underlying molecular mechanisms remain incompletely elucidated. Our study identifies PAGR1 as a glucose-responsive regulator in skeletal muscle, where its expression is upregulated under high glucose conditions. Muscle-specific PAGR1 deletion enhances insulin signaling, promotes GLUT4 translocation, and increases glucose uptake. Mechanistically, PAGR1 transcriptionally activates TBC1D4, a RAB GTPase Activating Protein (RabGAP) that negatively regulates GLUT4 trafficking. Furthermore, muscle-specific PAGR1 knockout protects against diet-induced insulin resistance and hepatic steatosis. These results establish PAGR1 as a key mediator of muscle glucose sensing and a potential therapeutic target for ameliorating glucotoxicity in T2D (Fig. 3).

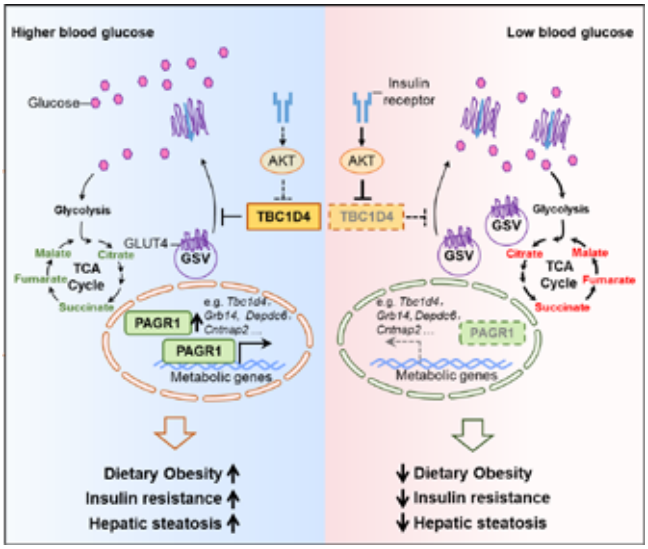

Fig 3. Glucose-Responsive PAGR1-Regulated Skeletal Muscle Gene Program Controls Systemic Glucose Homeostasis and Hepatic Metabolism. PAGR1 is a glucose-sensing transcriptional regulator that limits muscle glucose uptake by activating TBC1D4, identifying it as a potential target to counteract insulin resistance and glucotoxicity in type 2 diabetes.

Selected publications

1. Yang L#, Liu L#, Wang W#, Ding C, Asokan AK, Feng T, Zhou D, Xu Z, Fu T, Guo Q, Zhou Z, Pei S, Shen G, Xiao L, Yin Y, Sun Z, Mao Y, Sun W, Li J, Xue J, Zhu MS, Ge K, Nair KS, Piao HL* and Gan Z*. Enhancer regulator MLL4 controls skeletal muscle metabolic efficiency by limiting AMPK-mediated fuel catabolism. Nat Commun. DOI:10.1038/s41467-025-66684-x
2. Ding C#, Jia Y#, Liu L#, Wang W#, Zhou D, Zhou Z, Yang L, Chen X, Chen D, Mao Y, Xiao L, Liu CZ, Du ZY, Yin Y, Guo Q, Sun Z, Ge K, Fu T*, Piao HL*, Gan Z*. Glucose-Responsive PAGR1-Regulated Skeletal Muscle Gene Program Controls Systemic Glucose Homeostasis and Hepatic Metabolism. Adv Sci (Weinh). 2025;12(39): e02763.
3. 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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Pathogenic Mechanisms and Therapeutic Development for Metabolism-Associated Diseases

Metabolic disorders, encompassing obesity, type 2 diabetes, non-alcoholic fatty liver disease (NAFLD), insulin resistance, sarcopenia and related conditions, represent a global public health crisis with escalating prevalence. Besides the well-recognized clinical features, metabolic disorders are increasingly associated with a spectrum of comorbidities, such as cardiovascular disease, neurodegeneration, and certain cancers. This underscores the urgent need to elucidate their molecular and cellular mechanisms for development of innovative diagnostic, preventive, and therapeutic strategies.

Our research group is dedicated to unraveling the complex mechanisms of metabolic disorders, bridging basic discovery to translational impact. By integrating molecular/cellular biology, genetics, omics technologies, and animal models, we dissect the key molecular circuits, organ crosstalk, and environmental factors that disrupt metabolic homeostasis to identify novel therapeutic targets and biomarkers.

Achievement 1

RalGAP complexes function as a critical regulator of both β cell homeostasis and insulin secretion. High-fat diet increased RalGAP complex and concomitantly decreased GTP-bound active RalA in pancreatic islets. Deletion of RalGAPβ, a common regulatory subunit of RalGAP complexes, destabilised RalGAPα1/α2 and elevated GTPRalA in β cells. RalGAPβ deficiency promoted proliferation of β cells, increased their sizes, and inhibited streptozotocin-induced β cell apoptosis. Moreover, β cell-specific deletion of RalGAPβ enhanced KCl-stimulated insulin secretion in isolated islets as well as GSIS in vivo. Consequently, RalGAPβ deletion in β cells improved glucose tolerance in mice fed a chow or high-fat diet. At the molecular level, RalGAPβ deletion may reset the glucostat consisting of GLUT1 and GLUT2 to modulate glycemic set point. Furthermore, RalGAPβ deficiency elevated p70 S6-kinase in islets, whose inhibition abrogated RalGAPβ deficiency-induced β cell proliferation. Our results have implications for the discovery of drugs targeting RalGAP complexes to protect β cells in type 2 diabetes. (Feng WK et al, 2025 Nat Commun)

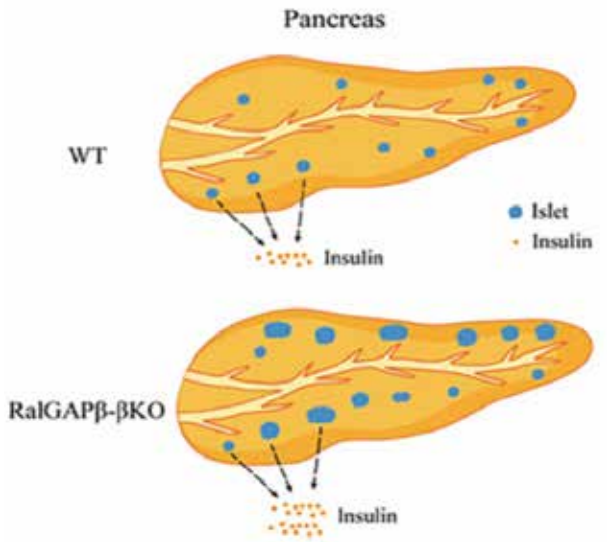

Figure 1, RalGAP complexes function as a critical regulator of both β cell homeostasis and insulin secretion

Achievement 2

Obesity is a major pathological factor that induces insulin resistance and consequent type 2 diabetes through multiple mechanisms. Inactivation of the insulin receptor (INSR) contributes to the development of insulin resistance, whose protein level is down-regulated in obesity through as yet-undefined mechanisms. Here we show that the E3-ligase TRAF6 is a critical regulator of INSR maturation, whose inactivation prevents palmitic acid- or high-fat diet-induced diminution of the INSR. Consequently, genetic inactivation of TRAF6 enhances insulin signaling that further increases muscle glucose uptake and inhibits hepatic gluconeogenesis. TRAF6 inactivation increases the proprotein convertase FURIN that controls the processing of pro-INSR to mature INSR. Mechanistically, TRAF6 associates with the Golgi apparatus, where it ubiquitinates the cytosolic tail of FURIN, leading to its lysosomal degradation. This TRAF6-FURIN axis also regulates cholesterol metabolism via PCSK9 processing in the circulation. Collectively, our results reveal a critical role of TRAF6 in regulating proprotein processing and have therapeutic implications for metabolic control

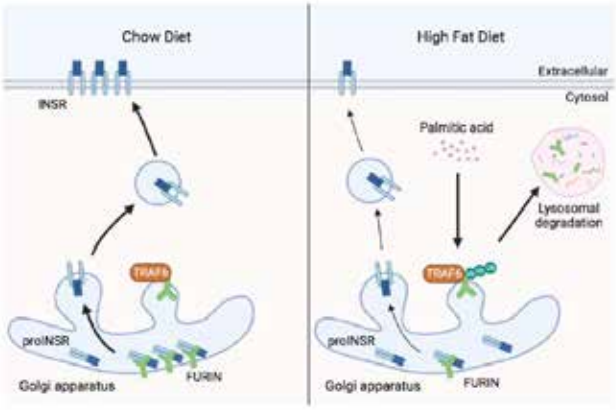

Figure 2, a model of the TRAF6-furin axis in regulation of INSR maturation.

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1. Xinyu Yang, Ye Cao, Yinqiu Mu, Yuwei Zhou, Li Zhang, Heng Ai, Dahai Zhu, Shuai Chen and Hong-Yu Wang. TBC1D1 functions as a negative regulator of satellite cells for muscle regeneration. Nature Communications, 2025, 16: 10091
2. Xinyu Yang, Ye Cao, Yuwei Zhou, Qing Yao, Ping Rong, Xu Wang, Qiaoli Chen, Weikuan Feng, Li Zhang, Heng Ai, Dahai Zhu, Lei Fang, Tong-Jin Zhao, Xinhua Ye, Hong-Yu Wang and Shuai Chen. Nuclear entry of AS160 as a transcriptional regulator of satellite cells for muscle regeneration. Nature Communications, 2025, 16: 9162
3. Minjun Liu, Kun Zhou, Yang Sheng, Wen Zhang, Qiaoli Chen, Ziyue Chen, Xinyu Yang, Yuxin Jin, Fangtong Liu, Shu Su, Weikuan Feng, Ping Rong, Jun Wang, Philip Cohen, Hui Liang, Tong-Jin Zhao, Shuai Chen and Hong-Yu Wang. Golgi-associated TRAF6 as a regulator of protein convertase FURIN for insulin receptor precursor processing. Science China Life Sciences, 2025, doi: 10.1007/s11427-025-2957-9
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5. Ping Rong, Yinqiu Mu, Meiqin Wang, Liang Chen, Fangtong Liu, Yuxin Jin, Weikuan Feng, Kun Zhou, Hui Liang, Hong-Yu Wang, Shuai Chen. Targeting IGF1 to alleviate obesity through regulating energy expenditure and fat deposition. Science China Life Sciences, 2025, doi: 10.1007/s11427-024-2768-y
6. Qi Wang, Ping Rong, Wen Zhang, Xinyu Yang, Liang Chen, Ye Cao, Minjun Liu, Weikuan Feng, Qian Ouyang, Qiaoli Chen, Hailong Li, Hui Liang, Fanguo Meng, Hong-Yu Wang, Shuai Chen. TBC1D1 is an energy-responsive polarization regulator of macrophages via governing ROS production in obesity. Science China Life Sciences, 2024, 67: 1899–1914
7. Shu Su, Chao Quan, Qiaol 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
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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

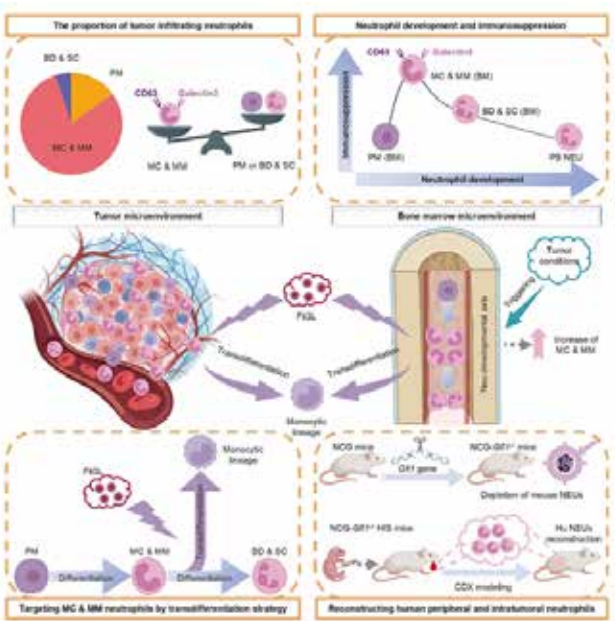
Not only the immune system, but also the study of multiple organs and tissues is limited by traditional mouse models, such as the inability of multiple human viruses or bacteria to infect mouse stromal cells, or even if they can infect, they show pathological features that are inconsistent with the clinic. 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:

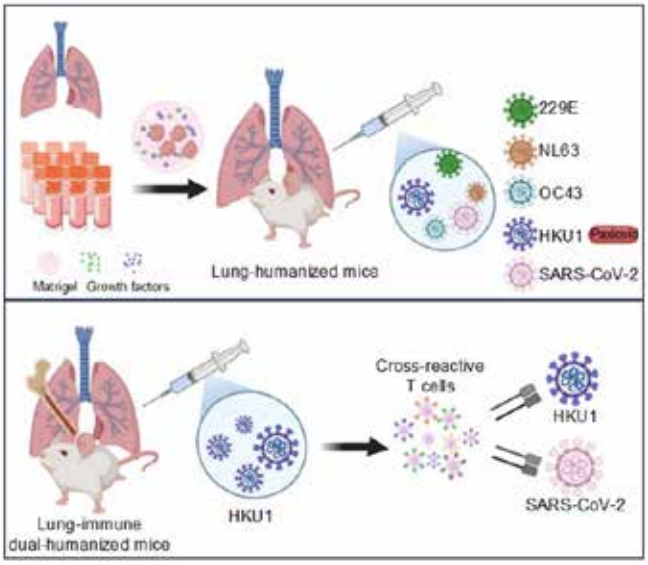
1. Based on immune system humanized mice, we transplanted human liver cells into mice with liver injury to construct immune system/liver double derived mouse model, which can be used as a research platform for pathological research, vaccine and new drug development of liver diseases (such as viral hepatitis).

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.

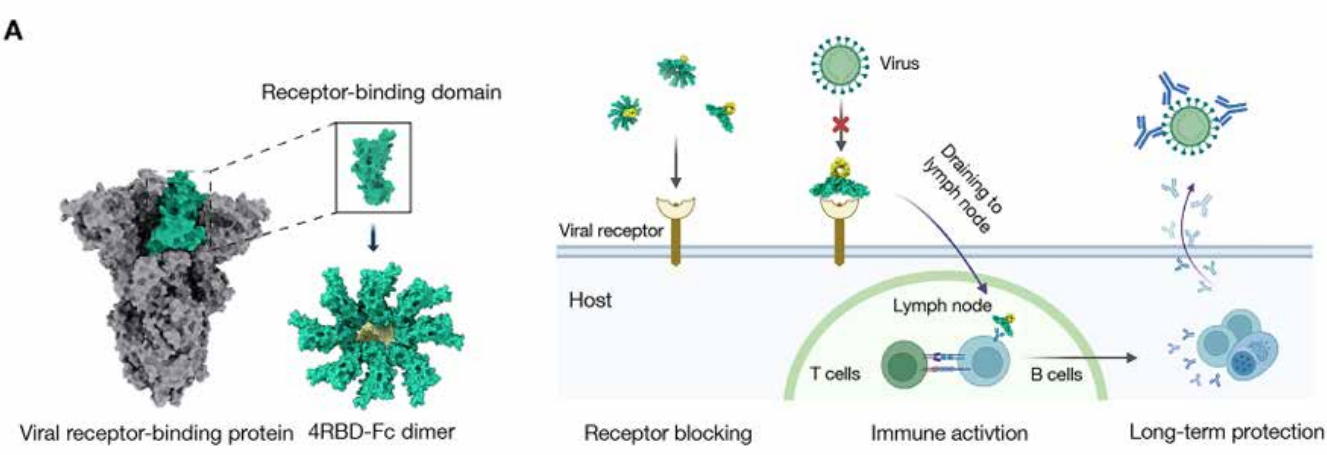
3. To explore the regulation of human immune cell development and function by eliminating and disturbing intestinal bacteria of humanized mice or transplanting human flora.



Human myelocyte and metamyelocyte-stage neutrophils suppress tumor immunity and promote cancer progression



A Lung-Immune Dual-Humanized Mouse Using Cryopreserved Tissue Enables Infection and Immune Profiling of Human Common Cold Coronaviruses



Single-dose infusion of engineered viral receptor binding domain confers rapid and durable protection against viral infection

Selected Publications

1. Zibin Wang#, Ting Zhou#, Hanbing Wang#, He Li, Wene Zhao, Feng Wang, Yan Li, Wen Liu*, Jia Wei*, Xianchi Dong*. (2025) LAG3-MHCII interaction induces a tight cell-cell interface at the immunological synapse. The Journal of Immunology. DOI:10.1093/jimmun/vkaf120
2. Xia Yang#, Yun-Zhong Nie# *, Chun Lu, Yang Li, Yoshihito Hayashi, Riana Plummer, Na Luo, Qinglin Li, Toshiharu Kasai, Takashi Okumura, Yumiko Isobe, Kiyoshi Yamaguchi, Yoichi Furukawa, Yan Li, Hideki Taniguchi*. (2025) Human pluripotent stem cell-derived fetal hepatic stellate cells promote vascularization and maturation in liver organoids. Developmental Cell. DOI: 10.1016/j.devcel.2025.09.002.
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5. Haiqiao Sun#, Bei Tong#, Deshan Ren#, Ao Hu#, He Li, Yixin Zhang, Shuang Liu, Xiang Duan, Zijian Zhang, Wei Liu, Haokun Yang, Jian Chen, Tunyu Jian, Huanying Zheng, Bixia Ke, Hanri Zeng, Changwen Ke, Xiaofang Peng, Yongzhen Liu, Kai Deng*, Xianchi Dong*, Yan Li*. (2025) Single-dose infusion of engineered viral receptor binding domain confers rapid and durable protection against viral infection. Communications Biology. DOI: 10.1038/s42003-025-08704-6
6. Tao Shi#, Wei Liu#, Yuting Luo, Kaijie Liang, Shiji Ren, Xueru Song, Fangcen Liu, Chun Lu, Daniel Hirschhorn, Hanbing Wang, Yipeng Zhang, Yiran Cai, Yue Wang, Yunfeng Pan, Wenqi Liu, Yang Nie, Ziliang Zhang, Lixia Yu, Shuai Ding, Baorui Liu, Taha Merghoub*, Yan Li*, Jia Wei*. (2025) CHI3L3+ immature neutrophils inhibit anti-tumor immunity and impede immune checkpoint blockade therapy in bone metastases. Cancer Cell. DOI:10.1016/j.ccell.2025.07.007
7. Wei Liu#, Tao Shi#, Chun Lu , Keying Che , Zijian Zhang , Yuting Luo , Daniel Hirschhorn,, Hanbing Wang , Shaorui Liu , Yan Wang , Shuang Liu , Haiqiao Sun, Jun Lu , Yuan Liu , Dongquan Shi , Shuai Ding , Heping Xu , Liaoxun Lu , Jianming Xu , Jun Xin , Yinming Liang ,Taha Merghoub*, Jia Wei*, Yan Li*. (2025) Human myelocyte and metamyelocyte-stage neutrophils suppress tumor immunity and promote cancer progression. Cell Research. DOI:10.1038/s41422-025-01145-0
8. Shuang Liu#, Linxing Wei#, Qian Yu#, Zhiwei Guo#, Changyouo Zhan, Leilei Chen*, Yan Li*, Dan Ye*. (2025) Targeting IRG1 in tumor-associated macrophages for cancer therapy. Protein & Cell. DOI:10.1093/procel/pwaf012
9. Jiancheng Gao# , Danling Gu# , Kailin Yang# , Junxia Zhang# , Qiankun Lin# , Wei Yuan# , Xu Zhu# , Deobrat Dixit , Ryan C Gimple , Hao You , Qian Zhang , Zhumei Shi , Xiao Fan , Qiulian Wu , Chenfei Lu , Zhangchun Cheng , Daqi Li , Linjie Zhao , Bin Xue , Zhu Zhu , Zhe Zhu , Hui Yang , Ningwei Zhao , Wei Gao , Yingmei Lu , Junfei Shao , Chuandong Cheng , Dapeng Hao , Shuo Yang , Yun Chen , Xiaoming Wang , Chunsheng Kang , Jing Ji , Jianghong Man , Sameer Agnihotri , Qianghu Wang , Fan Lin , Xu Qian , Stephen C Mack , Zhibin Hu , Chaojun Li , Michael D Taylor , Yan Li* , Nu Zhang* , Jeremy N Rich* , Yongping You* , Xiuxing Wang*.（2025)Infiltrating plasma cells maintain glioblastoma stem cells through IgG-Tumor binding. Cancer cell. DOI: 10.1016/j.ccell.2024.12.006

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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).

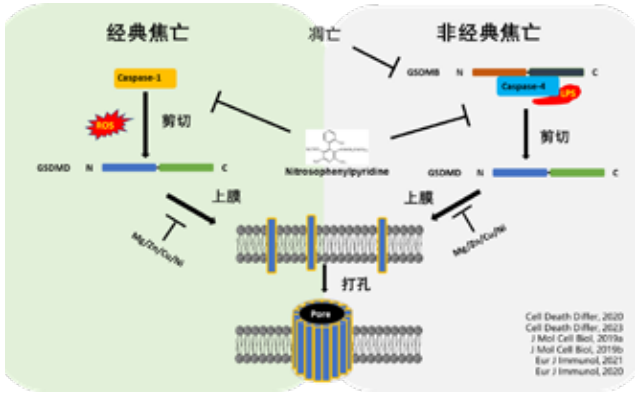

Figure 1. Gsdmd could be the target to block pyroptosis in autoimmune diseases

Figure 2. The role of immune cells in obesogenic memory

Selected Publications

1. Lin, Z*. and H.B. Ruan*, Cutting the Gordian knot: Untangling gasdermin C from pyroptosis. Immunity, 2025. 58(10): p. 2359-2361.
2. Fan, C., X. Huang, J. Mei, X. Shi, H. Zhang, C. Liang, S. Cui, Y. Xing, B. Cao, W. Liu, H. Liu, B. Liu, W. Chang, M. Shao, G.H. Wei, Y.J. Liu, Z.J. Chen, Z. Lin*, T. Xu*, and Y. Jiu*, Macrophages form dendrite-like pseudopods to enhance bacterial ingestion. EMBO J, 2025. 44(17): p. 4772-4802.
3. Zhang, Z., L. Li, Y. Ge, A. Chen, S. Diao, Y. Yang, Q. Chen, Y. Zhou, J. Shao, F. Meng, L. Yu, M. Tian, X. Qian, Z. Lin, C. Xie, B. Liu*, and R. Li*, Verteporfin-Mediated In Situ Nanovaccine Based on Local Conventional-Dose Hypofractionated Radiotherapy Enhances Antitumor and Immunomodulatory Effect. Adv Sci (Weinh), 2025. 12(20): p. e2413387.
4. 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.
5. 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).
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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. Feng, Weikuan#, Sangsang Zhu#, Lingchen Kong, Wen Zhang, Fangtong Liu, Yuxin Jin, Ting Yu, Xiaowei Chen, Zhuo-Xian Meng, Qiaoli Chen*, Shuai Chen*, and Hong-Yu Wang*. 2025. "Deletion of RalGAP β Protects Pancreatic β Cells and Improves Glycemic Control." Diabetes Obes Metab. 2025;1–21.
2. 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
3. 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
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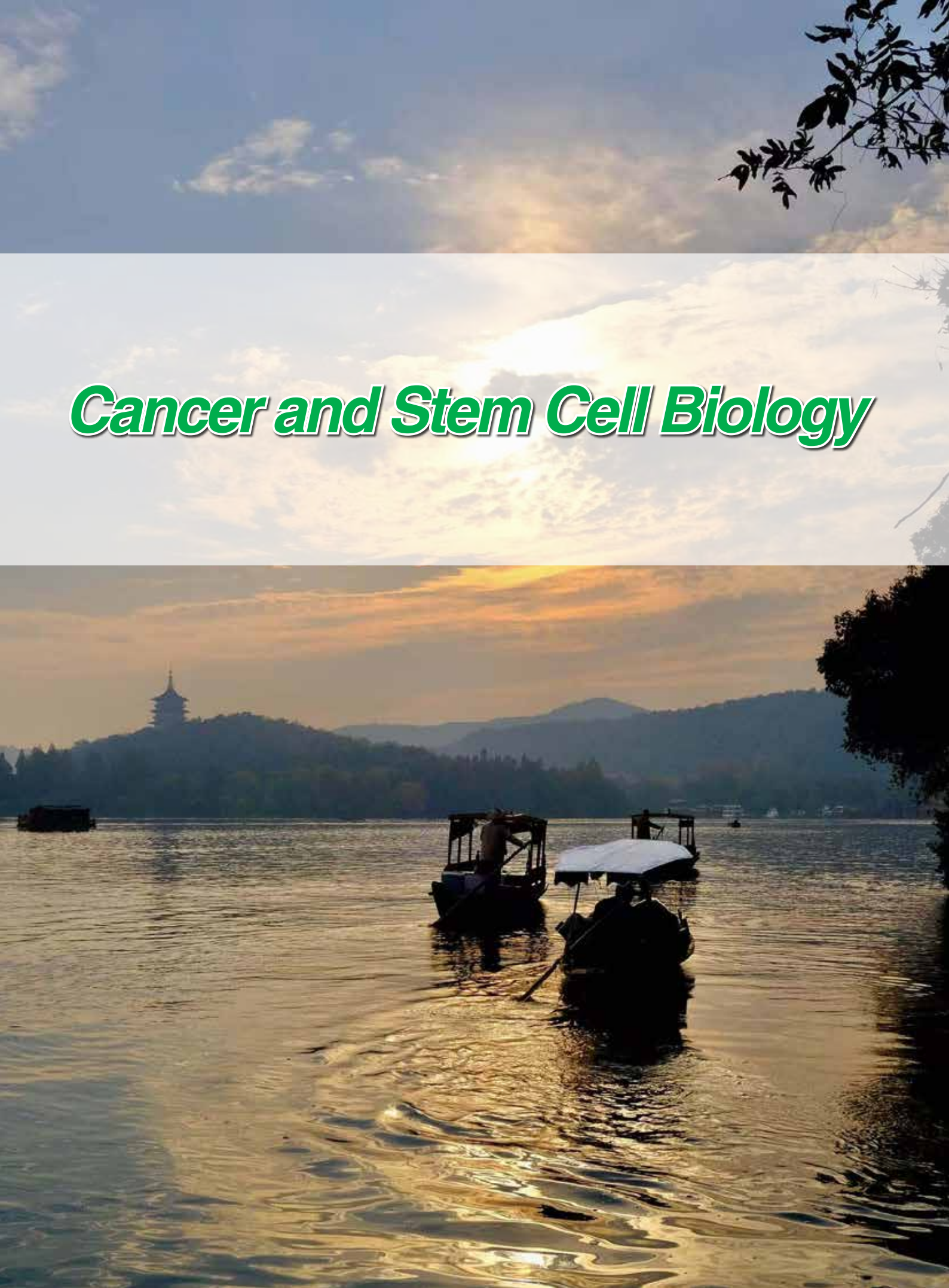

Cancer and Stem Cell Biology

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 Zhang et al., 2023). 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.

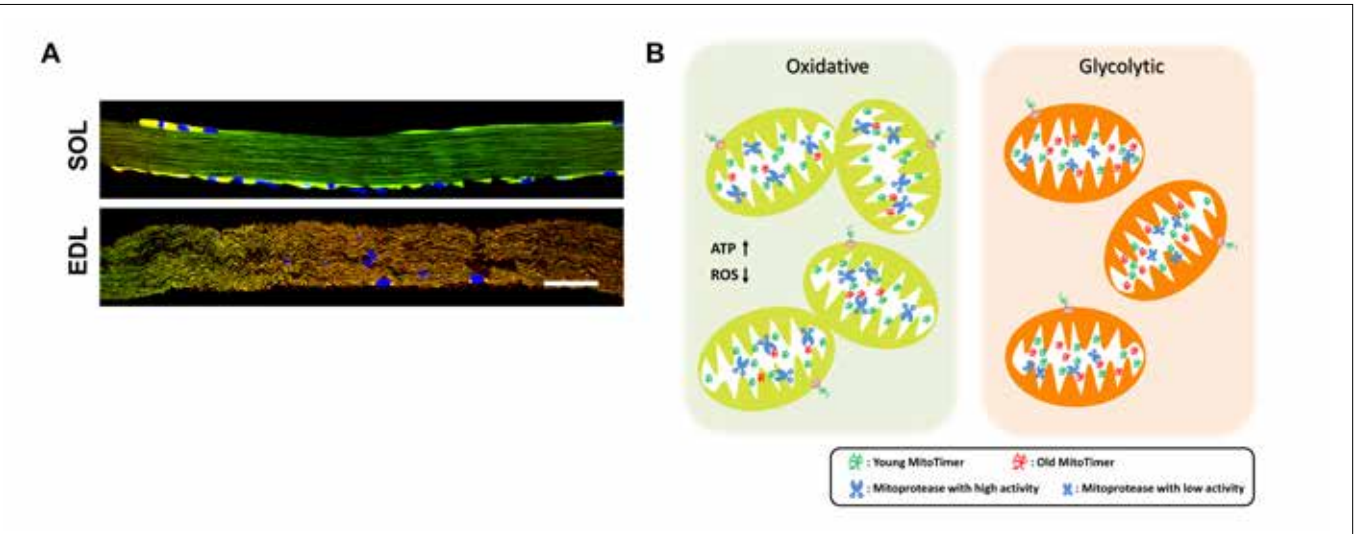

Figure 1. MitoTimer fluorescence reveals an active mitochondrial state tightly coupled with mitoproteolysis in the mouse oxidative skeletal muscle fibers

(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.

Recent publications

1. Zhang YN, Zheng FF, Wang F, Liu XQ, Xiang C, Fu SY, Shen K, Liu G*.The Expression of Two Distinct Sets of Glycolytic Enzymes Reveals Differential Effects of Glycolytic Reprogramming on Pancreatic Ductal Tumorigenesis in Mice. Biomedicines 2023, 11(11): 2962.
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9. Zhang Q, He X, Chen L, Zhang C, Gao X, Yang Z, Liu G*. Synergistic regulation of p53 by Mdm2 and Mdm4 is critical in cardiac endocardial cushion morphogenesis during heart development. J Pathol. 2012, 228(3):416-28.

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Genetic rewiring with precise genome editors

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. 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 DSB repair-regulatory protein module, the uPEn showed marked improvements in "copying" accuracies (Fig. 1B, 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. 1C). 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. The tool is suitable for application in animal zygotes to install previously-difficult genetic modifications (Fig. 1D, E, Mao W, Wang P et al., 2025). Indeed, in Hu sheep zygotes, uPEn results in efficient, multiplexed knock-in/knockout edits at two loci (Fig. 1F). We envision that these new tools have laid a solid foundation for future applications to rewire genetic circuits in cells/organisms (Fig. 1G).

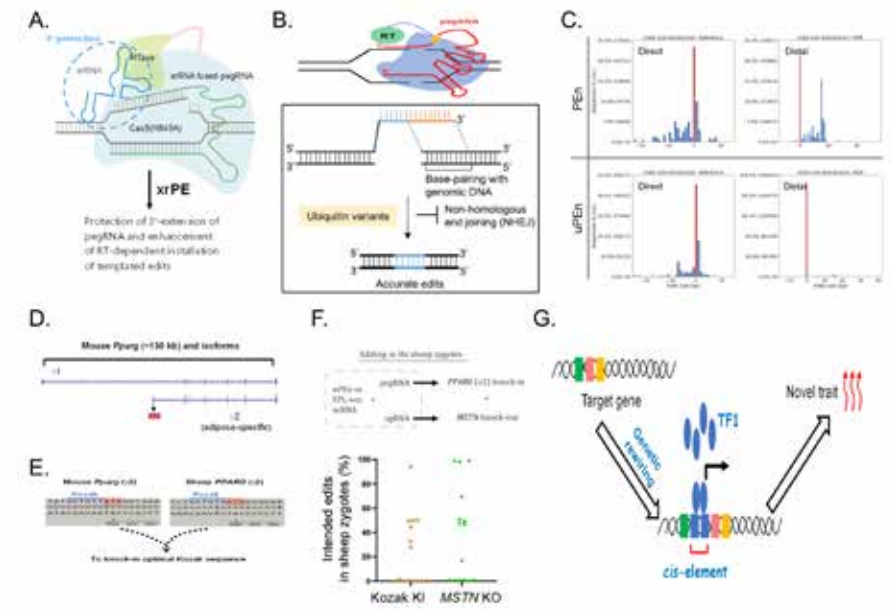

Figure 1: Writing-enabled genome editing tools.

(A) The xrPE platform is further applied to precisely install primary and reverse mutations in cells. (B, C) 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. (D-F) The uPEn tool is suitable for installing regulatory element in animal zygotes. For instance, in Hu sheep zygotes, uPEn results in efficient, multiplexed knock-in/knockout edits at two loci. (G) These advanced "writing-enabled" genome editing tools provide exciting opportunities to purposeful modifications of genetic circuits in cells and organisms.

2. Improvement of PE nuclease:

The standard uPEn introduces edits only downstream of the nuclease-induced DNA break. To expand the editable space of uPEn, we seek innovative designs to enable upstream-directed editing by re-configuring guide/template RNAs to drive prime edits into the target strand (TS), instead of the conventional non-TS (Fig. 2A, Chen P et al., 2025). We first devise a dual-RNA uPEn strategy by supplementing a cleavage-competent sgRNA with an accessory template RNA for modifying target strand (ActRNA:t). Remarkably, the design not only allows TS extension-mediated editing, but also enables installation of edits at some previously refractory sites (Fig. 2B). Characterization of the dual-RNA system inspires us to next develop a bifunctional target strand-programming pegRNA (Fig. 2C, tsp-pegRNA). Indeed, the single-RNA upstream-modifying uPEn form (versions 3.2) also achieves commendable prime editing efficiencies (Fig. 2D). Moreover, we provide insights on the role of uPEn's helper module (i.e., i53) in driving TS prime edits (Fig. 2E). Together, these advances transform uPEn into a highly applicable tool with much-expanded editable space, and lay strong foundation for future development of PEn/PE platforms.

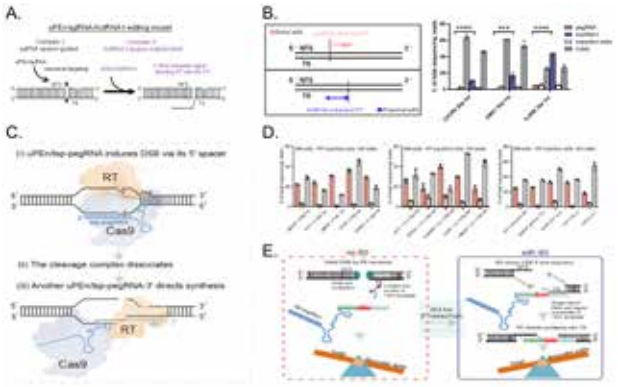

Figure 2: Improvement of PE nuclease.

(A) To seek an approach to expand the editable space of uPEn, we configured a dual-RNA strategy to first program a targeted DSB and to subsequently drive reverse transcription of edits into the target strand (TS), instead of the conventional non-TS. (B) This design enabled installation of small-sized edits into previously refractory locations. (C, D) Further characterization of the dual-RNA system inspires us to develop a bifunctional single-RNA (tsp-pegRNA) that programs efficient uPEn editing of TS. (E) We also provide insights on the role of DSB repair-regulatory module i53 in promoting TS editing by uPEn.

Selected publications: (*corresponding author)

1. Chen P†, Li X†, Zhou Q, Chen J, Lu L, Wang P, Zhang G, Sun D, Huang X*, Liu J*, Wang X*. Configuration of adaptable template RNA architectures to unfold the editable space of a nuclease prime editor. Nucleic Acids Res 2025, Jun 11;53(11):gkaf522.
2. Mao W†, Wang P†, Zhou L, Li D, Li X, Lou X, Huang X, Wang F, Zhang Y*, Liu J* and Wan Y*. An upgraded nuclease prime editor platform enables high-efficiency singled or multiplexed knock-in/knockout of genes in mouse and sheep zygotes. Protein Cell 2025, pwaf006.
3. Song Z†, Guo J†, Fan Z†, Huang S†, Li G, Zhao Z, Chen B, Huang S, Zheng W, Wei Y, Chen Y, Huang X, Liu J*, Wu L*, Wang X*. Noncanonical target-strand cytosine base editing via engineered Un1Cas12f1 platform. Nat Commun 2025, Oct 28;16(1):9499.
4. 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.
5. 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.
6. 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.
7. 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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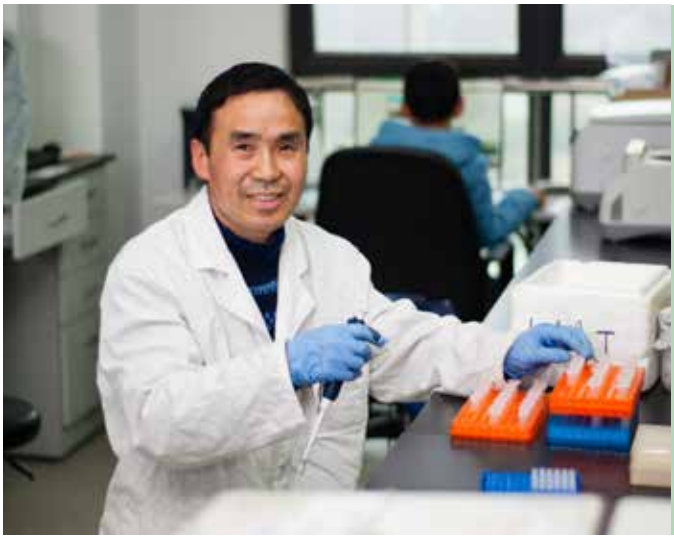
Dr. Gui-quan Zhang (PI, Nanjing Medical University)
Ms. Yu-yan Zhang (in Biotech industry)



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.

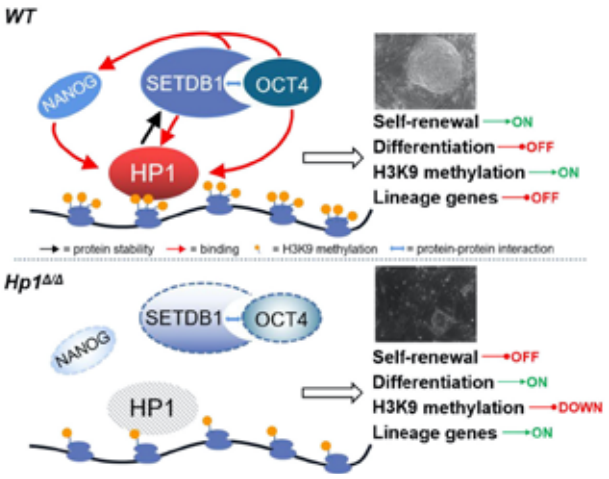

Figure 1. Schematic representing of the role of HP1 family in the maintenance of ESC pluripotency. HP1 and SETDB1 is integrated with the major pluripotent transcription factors OCT4 and NANOG to safeguard ESC identity.

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.

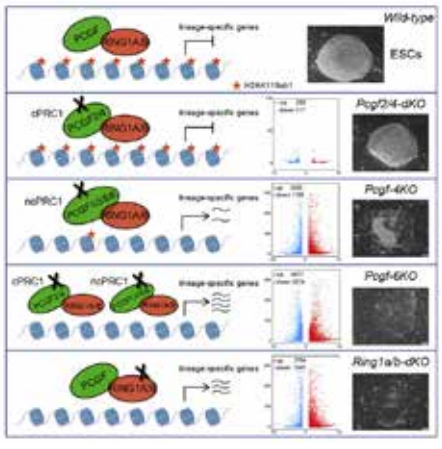

Figure 2. Canonical PRC1 and non-canonical PRC1 act redundantly to suppress lineage-specific genes and preserve ESC identity.

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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Metabolic programming of macrophages and cell therapy techniques

1. In Situ CAR-M Programming via ZIF-8@Au Nanocarriers for Prostate Cancer Immunotherapy

In this study, we develop a novel in vivo immune cell editing technique based on Zeolitic Imidazolate Framework-8 (ZIF-8), which enables efficient CAR genes encapsulation and targeted delivery to macrophages within solid tumor microenvironment. This technique offers three key advantages: ① reduced non-specific hepatic accumulation; ② pH sensitivity that permits the precise release of CAR plasmid at the tumor site; ③ mannose modification that confers specific binding with macrophages. By using this technique, we deliver a plasmid encoding IFNγ armored CAR gene to tumor-resident macrophage, and successfully reprogram them into CAR-M. The in situ reprogrammed CAR-M possesses the capability of sustain the robust M1 polarization and powerfully kill the tumor cells. In the prostate tumor model, the in situ edited CAR-M achieves 95.54% tumor growth suppression and prolongs the mouse survival significantly. Based on these discoveries, we have established a novel immunotherapy strategy for prostate cancer.

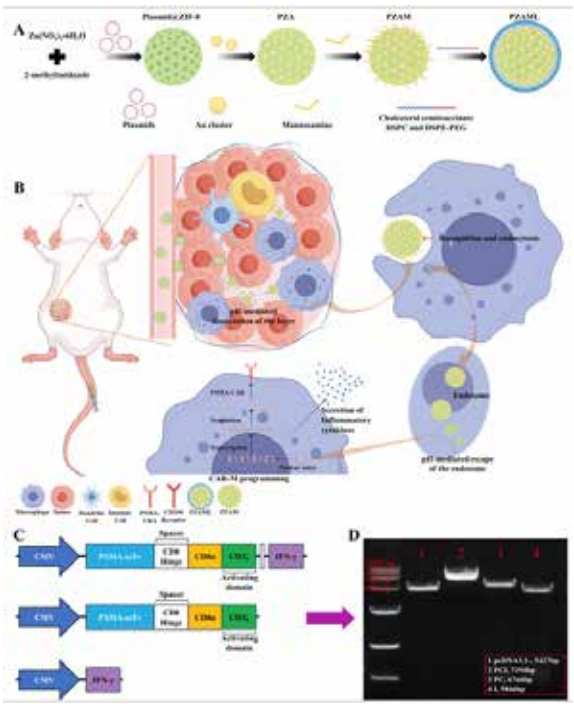

Fig1. The schematic representation clarifies the process of constructing CAR-M in vivo by employing PZAML nanocarriers.

2. Identification and Functional Characterization of a Pro-inflammatory IL-21RhiLDhi Macrophage Subset in Autoimmune Hepatitis

We identified a unique macrophage subset, marked by high IL-21 receptor levels and lipid droplet content (termed as IL-21RhiLDhi). The infiltration and accumulation of this cell subset are highly correlated with AIH development. The functional study of IL-21RhiLDhi macrophage reveals that this subset secretes abundant pro-inflammatory mediators, which stimulates Th1 cells and suppresses Tregs in the liver, triggering hepatocyte death and accelerating the pathological progression of AIH. Mechanistically, this certain macrophage subset responds to IL-21 level, activating IL-21R signaling and reprogramming fatty acid oxidation to enhance pro-inflammatory factor expression and release. Targeting IL-21RhiLDhi macrophage activation with an IL-21R-neutralizing antibody markedly reduced disease severity in an AIH mouse model. Our results uncover the pivotal contribution of IL-21RhiLDhi macrophage to AIH pathogenesis and position the IL-21/IL-21R axis as a promising therapeutic target.

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 PPARγ T166 dephosphorylation, sustains reparative function of macrophages during tissue repair. Nat. Commun. 2024; 15:7269.
2. Bei YC, Wang SJ, Wang R, Owais Ahmad, Jia M, Yao PJ, Ji JG*, Shen PP*. CDK5-triggered G6PD phosphorylation at threonine 91 facilitating redox homeostasis reveals a vulnerability in breast cancer. Acta Pharm. Sin. B. 2025, 15(3):1608-1625.
3. Bei YC, He J, Dong XH, Wang YX, Wang SJ, Guo W, Cai HJ, Xu ZY, Wei J, Liu BR, Zhang N, Shen PP*. Targeting CD44 variant 5 with an antibody-drug conjugate is an effective therapeutic strategy for intrahepatic cholangiocarcinoma. Cancer Res. 2023; 83(14):2405-2420.
4. 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 PPARγ T166 phosphorylation enhances the inducibility of beige adipocytes and improves metabolic dysfunctions. Cell Death Differ. 2023; 30:766-778.
5. 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.
6. Shu YX, Yang NF, Cheng N, Zou ZY, Zhang WL, Bei YC, Shi Q, Qin MH, Zhu WG*, Shen PP*. Intervening pyruvate carboxylase stunts tumor growth by strengthening anti-tumor actions of tumor-associated macrophages. Signal Transduct Target Ther. 2022; 7:34.
7. Xie YY, Li Y, Xu CW, Zhang WT, Jiang Y, Wang LD, Tang YJ, Sun Q, Yang H, Mai XL, Shen PP*, Wang B*. A cell-free TLR5high MSC membrane nanoparticle therapy for Crohn's disease: Targeted immunomodulation via the flagellin/TLR5 axis. J. Control. Release. 386 (2025): 114121.
8. Yang NF, Tian Q, Lei ZL, Wang SX, Cheng N, Wang Z, Jiang XQ, Zheng XQ, Xu WJ, Ye MY, Zhao LW, Wen MY, Niu JL, Sun WJ, Shen PP*, Huang ZF*, Li XK*. FGF2 Mediated USP42-PPAR Axis Activation Ameliorates Liver Oxidative Damage and Promotes Regeneration. Adv. Sci. 2025, 2408724.

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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

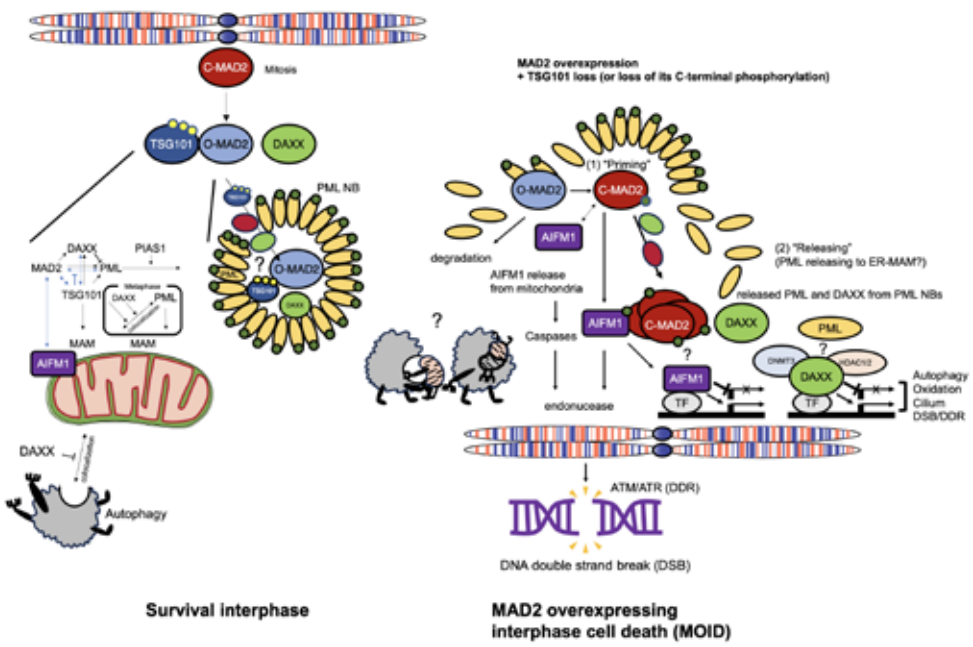


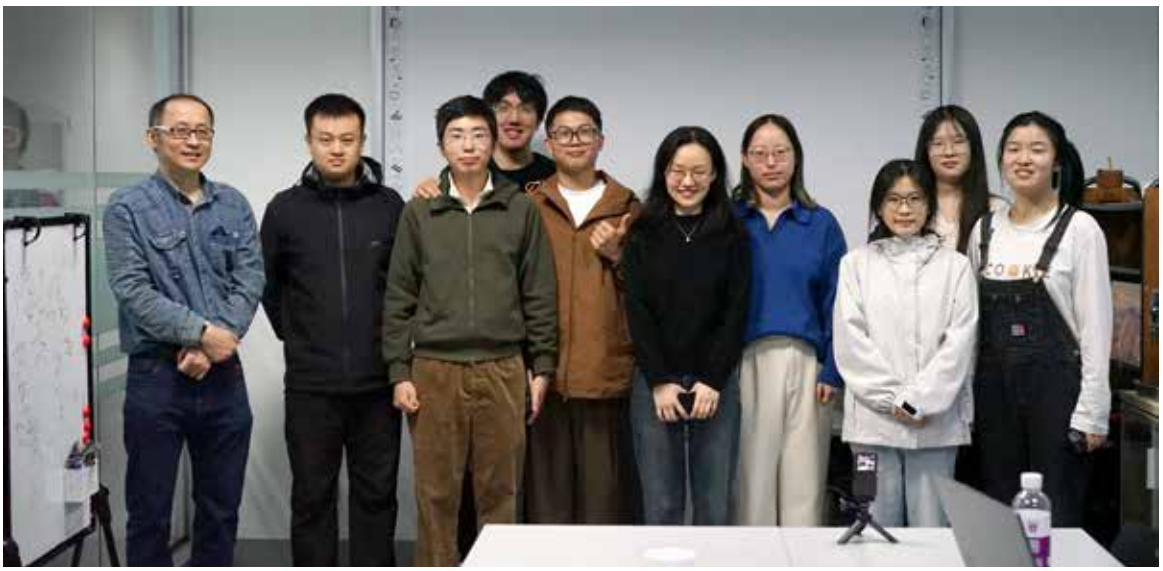
Figure 1. A hypothetical model depicting that PML-MAD2 interaction at PML NBs and formation of PML NBs regulates MOID.

(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.

Recent 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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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.

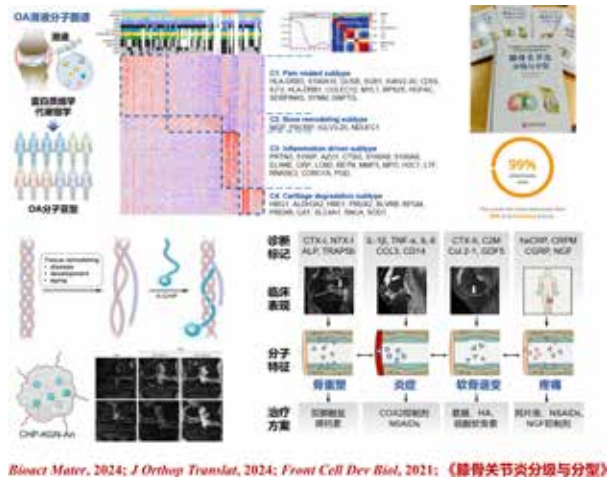

Figure 1. Molecular classification of knee osteoarthritis

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.

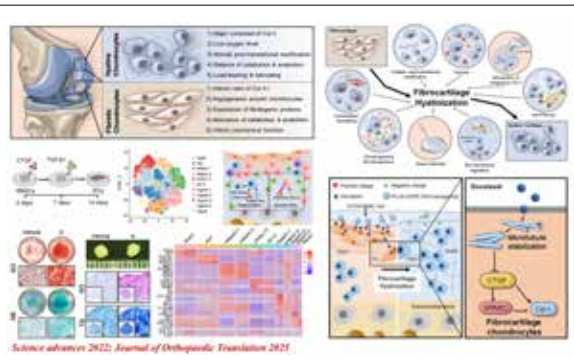

Figure 2. Microtubule stabilization promotes the fibrocartilage hyalinization

Selected publications (*Co-corresponding author)

1. Lv J, Muhammad F, Wang Z, Qiao C, Gu X, Liu Y, Li W, Gong W, Lv Z, Fei Y, Peng L, Lu Z, Xu N, Hu C, Zhang H, Wu R, Xu X, Wei H*, Sun Z*, Shi D*. Defective RuO Nanospheres Attenuate Osteoarthritis Progression via Suppressing the ROS/NLRP3/Caspase-1 Signaling Pathway. ACS Nano. 2025 Jul 1;19(25):23080-23095.
2. Jin X, Wang X, Xu S, Xu N, Wang Z, Hu C, Liu W, Zhang Z, Liu X, Fan J, Jiang R, Wu R, Lv Z*, Shi D*. Growth factor independence 1 ameliorates osteoarthritis by inhibiting chondrocyte ferroptosis via inactivation of MAPK signaling pathway. J Orthop Transl. 2025 Jul 29;54:101-114.
3. 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.
4. 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.
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6. 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.
7. Li J, Fan C, Lv Z, Sun Z, Han J, Wang M, Jiang H, Sun K, Tan G, Guo H, Liu A, Sun H, Xu X, Wu R, Yan W, Jiang Q, Ikegawa S, Chen X, Shi D*. Microtubule stabilization targeting regenerative chondrocyte cluster for cartilage regeneration. Theranostics. 2023 Jun 12;13(10):3480-3496.
8. Li J, Jiang H, Lv Z, Sun Z, Cheng C, Tan G, Wang M, Liu A, Sun H, Guo H, Chen F, Liu Z, Fei Y, Liu Y, Wu R, Xu X, Yan W, Jiang Q, Shi D*. Articular fibrocartilage-targeted therapy by microtubule stabilization. Science Advances. 2022 Nov 16;8(46): eabn8420.

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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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Animal Keeper	Fan Junluan
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	Xu Dong
	Wang Chuanhong
	Hou Min
	Zhou Anqin
	Ji Kaizheng
	Zhao Dingfu
	Wu Zixing
	Zhang Di
Engineering Department	Zhuo Zaijun
	Li Lin
	Wu Jinyin

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 8 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 170000 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

符亚丽-仪器平台实验技术专员

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
- Leica M205FCA High-Resolution Fully Automated Stereo Fluorescence Microscope

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
- Roche LightCycler 480II

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

DCS (DNA Omics-Cell Omics-Spatial Omics) Lab

► Services

- High-throughput genomic sequencing
- Single-cell transcriptomic and epigenomic profiling
- High-resolution spatial transcriptomics
- End-to-end bioinformatics and visualization tools

► Equipment

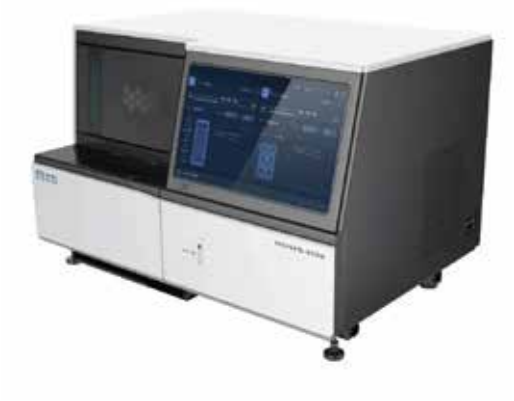
- MGISEQ-2000 Sequencer
- CycloneSEQ-WT02 Nanopore Gene Sequencer
- MGISP-100 Sequencing Library Preparation Instrument
- BGI Go Optical Spatiotemporal Microscope
- BGI Multifunctional Droplet Sorting System
- BGI MGICLab-LN55K IC-50 Automated Liquid Nitrogen Storage System

Others

► Equipment

- Beckman OPTIMA XPN-100 centrifuge
- BOTETF GL - 21R
- DAKEWE HP300 fully enclosed intelligent tissue dehydrator
- DAKEWE Automated Stainer-Coverslipper System DP260+CS500
- VNP-32P Fully Automated Nucleic Acid Extractor

New equipment



► MGISEQ-2000 Sequencer

Key Advantages

- Dual-Flow Cell System: Supports 1–2 flow cells running independently with interchangeable small (FCS) or large (FCL) flow cell options.
- Flexible Throughput: Generates 300 M–1,800 M reads per flow cell, supporting read lengths from SE50 to PE300.
- Speed: Completes sequencing in as fast as 25 hours (SE400-FCL mode), with >90% of bases achieving Q30 quality.
- Broad Compatibility: Suitable for diverse applications including research, clinical diagnostics, forensic identification, and agricultural genomics.

Primary Applications

- Genomics Research: Whole-genome sequencing, single-cell transcriptomics.
- Clinical Diagnostics: Tumor variant detection, pathogen identification.
- Spatial Omics: Captures spatial proteomics information when combined with multiplex immunofluorescence modules.

► CycloneSEQ-WT02 Nanopore Gene Sequencer

Key Advantages

- Long Read Length: Capable of sequencing from hundreds of base pairs up to megabase-scale, enabling comprehensive analysis of repetitive regions and structural variations.
- Real-Time Analysis: Delivers dynamic data output, allowing on-demand run termination and rapid detection within minutes.
- Portability: Compact, palm-sized device with room-temperature-storable flow cells, suitable for fieldwork and emergency outbreak scenarios.
- High Accuracy: Achieves 97% raw accuracy and >99% consensus accuracy with advanced algorithmic optimization.

Primary Applications

- Clinical Diagnostics: Rapid pathogen identification, tumor variant detection.
- Research: Full-length transcriptome analysis, epigenetic modification studies.
- Field Testing: On-site genetic testing during outbreaks or in resource-limited settings.

▶ MGISP-100 Sequencing Library Preparation Instrument

Key Advantages

- End-to-End Automation: Integrates nucleic acid extraction, library preparation, and PCR amplification, minimizing manual intervention and reducing operational errors.
- High Throughput: Supports both 96-well and 384-well plate formats, enabling scalable and efficient library preparation for diverse project sizes.
- Broad Compatibility: Compatible with multiple sequencing platforms and various sample types, including DNA, RNA, and single cells.
- Workflow Efficiency: Streamlines complex processes into a single automated workflow, significantly reducing hands-on time and enhancing reproducibility.

Primary Applications

- Genomics Research: Whole-genome sequencing, transcriptome analysis, and single-cell library preparation.
- Clinical Diagnostics: Targeted sequencing panels for tumor genomics, genetic disease screening, and pathogen detection.
- Agricultural Genomics: Library preparation for genomic studies in crops and livestock.

▶ BGI Go Optical Spatiotemporal Microscope

Key Advantages

- High Resolution: Delivers subcellular-level imaging for precise spatial transcriptomics and tissue structure analysis.
- Whole-Slide Imaging: Capable of large-area, high-speed scanning, enabling comprehensive spatial gene expression profiling.
- Multimodal Compatibility: Supports various fluorescence and brightfield imaging modes, suitable for diverse sample types and experimental designs.
- User-Friendly Automation: Fully automated focusing and scanning, minimizing manual operation and improving experimental reproducibility.

Primary Applications

- Spatial Transcriptomics: High-resolution gene expression mapping in tissue sections.
- Developmental Biology: Spatiotemporal analysis of embryogenesis and organ development.
- Pathology Research: Spatial profiling of tumor microenvironments and disease biomarkers.

New equipment

► BGI Multifunctional Droplet Sorting System

Key Advantages

- Integrated Workflow: Combines droplet generation, incubation, detection, and sorting into a single automated platform, minimizing manual handling and cross-contamination.
- High Throughput: Enables screening and sorting of millions of droplets per hour, significantly accelerating directed evolution and enzyme screening.
- Multiparameter Detection: Supports multi-channel fluorescence and absorbance detection for complex assays and precise target identification.
- Flexible Sorting Modes: Offers single- or multiple-droplet sorting options, accommodating diverse experimental requirements and downstream applications.

Primary Applications

- Directed Evolution: High-throughput screening of enzyme variants and metabolic pathways.
- Single-Cell Analysis: Droplet-based single-cell sequencing library preparation and functional assays.
- Synthetic Biology: Screening of engineered microbial strains and biosynthetic pathways.

► BGI MGICLab-LN55K IC-50 Automated Liquid Nitrogen Storage System

Key Advantages

- Ultra-High Capacity: Stores up to 55,000 standard 2D barcoded vials, maximizing sample density within a compact footprint.
- Full Automation: Robotically handles sample storage and retrieval, eliminating manual searching and ensuring consistent, error-free operations.
- Temperature Stability: Maintains a stable liquid-phase nitrogen environment (-190°C) to guarantee long-term sample integrity and viability.
- Intelligent Management: Integrated with a Laboratory Information Management System (LIMS) for real-time sample tracking, inventory management, and audit trails.

Primary Applications

- Biobanking: Large-scale, long-term storage of genomic DNA, RNA, and cell lines.
- Clinical Resources: Secure archiving of patient samples, tumor tissues, and diagnostic specimens.
- Agricultural Genomics: Preservation of germplasm resources, including seeds, pollen, and animal genetic materials.

▶ DAKEWE Automated Stainer-Coverslipper System DP260+CS500

Key Advantages

- Integrated Workflow: Fully automates staining, dehydration, and coverslipping, enhancing consistency of histopathological slides.
- High Throughput: Processes up to 260 slides per hour, ideal for high-volume pathology diagnostics.

Primary Applications

- Histopathology: H&E staining and immunohistochemical counterstaining of tumor sections.
- Biobanking: Standardized slide preparation and long-term storage.

▶ VNP-32P Fully Automated Nucleic Acid Extractor

Key Advantages

- High-Purity Extraction: Magnetic bead-based purification compatible with blood, tissue, swabs, and other sample types.
- Rapid Processing: Handles 32 samples in 40 minutes, supports integration into fully automated workstations.

Primary Applications

- Pathogen Sample Prep: Rapid extraction of viral DNA/RNA (e.g., SARS-CoV-2 screening).
- Forensic Identification: Nucleic acid enrichment from trace samples (e.g., oral swabs, bloodstains).

▶ Roche LightCycler 480II

Key Advantages

- Sensitivity: Detects single-copy genes.
- Speed: Completes 40 PCR cycles in 40 minutes (384-well mode).
- Flexibility: Interchangeable 96/384-well modules; compatible with third-party consumables and dyes.
- Automation: Integrates with LIMS and robotic arms for fully automated workflows.

Primary Applications

- Clinical Diagnostics: Tumor mutation profiling, genetic disorder screening.
- Research: Gene expression analysis, epigenetic studies.
- Food Safety: Rapid pathogen identification.

New equipment

► Leica M205FCA High-Resolution Fully Automated Stereo Fluorescence Microscope

Main Functionalities

- Fully Motorized Macro Imaging: Ideal for whole-organism or organ imaging of model organisms such as zebrafish, fruit flies, and nematodes.
- High-Resolution Fluorescence: Delivers superior resolution for detailed macroscopic fluorescent expression.
- Fast and Low Phototoxicity: Enables high-speed imaging with minimal sample damage, suitable for live imaging and time-lapse studies.

Key Advantages

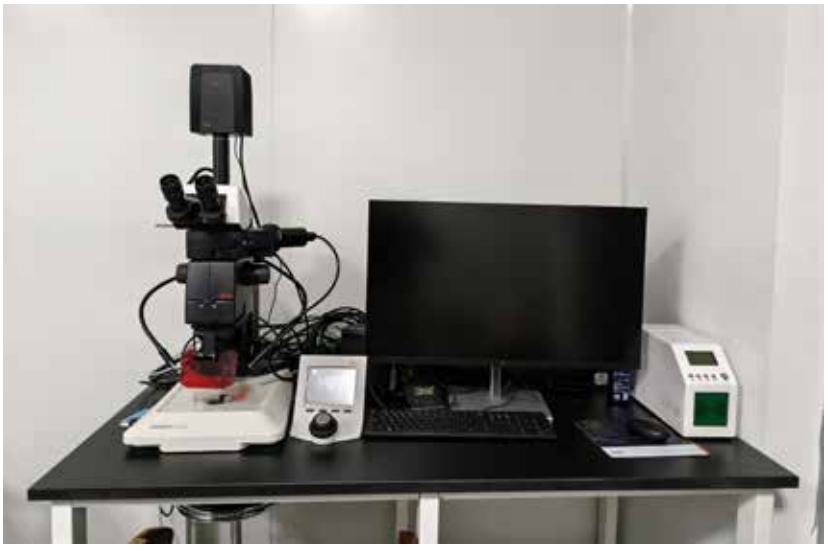
- High-Resolution and High-Contrast Imaging: Automatically distinguishes in-focus and out-of-focus signals, removing background blur while retaining weak signals—no post-processing required.
- Efficient Signal Acquisition: Combines widefield speed with high-resolution imaging by capturing effective signals and eliminating interference.
- No Image Stitching: Captures macro-samples in a single high-resolution field, avoiding time-consuming tiling.

Primary Applications

- Developmental Biology: High-resolution imaging of embryogenesis and organ development.
- Genetic Screening: Rapid visualization of fluorescently labeled transgenic models.
- Histology & Pathology: Multiplex fluorescence imaging for disease diagnosis and research.

Significance

- Bridges the gap between conventional stereomicroscopy (low resolution) and confocal microscopy (slow and complex), providing a fast, high-resolution, and user-friendly solution for macro-imaging needs.



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 of China. It provides services related to the preservation and supply of mouse resources, the creation of disease models, the training of experimental animal talents, and international exchanges.

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

By the end of 2025, NRCMM had 31,232 rat and mouse models, making it the world's largest resource center of mouse strains. NRCMM has served more than 2,000 universities, hospitals, biotechnology companies, CRO enterprises and pharmaceutical enterprises worldwide. A total of 5,060 SCI papers based on its mouse models have been published, with a combined impact factor (IF) of 49,087—including 1,606 papers in 2025 alone (total IF: 15,024). Research fields span tumors, autoimmunity, metabolism, and neuroscience.

In 2025, NRCMM continued its "Key Model for Research Project" (KMR Project) and its independent R&D projects. It supported over 200 scientists in cutting-edge research with more than 18 million yuan in funding, developed over 380 innovative mouse models, and published 55 SCI papers (cumulative IF: 794.04) in journals such as Science, Cell, Advanced Materials, Journal of Hepatology, Immunity, Nature Cancer, ACS Nano, Bioactive Materials, Advanced Science, Nature Communications, and Brain. Notably, building on its existing models, NRCMM conducted in-depth research on genetically engineered aging mouse models, aiming to develop a series of models simulating human aging through gene editing technology.In addition, NRCMM has performed bulk RNA-seq library construction and sequencing on 180 mouse nucleic acid samples, enriching its data repository.

That same year, NRCMM hosted the China-Germany Seminar,Immunity at the Crossroads: Shared Challenges in Cancer and Metabolic diseases, where top experts in the fields of metabolism and immunity from China and Germany participated to discuss the latest research progress and future development directions of metabolic disorders and immunity. The 15th AMMRA & AMPC Meeting was held in Japan. Director Gao Xiang of NRCMM was invited to deliver two important reports, laying a foundation for subsequent transnational cooperation and promoting the global sharing of experimental animal resources.

As a tradition, the 5th Summit Forum on the Development and Cooperation of the Laboratory Animal Industry was held in Nanjing, where hundreds of scholars and practitioners from related fields gathered to exchange ideas. The forum was live-streamed on multiple online platforms, attracting thousands of viewers and exerting a significant impact on the laboratory animal industry.

An annual embryo manipulation technology training program is held, and the 8th session took place in 2025, with over 30 experimental animal technicians participating in the four-day course. The program included both theoretical lectures and practical operations, allowing trainees to gain a solid theoretical foundation and proficient practical skills.The Tumor Model Animal Experiment Technology Training Course, hosted by NRCMM, was successfully held in Nanjing from December 3rd to 6th. Through a combination of expert lectures, hands-on demonstrations, and participants' practical operations, the training has enhanced the participants' capabilities in the construction, identification, and application of patient-derived xenograft (PDX) models and cell line-derived xenograft (CDX) models.

In 2025, NRCMM completed a full-scale upgrade of its official website, established a strain database and a mouse phenotypic analysis database the phenotypic database integrates over 14,000 strain information from authoritative databases such as the International Mouse Phenotypic Analysis Consortium (IMPC) and the RIKEN of Japan, providing a unified resource information sharing platform for researchers..NRCMM has also realized the open sharing of scientific data related to the mouse strains it has collected.

In the future, NRCMM will continue to provide high-quality mouse resources and services to support the innovation and development of life science research and pharmaceutical R&D.

Event in 2025

Laboratory Open Day

We also participated in the "National Linkage 'Laboratory Open Day' Activity" to bring the public closer to science and stimulate interest in science among young people. It is a rare learning opportunity for teenagers, who can not only understand the process and methods of scientific research, but also communicate face-to-face with scientists and feel the charm and challenges of scientific research. Such an experience will lay a solid foundation for their future scientific path.

Publications in 2025

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Seminar

MARC Alumni Forum

	Date	Speaker	Title	Unit
1	2025/4/16	Xuan Jiang Ph.D.	The role of Drosha in stromal cells	Sun Yat-sen University
2	2025/5/7	Zai Chang Ph.D.	The Impact of MARC on My Academic Career and Development	Tsinghua University Laboratory Animal Center
3	2025/6/11	Wen Luo Ph.D.	Signaling pathways in coronary vessel development and arterialization	Institute of Modern Biology
4	2025/10/13	Hu Zeng Ph.D.	B cells in distress- metabolic regulation and immune checkpoint inhibition induced autoimmunity	Mayo Clinic, USA
5	2025/10/29	Bin Shen Ph.D.	Precision Genome Editing of Mitochondria	Nanjing Medical University
6	2025/11/12	Zizhang Zhou Ph.D.	The Hippo Pathway:Orchestrating Cell Fate Between Survival and Death	Shandong Agricultural University
7	2025/12/24	Xiuxing Wang Ph.D.	Mechanisms of Self-Renewal and Therapeutic Strategies in Glioblastoma Stem Cells	Nanjing Medical University

MARC Forum

	Date	Speaker	Title	Unit
1	2025/3/20	Ye Yin Ph.D.	Silicon-Based Emergent Intelligence andCarbon-Based Longevity:Future Perspectives	CEO of BGI Group
2	2025/5/14	Jichang Wang Ph.D.	Human Embryonic Development and Strategies for Organ Xenotransplantation	Sun Yat-sen University
3	2025/5/23	Huiyuan ZhangPh.D.	From Stemness to Diverse Lineages-the emerging roles for transcriptional, metabolic and epigenetic regulations	West China Hospital, Sichuan University
4	2025/6/4	Lijia Ma Ph.D.	Optimization of Capsid and Transgene Expression for Efficient and Safe Low-Dose AAVGene Therapy	Westlake University
5	2025/6/11	Wei Ying Ph.D.	Regulatory T cells in the liver: friend or foe?	University of California, San Diego.
6	2025/8/2	Alexander PlossPh.D.	New insights into (re-) emerging flavivirus infections	Princeton University(NJ)
7	2025/10/22	Xin YangPh.D.	Trace(ing) micronutrients in determining ferroptosis	Soochow University

Courses and Lecturers

The MARC, as an institute of the Nanjing University Medical School, is home to more than 230 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 2025, 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

Qiaoli Chen

Danlu Shi

Zhaoyu Lin

Yingnan Ding

Yongzhen Liu

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 English 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 2025

Group Yan Li

Chunyu Cheng
A Lung-Immune Dual-Humanized Mouse Using Cryopreserved Tissue Enables Infection and Immune Profiling of Human Common Cold Coronaviruses.

Shuang Liu
Functional Study of Macrophages in Human Red Blood Cell Reconstruction in Human Immune System Mice.

Group Guoqiang Wan

Cui Qiu
Molecular regulations and physiological functions of human deafness genes DIAPH3 and ZBTB41

Group Yohei Niikura

Yao Xi
Functional study of MAD2 overexpression in cancer progression and cell death: insights from rhabdomyosarcoma and synthetic dosage lethality.

Group Zhaoyu Lin

Lulu Kang
The molecular pathways of cell death induced by Monosodium urate crystals and their potential applications in gout treatment.

Group Shuai Chen

Ye Cao
The function and mechanism of TBC1D1 in regulating muscle regeneration and metabolism.

Weikuan Feng
The function and mechanism of RalGAP complexes on pancreatic β cells.

Ruizhen Wang
Functional and regulatory study of SPEG protein homeostasis in obese cardiomyopathy.

Group Zhenji Gan

Zheng Zhou
The function and mechanism of the enhancer-binding protein BRD4 in regulating skeletal muscle fiber type switching and metabolism.

Likun Yang
Epigenetic regulator MLL4 controls skeletal muscle and systemic metabolic homeostasis.

GroupYun Shi

Guizhou Li
The Role and Mechanism of Mechanosensitive TMEM63B Channel in Brown Adipose Tissue Energy Metabolism.

Yanyu Zang
Investigation of Ketogenic Diet and Metabolite Betaine in Alleviating Epilepsy in Lgi1 Mutant Mice.

Shiyu Zhan
Study on the mechanism of TMEM63B channel as a mechanosensor to regulate the secretion of alveolar epithelial type II cells.

Group Guiquan Chen

Yizhi Zhang
PDK1 governs astrocyte differentiation by modulating STAT3 phosphorylation in mice.

Liyang Yao
Aberrant Neuronal AKT Drives Amyloid Pathogenesis by Disrupting Proteostatic Homeostasis.

Group Qing Zhang

Xiuxiu Ti
Molecular Mechanisms of Coa8-Mediated Mitochondrial Defects in pink1 RNAi Drosophila.

Shengnan Li
The mechanism of mitochondria-lysosomes communication mediated by LManVI

Group Jiong Chen

Zhixiang Dong
TRPM-mediated mechanoreception regulates myosin oscillation during tissue elongation.

Group Chaojun Li

Hongyu Nie
Dysregulation of the mevalonate pathway influences the development of metabolically unhealthy obesity.

Group Minsheng Zhu

Tiantian Qiu
Phage therapy for intractable functional constipation and the mechanisms of bacteriophage resistance.

Group Qingshun Zhao

Zhaojunjie Zhang
Optimization of CRISPR/Cas9 based zebrafish gene knock-in and single cell lineage tracing.

2025 Summer Camp

As the primary mission of MARC is to excel in scientific research and education, graduate students are the most vital resource of our center. To attract more outstanding students, we held the 16th Summer Camp on July 3th this year, jointly organized with the Medical School of Nanjing University.

The camp attracted 45 undergraduate students from 21 universities. During the event, Dr Yan Li, director of the MARC, introduced the history, research directions and groups of the research center. Shuang Liu, recipient of the 2023 Gempharmatech Cup Outstanding Award, shared his experience and knowledge on scientific research and life at MARC. Principal investigators (PIs) also shared their research experiences and scientific insights at MARC and at global stages. This year's program also featured poster presentations from all research teams, where PIs and senior lab members held face-to-face academic exchanges with participants.

The overarching goal of the Summer Camp is to identify and train future leaders in model animal–based biomedical research, both at MARC and globally. Overall, the camp provided participants with an immersive experience of MARC's dynamic research environment and further ignited their enthusiasm for biomedical science.

2025 Students Activities

In the past year, as a bridge between teachers and students, the Student Union has been adhering to the purpose of serving classmates and actively carried out a series of fruitful tasks.

In terms of academic activities, we held a number of professional knowledge lectures, inviting well-known scholars and experts inside and outside the school to answer questions and broaden everyone's academic horizons. At the same time, it further strengthens the exchange between MARC's different laboratories, the extensive knowledge of the teachers and the brainstorming of students, providing some new ideas and building an open and inclusive academic platform.

We also participated in the "National Linkage 'Laboratory Open Day' Activity" to bring the public closer to science and stimulate interest in science among young people. It is a rare learning opportunity for teenagers, who can not only understand the process and methods of scientific research, but also communicate face-to-face with scientists and feel the charm and challenges of scientific research. Such an experience will lay a solid foundation for their future scientific path.

We also held the 2025 Outstanding College Student Summer Camp. Under the leadership of MARC College volunteers, the campers visited the laboratory, instrument center, animal room, and other scientific research platforms, and had face-to-face exchanges with teachers and students of the Model Institute. Many students said that this zero-distance contact gave us a more intuitive understanding of graduate life.

On the occasion of bidding farewell to the old and welcoming the new, we held the 2025 Orientation Party, where teachers and students gathered together to welcome new students and celebrate the arrival of the New Year.

In the future, we will listen more to students' voices, continuously improve our organizational strength and creativity, create more new activities for the MARC family, and serve everyone seriously.

Marc Academy

Established in 2021, Marc Academy is a teacher-student organization within MARC designed to foster interaction between faculty and students and to break down communication barriers across different laboratories. The academy is currently composed of four colleges, each led by a student-elected dean. These colleges serve as units for friendly inter-college competitions and activities.

Each college includes both students and faculty from various laboratories, ensuring rich communication and interaction through a mix of internal college events and cross-college activities. Every activity is hosted by one of the four colleges, with funding allocated based on performance rankings in these events. This system supports self-directed and engaging activities within each college.

We have organized a variety of events that have been met with widespread and positive feedback. The Table Tennis Competition highlighted the athletic talent of MARC students, while the Fun Games showcased a strong sense of unity and collective honor. The First MARC Singer Contest created a vibrant and uplifting cultural atmosphere, and the Fishing Contest drew enthusiastic participation from many students and teachers.

Beyond organizing competitions, the deans and students of Marc Academy have played an active role in supporting broader MARC events. During the 2025 Summer Camp, the deans guided new students through the MARC environment, helping them familiarize themselves with the facilities and community. We also mobilized participation in the Badminton League hosted by the School of Architecture and Urban Planning at Nanjing University. Additionally, the deans contributed to the organization of the 2024 MARC Welcome Party, further strengthening our community bonds.

China-French Biomedical Industry Cooperation Symposium for Chinese Scientists in France

On July 9, 2025, the Model Animal Research Center (MARC)of Nanjing University, in collaboration with the Jiangsu Overseas Talents Innovation and Entrepreneurship Alliance and other partner institutions, successfully organized the "China-France Biomedical Industry Cooperation Symposium for Chinese Scientists in France & Nanjing Tour for High-Level Overseas Experts and Chief Liaison Officers of World-Renowned University Alumni."

The event was hosted at MARC, recognized for its role in incubating the listed company GemPharmatech, and was conducted in a hybrid online-offline format. It attracted over 80 participants, including scholars, experts, mid-career and senior talents from China and abroad, executives from pharmaceutical companies, as well as faculty and students from the Center.

The program comprised three main segments: keynote presentations, project showcases, and a roundtable forum. The keynote speeches focused on cutting-edge areas such as humanized immune system mouse models, precision therapy for pancreatic cancer, AI-enabled innovation in traditional Chinese medicine, drug development and evaluation platforms for inner ear diseases based on organoids and animal models, multi-organ chip technologies, and intelligent manufacturing in biotechnology, demonstrating deep integration across multiple disciplines. The roundtable forum, centered on the theme "Innovation and International Cooperation in the China-France Biomedical Industry," facilitated in-depth discussions that helped chart a clear direction for future collaboration.

Through this event, the Center effectively demonstrated its distinctive strengths in both scientific research and translational applications. Representatives from the Jiangsu Overseas Talents Innovation and Entrepreneurship Alliance reaffirmed their commitment to continuously developing the China-France Biomedical Innovation Cooperation Platform. They expressed hope that MARC would further leverage its bridging role to enhance cooperation with leading French institutions, jointly promote the localization and translation of cutting-edge technologies in China, explore new models for industry-academia-research integration, and provide stronger support for the advancement of the biomedical industry.

Nanjing University and BGI Group Forge Industry-Academia Partnership in Ceremony and Forum

On February 28, 2025, Nanjing University and BGI Group successfully concluded a signing and unveiling ceremony alongside a collaborative forum to mark their new industry-academia partnership. The event also saw the official inauguration of the "Nanjing University–MGI DCS Lab Omics Frontier Laboratory."

Distinguished attendees included Wang Wei, Party Secretary and Deputy Director of the Administrative Committee of Jiangbei New Area; Sun Jian, Deputy Dean of the Institute of Science and Technology at Nanjing University; Xu Xun, Executive Director of BGI Group and Dean of the BGI Shenzhen Institute of Life Sciences; Guo Zijian, Academician of the Chinese Academy of Sciences and Dean of the Nanjing University Institute of Chemistry and Biomedicine Innovation; Wang Hongwei, Vice Dean of Nanjing University School of Medicine; Wei Jia, Vice President of Nanjing Drum Tower Hospital; Gao Xiang, Founder of the Model Animal Research Center (MARC), Director of the National Resource Center for Mutant Mice, and Chairman of GemPharmatech Co., Ltd.; along with other invited scholars and experts from both institutions. The forum was hosted by Li Yan, Director of MARC under the Nanjing University School of Medicine.

Opening addresses were delivered by Wang Wei, Sun Jian, and Academician Guo Zijian. Subsequently, Deputy Director Wang Wei, Dean Xu Xun, and Director Li Yan elaborated on three key questions: Why was the new DCS Lab Omics Frontier Laboratory located in Jiangbei New Area? Why was it housed within the Model Animal Research Center? And what are the major objectives of the collaboration between MARC and MGI?

The forum also featured academic presentations by a roster of leading scientists, including Miguel Esteban (Research Scientist, BGI Research), Jin Xin (Chief Scientist for Domain Directions, BGI Research), Chen Liang (Principal Scientist, BGI Research), Dong Xuan (Principal Scientist, BGI Research), Professor Dong Lei (Associate Dean, School of Life Sciences, Nanjing University), Professor Li Jie (College of Chemistry, Nanjing University), Professor Wei Jia (Vice President of Nanjing Drum Tower Hospital and Deputy Director of the Nanjing University Clinical Cancer Institute), Shi Dongquan (Chief Physician, Sports Medicine and Adult Joint Reconstruction, Drum Tower Hospital), and Professor Li Yan (Director of MARC).

In his concluding remarks, Professor Gao Xiang—founder of MARC and Chairman of GemPharmatech—emphasized the importance of collaboration between the Model Animal Research Center, the National Resource Center for Mutant Mice, and BGI Group. He noted that by integrating their respective strengths in animal models, genomics, and big-data technologies, the partnership aims to accelerate life sciences research and the biopharmaceutical industry. This initiative, he said, will not only help unravel the mechanisms underlying major human diseases and advance therapeutic solutions but also provide valuable research resources and data to the global scientific community, helping to consolidate China's leading position in the life sciences.

南京大學
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