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

2023 ANNUAL REPORT

Director's Words

In 2023, the Model Animal Research Center (MARC) at Nanjing University celebrated its 20th anniversary at Chizhou, a significant milestone that marked two decades of innovation and excellence in the field of model animal research. This year was distinguished by several notable achievements and initiatives, solidifying MARC's leadership in biomedical research.

2023 was marked by a series of publications in prestigious journals, such as Nature Cell Biology, Cell Discovery, Brain, Nature Communications and Developmental Cell. These studies and advancements rely on the genetic mouse models created in MARC, and contribute to understanding disease mechanisms and the development of novel therapeutics.

MARC's 2023 calendar was enriched by visits from numerous overseas and domestic scholars, such as endowed chair professor Jianzhu Chen from MIT and Tim Sparwasser from IMB Maiz, fostering a global academic environment. The 3rd CSCB training course welcomed over 30 participants from "One Belt One Road" nations, reinforcing international collaboration in genetic engineering research.

MARC also emphasized community and academic engagement. The center conducted various workshops and seminars, enhancing the skills of young researchers and students. Of note, MARC hosted CSCB Laboratory Open Day event, showcasing its state-of-the-art facilities and winning the "2023 Excellent Science Popularization Laboratory" award, engaging the public and promoting scientific awareness.

In 2023, the center organized a summer camp as part of its initiative to attract and mentor future researchers, highlighting its commitment to nurturing biomedical talent. Also, we have selected a new MARC Star Lulu Kang based on her outstanding research achievement. Shuang Liu, a Ph.D student of MARC, competed with students from School of Life Sciences and won the 2nd Gempharmatech Award.

Looking ahead, MARC not only reflected on its past achievements but also laid the groundwork for future innovation and collaboration. With a steadfast focus on international cooperation, educational outreach, and research excellence, MARC continues to forge a path as a premier institution in the model animal research community.

Yan Li
Director

IN FOCUS

Director's Words
Research Highlight in 2023 2
Student of The Year 6

IN DEPTH

Neurobiology

Yun Shi 8
Guiquan Chen 10
Huiming Gao 12
Guoqiang Wan 14

Organogenesis

Jiong Chen 17
Qing Zhang 19
Ying Cao 21
Qingshun Zhao 23
Lei Dong 26

Metabolism and Immunity

Xiang Gao 29
Shuai Chen 31
Chaojun Li 33
Zhenji Gan 36
Hongyu Wang 39
Yan Li 41
Zhaoyu Lin 44
Qiaoli Chen 46
Tingting Fu 47

Cancer and Stem Cell Biology

Geng Liu 49
Qing Jiang 51
Jianghuai Liu 53
Jinzhong Qin 55
Pingping Shen 57
Yohei Niikura 59
Dongquan Shi 62

NJU-MARC Experimental Animal Center 65
NJU-MARC Core Facilities 66
National Resource Center for Mutant Mice of China 69

IN ADDITION

Event in 2023 70
Publications in 2023 73
Seminar 75
Courses and Lecturers 76
PhD Theses 77
2023 Summer Camp 78
2023 Students Activities 79
Marc Academy 81

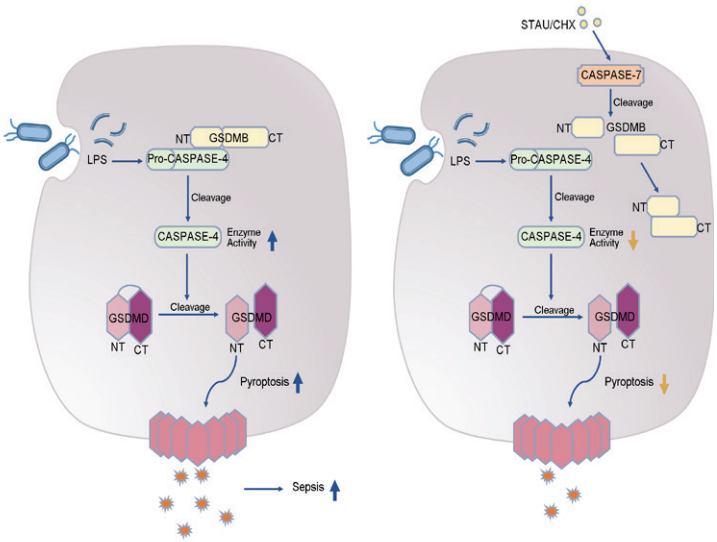
Research Highlight in 2023

Group Zhaoyu Lin, Xiang Gao

Apoptotic caspase-7 activation inhibits non-canonical pyroptosis by GSDMB cleavage

Xu Li, Tianxun Zhang, Lulu Kang,Ruyue Xin, Minli Sun, Qianyue Chen, Jingwen Pei, Qin Chen, Xiang Gao* and Zhaoyu Lin*

GSDMB is associated with several inflammatory diseases, such a asthma, sepsis and colitis. GZMA is released by cytotoxic lymphocyte and cleaves GSDMB at the K244 site and to induce GSDMB N-terminu dependent pyroptosis. This cleavage of GSDMB is noncell autonomous In this study, we demonstrated that the GSDMB-N domain (1-91 aa) wa important for a novel cell-autonomous function and that GSDMB coul bind caspase-4 and promote noncanonical pyroptosis. Furthermore activated caspase-7 cleaved GSDMB at the D91 site to block GSDMB mediated promotion of noncanonical pyroptosis during apoptosis Mechanistically, the cleaved GSDMB-C-terminus (92-417 aa) binds to th GSDMB-N-terminus (1-91 aa) to block the function of GSDMB. During E coli and S. Typhimurium infection, inhibition of the caspase-7/GSDMI axis resulted in more pyroptotic cells. Furthermore, in a septic mous model, caspase-7 inhibition or deficiency in GSDMB-transgenic mic led to more severe disease phenotypes. Overall, we demonstrate tha apoptotic caspase-7 activation inhibits non-canonical pyroptosis b cleaving GSDMB and provide new targets for sepsis therapy.

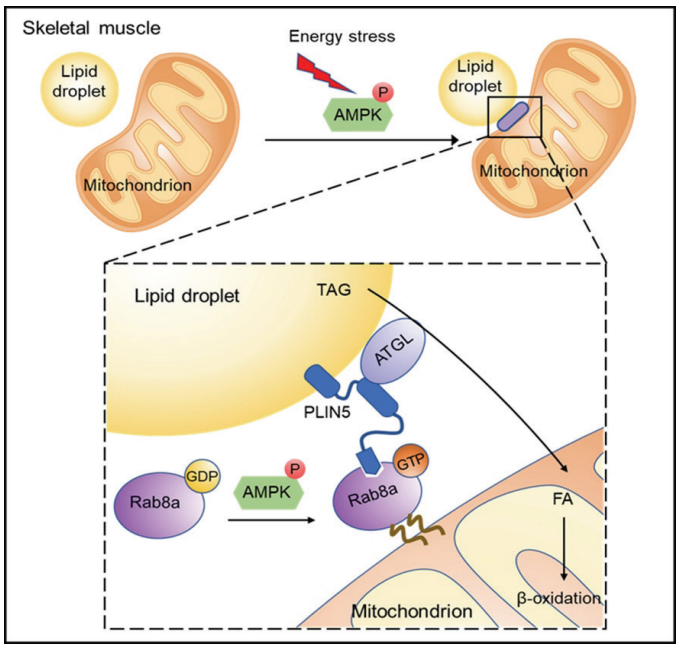


Group Shuai Chen

Rab8a as a mitochondrial receptor for lipid droplets in skeletal muscle

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*

Skeletal muscle, as the largest organ in the body, plays a critical role in regulating whole-body lipid homeostasis, and its dysfunction can cause dyslipidemia and hepatosteatosis. It is also an important organ in the locomotor system, conferring many beneficial effects of exercise on lipid homeostasis. Dynamic interaction between lipid droplets (LDs) and mitochondria controls mobilization of long-chain fatty acids (LCFAs) from LDs for mitochondrial β-oxidation in skeletal muscle under energy stress conditions such as exercise. However, it remains unclear about the composition and regulation of the tethering complex mediating LD-mitochondrion interaction. We identify Rab8a as a mitochondrial receptor for LDs forming the tethering complex with the LD-associated PLIN5 in skeletal muscle. In rat L6 skeletal muscle cells, the energy sensor AMPK increases the GTP-bound active Rab8a that promotes LD-mitochondrion interaction through binding to PLIN5 upon starvation. The assembly of Rab8a-PLIN5 tethering complex also recruits the adipose triglyceride lipase (ATGL), which couples LCFA mobilization from LDs with its transfer into mitochondria for β-oxidation. Rab8a deficiency impairs fatty acid utilization and decreases endurance during exercise in a mouse model. These findings may help to elucidate the regulatory mechanisms underlying the beneficial effects of exercise on lipid homeostasis control.



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

Group Guoqiang Wan

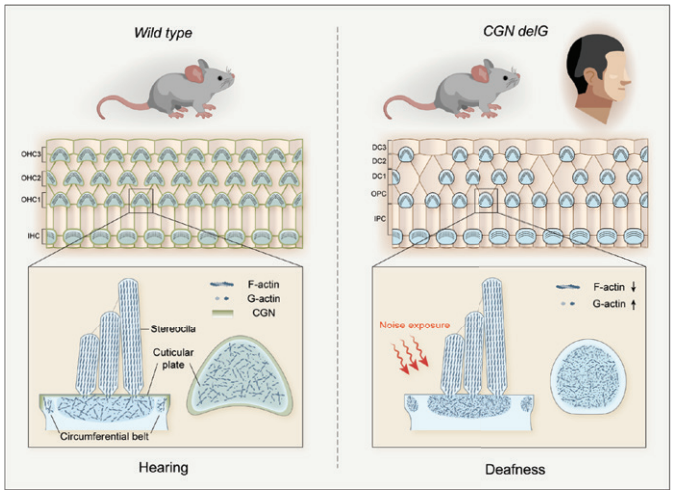
Cingulin regulates hair cell cuticular plate morphology and is required for hearing in human and mouse

Problem: Non-syndromic hearing loss (NSHL) is the most common hereditary sensory impairment. Half of the congenital deaf patients are associated with genetic defects. While more than 100 deafness genes have been identified, the etiologies and pathological mechanisms in a great number of deaf patients are still unknown. Cingulin (CGN) is a cytoskeleton-associated protein and an important component of the tight junction in vertebrate epithelia cells; however, associations of CGN mutations with human diseases have not been reported.

Results: We report a novel CGN variant (c.3330delG, p.L1110Lfs*17) that co-segregates with the deaf patients in an autosomal dominant NSHL family. CGN is preferentially enriched at the apical cuticular plates and circumferential belts of the hair cells. The CGN mutation abolishes the expression and subcellular localization of CGN protein and fails to promote actin polymerization. A knockin mouse model carrying the disease mutation shows altered morphology of the actin-enriched cuticular plates and hair bundles of sensory hair cells. Importantly, the Cgn mutation results in progressive and noise-sensitive hearing impairment and hair cell degeneration in the knockin mouse model.

Impact: Identifying novel deafness genes and the underlying pathogenic mechanisms are essential to personized treatment for genetic hearing loss. Combining human genetics, cell culture and animal model studies, we demonstrate that CGN is a novel deafness gene and plays an important role in the maintenance of hair cell cuticular plate and auditory function. This work not only provides mechanistic insights into development and maintenance of hair cell cuticular plates, but also affords an experimental basis for genetic counselling and personalized therapeutics to deaf patients carrying CGN mutations.

This work has been published in the journal EMBO Molecular Medicine.

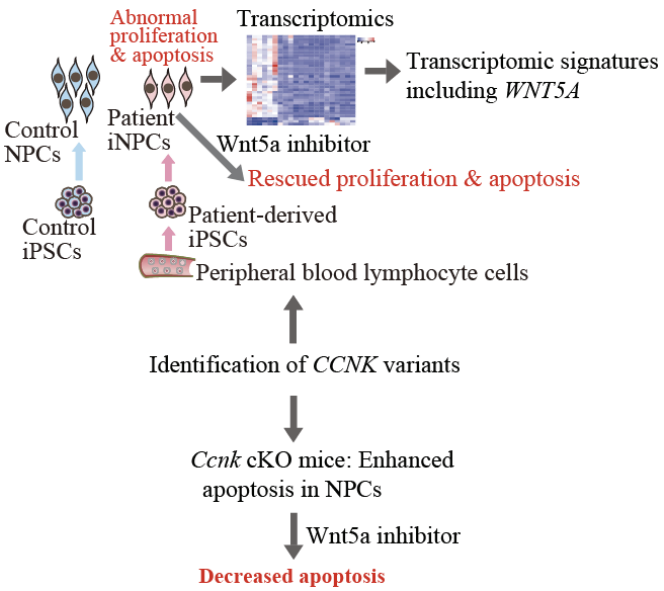


Group Guiquan Chen

CCNK gene deficiency influences neural progenitor cells via Wnt5a signaling in CNK-related syndrome

Weiqian Dai, He Wang, Yongkun Zhan, Nan Li, Fei Li, Jingmin Wang, Huifang Yan, Yu Zhang, Junyu Wang, Lingqian Wu, Huili Liu, Yanjie Fan, Yue Tao, Xi Mo, Jian-Jun Yang, Kun Sun, Guiquan Chen, Yongguo Yu

Our colleagues have previously identified rare variants of CCNK (cyclin K) in a syndrome displaying intellectual disability and neurodevelopmental abnormality (Fan et al., 2018). However, the underlying molecular mechanisms have remained unknown. To address this question, we generated patient-induced pluripotent stem cells (piPSCs), NPCs derived from piPSCs and neural progenitor cell (NPC)-specific Ccnk knockout (KO) mice. We have found that piPSCs and NPCs derived from piPSCs exhibit decreased expression of CCNK. We show that patient-derived NPCs and Ccnk cKO NPCs exhibit deficient proliferation and robust apoptotic cell death. RNA sequencing and molecular analyses reveal that WNT5A/Wnt5a is a key mediator for CCNK-dependent proliferation and survival of NPCs. Our rescue experiments have shown that inhibition of Wnt5a significantly improves proliferation and reduces apoptosis in NPCs derived from piPSCs and in NPCs in Ccnk KO mice. Our findings suggest that WNT5A may be a promising therapeutic candidate for the intervention of the CCNK-related syndrome.

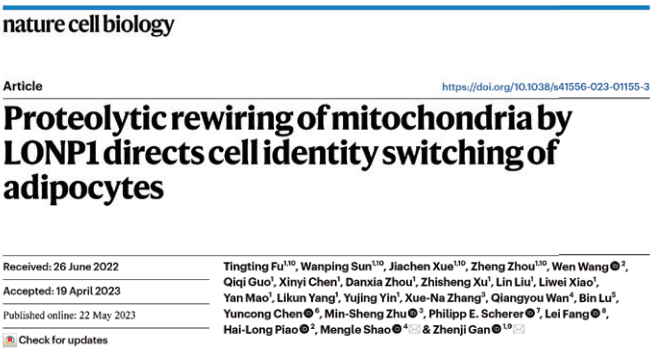


Group Zhenji Gan

Proteolytic rewiring of mitochondria by LONP1 directs cell identity switch of adipocytes.

Fu T #, Sun W#, Xue J#, Zhou Z#, Wang W, Guo Q, Chen X, Zhou D, Xu Z, Liu L, Xiao L, Mao Y, Yang L, Yin Y, Zhang XN, Wan Q, Lu B, Chen Y, Zhu MS, Philipp E. Scherer, Fang L, Piao HL, Shao M* and Gan Z*.

Mitochondrial proteases are emerging as key regulators of mitochondrial plasticity and acting as both protein quality surveillance and regulatory enzymes by performing highly regulated proteolytic reactions. However, it remains unclear whether the regulated mitochondrial proteolysis is mechanistically linked to cell identity switching. Here we report that cold-responsive mitochondrial proteolysis is a prerequisite for white-to-beige adipocyte cell fate programming during adipocyte thermogenic remodelling. Thermogenic stimulation selectively promotes mitochondrial proteostasis in mature white adipocytes via the mitochondrial protease LONP1. Disruption of LONP1-dependent proteolysis substantially impairs cold- or β3 adrenergic agonist-induced white-to-beige identity switching of mature adipocytes. Mechanistically, LONP1 selectively degrades succinate dehydrogenase complex iron sulfur subunit B and ensures adequate intracellular succinate levels. This alters the histone methylation status on thermogenic genes and thereby enables adipocyte cell fate programming. Finally, augmented LONP1 expression raises succinate levels and corrects ageing-related impairments in white-to-beige adipocyte conversion and adipocyte thermogenic capacity. Together, these findings reveal that LONP1 links proteolytic surveillance to mitochondrial metabolic rewiring and directs cell identity conversion during adipocyte thermogenic remodelling.

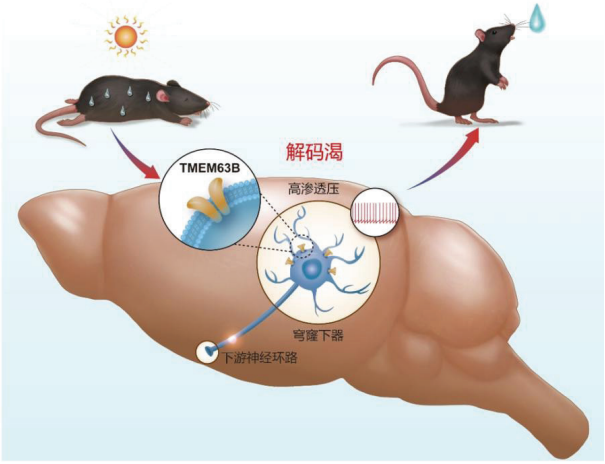


Group Yun Shi

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

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

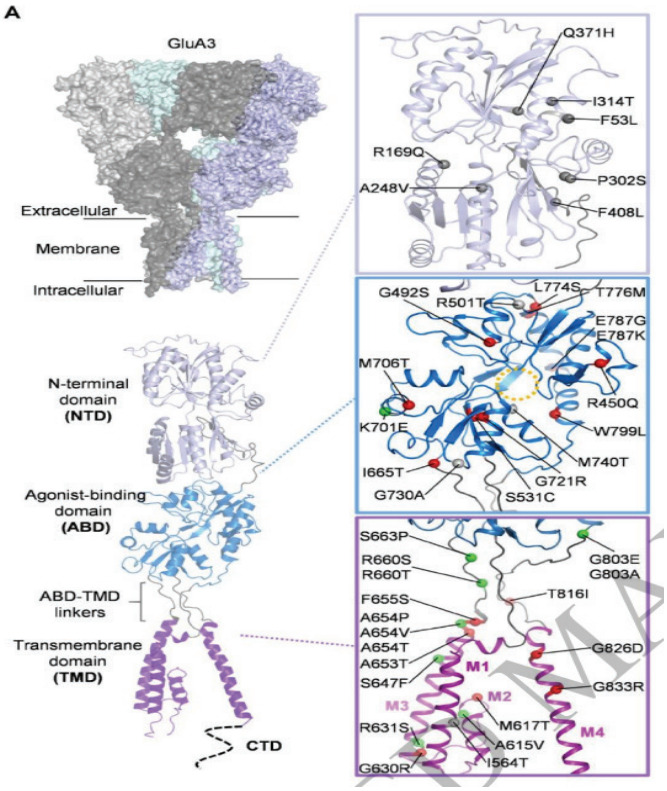
Thirst plays a vital role in the regulation of body fluid homeostasis and if deregulated can be life-threatening.Interoceptive neurons in the subfornical organ (SFO) are intrinsically osmosensitive and their activation by hyperosmolarity is necessary and sufficient for generating thirst. However, the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



Gain-of-function and loss-of-function variants in GRIA3 lead to distinct neurodevelopmental phenotypes

Rinaldi B, Bayat A, Zachariassen LG, Sun JH, Ge YH, Zhao D, Bonde K, Madsen LH, Awad IA A, Bagiran D, Sbeih A, Shah SM, El-Sayed S, Lyngby SM, Pedersen MG, Stenum-Berg C, Walker LC, Krey I, Delahaye-Duriez A, Emrick LT, …, Shi YS*, Kristensen AS* (2023).

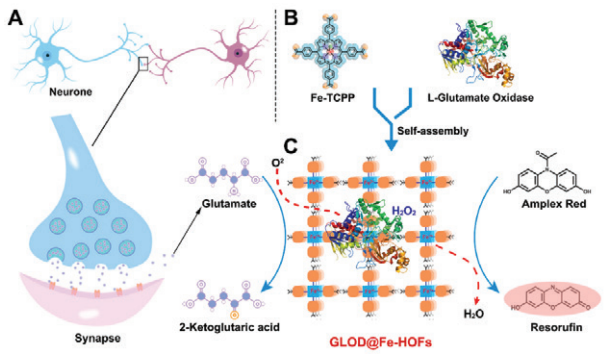
AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid) receptors (AMPARs) mediate fast excitatory neurotransmission in the brain. AMPARs form by homo- or heteromeric assembly of subunits encoded by the GRIA1-GRIA4 genes, of which only GRIA3 is X-chromosomal.Increasing numbers of GRIA3 missense variants are reported in patients with neurodevelopmental disorders (NDD), but only a few have been examined functionally.



Enhanced performance of enzymes confined in biocatalytic hydrogen-bonded organic frameworks for sensing of glutamate in the central nervous system

Ye C, Zhou TC, Deng Y, Wu S, Zeng TY, Yang J, Shi YS*, Yin YM*, Li GX*. (2024).

Glutamate (Glu) is a key excitatory neurotransmitter associated with various neurological disorders in the central nervous system, so its measurement is vital to both basic research and biomedical application. In this work, we propose the first example of using biocatalytic hydrogen-bonded organic frameworks (HOFs) as the hosting matrix to encapsulate glutamate oxidase (GLOD) via a de novo approach, fabricating a cascaded-enzyme nanoreactor for Glu biosensing. In this design, the ferriporphyrin ligands can assemble to form Fe-HOFs with high catalase-like activity, while offering a scaffold for the in-situ immobilization of GLOD. Moreover, the formed GLOD@Fe-HOFs are favorable for the efficient diffusion of Glu into the active sites of GLOD via the porous channels, accelerating the cascade reaction with neighboring Fe-HOFs. Consequently, the constructed nanoreactor can offer superior activity and operational stability in the catalytic cascade for Glu biosensing. More importantly, rapid and selective detection can be achieved in the cerebrospinal fluid (CSF) collected from mice in a low sample consumption. Therefore, the successful fabrication of enzyme@HOFs may offer promise to develop high-performance biosensor for further biomedical applications.

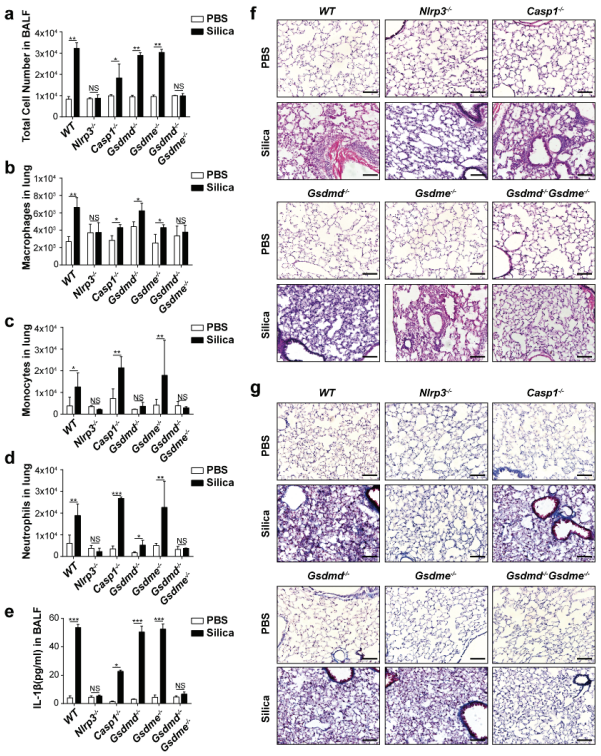


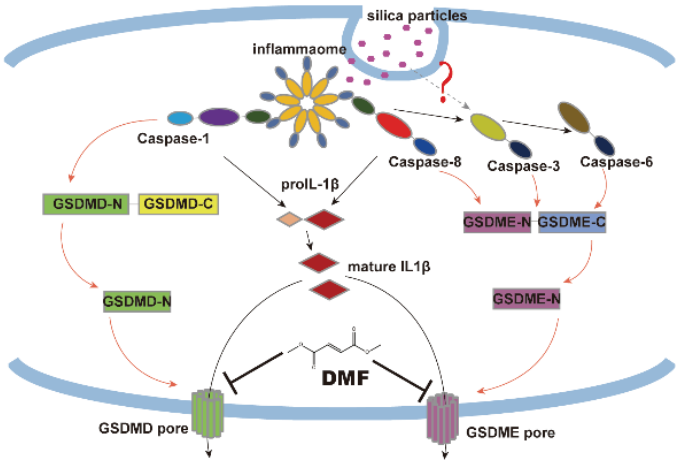
Student of the Year

Lulu Kang

Lulu Kang received her Bachelor's degree of Biological Technology in 2019 from the College of Innovation and Experiment, Northwest A&F University. She joined Dr. Gao Xiang and Zhaoyu Lin's lab at the year of 2019 to study cell death and inflammation signaling pathways.

For the past four years, her work focused on the silica and MSU crystal-induced cell death and inflammation pathways. This year, she and her colleagues reported a new molecular mechanism of silicosis-related pyroptosis. They found that Caspase-1/Gsdmd and Caspase-3/-8/Gsdme pathways are both essential for the development of pulmonary inflammation and fibrosis. Inactivation of Gsdme and Gsdmd cleavage significantly blocked silica-induced pyroptosis and alleviated mice pulmonary inflammation and fibrosis. These findings provide new targets for the therapy of silicosis.





Selected publications

1. Kang L, Dai J, Wang Y, Shi P, Zou Y, Pei J, Tian Y, Zhang J, Buranasudja VC, Chen J, Cai H, Gao X, Lin Z. Blocking Caspase-1/Gsdmd and Caspase-3/-8/Gsdme pyroptotic pathways rescues silicosis in mice. PLoS Genet. 2022 Dec 2;18(12):e1010515.
2. Li X, Zhang T, Kang L, Xin R, Sun M, Chen Q, Pei J, Chen Q, Gao X, Lin Z. Apoptotic caspase-7 activation inhibits non-canonical pyroptosis by GSDMB cleavage. Cell Death Differ. 2023 Sep;30(9):2120-2134.

Neurobiology

Yun Shi , Ph.D

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

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The Mechanisms of Neural Plasticity

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

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

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

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

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

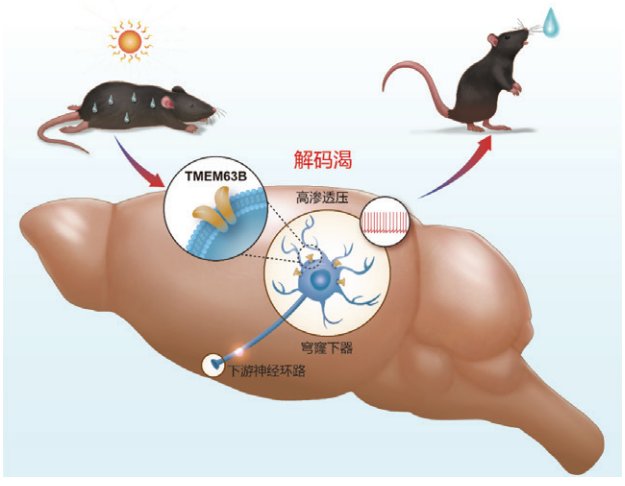

Figure 1. TMEM63B channel is the osmosensor required for thirst drive of interoceptive neurons (Cell discovery 2024).

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

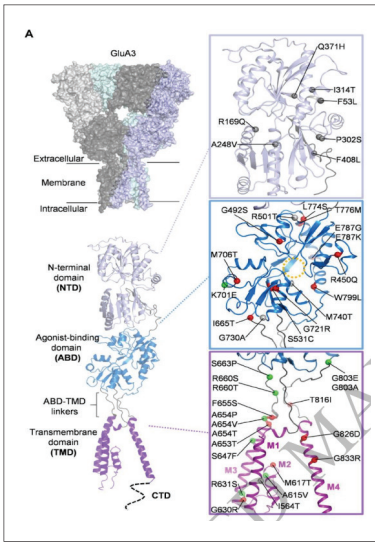

Figure 2. Gain-of-function and loss-of-function variants in GRIA3 lead to distinct neurodevelopmental phenotypes. (Brain 2023).

The GluA3 subunit proteins are highly similar and have a modular architecture of two extracellular domains, the N-terminal domain (NTD) and the agonist binding domain (ABD), a channel-forming transmembrane domain (TMD), and an intracellular carboxy-terminal domain (CTD) of unknown structure.

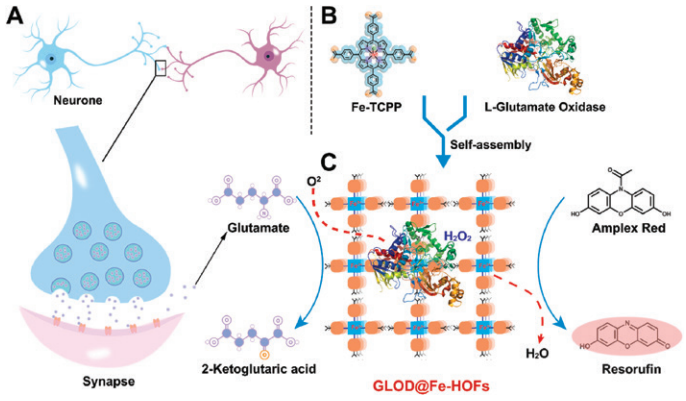

Figure 3. Enhanced performance of enzymes confined in biocatalytic hydrogen-bonded organic frameworks for sensing of glutamate in the central nervous system (Biosensors and Bioelectronics 2023).

The principle and workflow of the developed cascade GLOD@Fe-HOFs nanoreactor for sensing of released Glu in the brain. Schematic drawings of: (A) released Glu from synapse for neuronal communication, (B) fabrication of GLOD@Fe-HOFs composites using Fe-TCPP as ligands, and (C) the process of cascade catalysis in this work.

Selected publications

1. 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 discovery. 10(1):1.
2. 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 communications. 14(1):7265.
3. Ye C, Zhang TZ, Zang YY, Shi YS*, Wan GQ*. (2023). TMEM63B regulates postnatal development of cochlear sensory epithelia via thyroid hormone signaling. Journal of genetics and genomics. Advance online publication.
4. Rinaldi B, Bayat A, Zachariassen LG, Sun JH, Ge YH, Zhao D, Bonde K, Madsen LH, Awad IA A, Bagiran D, Sbeih A, Shah SM, El-Sayed S, Lyngby SM, Pedersen MG, Stenum-Berg C, Walker LC, Krey I, Delahaye-Duriez A, Emrick LT, …, Shi YS*, Kristensen AS*. (2023). Gain-of-function and loss-of-function variants in GRIA3 lead to distinct neurodevelopmental phenotypes. Brain. Advance online publication.
5. Wu D, Xu L, Cai WM, Zhan SY, Wan GQ, Xu Y*, Shi YS*. (2023). A splicing-dependent ER retention signal regulates surface expression of the mechanosensitive TMEM63B cation channel. The Journal of biological chemistry. 299(1), 102781.
6. 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.
7. 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.
8. 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.
9. Sun JH, Chen J, Ayala Valenzuela FE, Brown C, Masser-Frye D, Jones M, Romero LP, Rinaldi B, Li WL, Li QQ, Wu D, Gerard B, Thorpe E*, Bayat A*, Shi YS*. (2021) X-linked neonatal-onset epileptic encephalopathy associated with a gain-of-function variant p.R660T in GRIA3. PLoS Genet. 17(6):e1009608.
10. Jiang CH, Wei M, Zhang C*, Shi YS*. (2021) The amino-terminal domain of GluA1 mediates LTP maintenance via interaction with neuroplastin-65. PNAS. 118(9): e2019194118.
11. Du H, Ye C, Wu D, Zang YY, Zhang L, Chen C, He XY, Yang JJ, Hu P, Xu Z, Wan G*, Shi SY*. (2020) The cation channel TMEM63B is an osmosensor required for hearing. Cell Reports. 31(5):107596.

Group members

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Yun Shi

Group Teacher

Chang Ye

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Graduate students

Jingjing Tu, Shiyu Zhan, Guizhou Li, Yanyu Zang, Yuhan Ge, Shuaifei Lu, Xiaofeng Tan, Tianzi Zhang, Jingwen Chen.

Guiquan Chen, Ph.D.

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

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Molecular and cellular mechanisms for neurodevelopmental and neurodegenerative diseases

1. Molecular mechanisms by which Akt regulates oligodendrocyte differentiation.

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

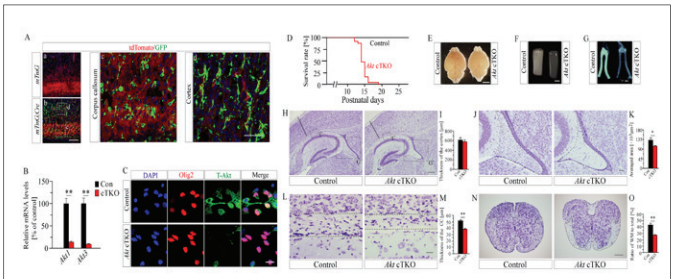

Figure 1. Deficient white matter development in Akt cTKO mice. (A-C) Characterization of Akt cTKO mice. (D) Survival rate. (E-G) Morphology of the brain, the spinal cord (SC) and the optic nerve (ON) in Akt cTKO mice. (H-O) Nissl analyses for the cortex (H), the fimbria (J), the corpus callosum (CC)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

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

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

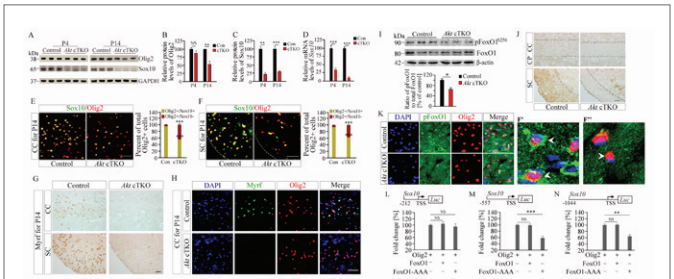

Figure 2. Down-regulation of Sox10 in Akt cTKO mice. (A-D) Decreased expression of Sox10 in Akt cTKO mice at P4 and P14. (E-F) Number of Sox10+/Olig2+ cells in the CC and the SC in Akt cTKO mice. (G,H) IHC analysis of Myrf+ cells in the CC and the SC in Akt cTKO mice at P14. (I-K) Western and IHC analyses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

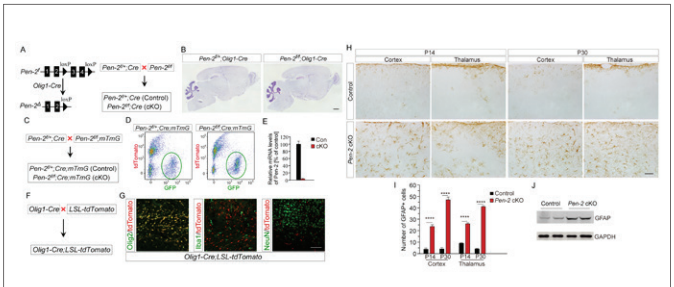

Figure 3. Enhanced generation of astrocytes in OL lineage cells specific Pen-2 cKO mice. (A-D) Characterization of OL lineage cells specific Pen-2 cKO mice. (F,G) Co-staining of Olig2/tdTomato in Olig1-Cre;LSL-tdTomato mice. (H) IHC on GFAP in Pen-2 cKO mice. (I) Number of GFAP+ cells in Pen-2 cKO mice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

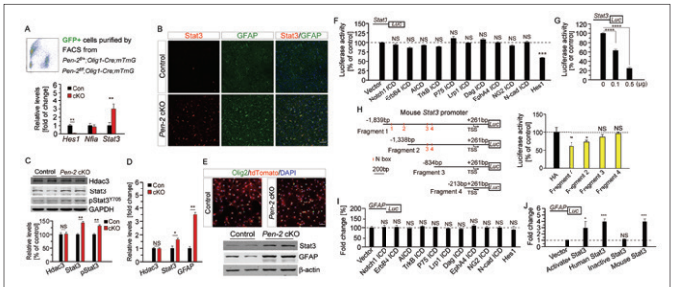

Figure 4. Increased expression of Stat3 in Pen-2 cKO mice. (A) Q-PCR analyses on Hes1, Nfia and Stat3 using Pen-2 cKO RNA samples. (B) IHC of Stat3/GFAP in Pen-2 cKO mice. (C) Western analysis on Hdac3, Stat3 and pStat3 in Pen-2 cKO mice. (D) Q-PCR analyses on Hdac3, Stat3 and GFAP mRNA levels in Pen-2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

Recent publications (*, Corresponding author)

1. 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.
2. Cheng Q, Wu J, Xia Y, Cheng Q, Zhao Y, Zhu P, Zhang W, Zhang S, Zhang L, Yuan Y, Li C*, Chen G*, and Xue B*, Disruption of protein geranylgeranylation in the cerebellum causes cerebellar hypoplasia and ataxia via blocking granule cell progenitor proliferation. Molecular Brain, 2023. 16: 24.
3. Xia Y, Zhang Y, Xu M, Zou X, Gao J*, Ji M*, 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.
4. Ye X, Yao L, Chen W, Shao W, Hu Y*, Zhang B*, and Chen G*, Emx1-Cre-mediated inactivation of PDK1 prevents plaque deposition in an Alzheimer's disease-like mouse model. Advanced Neurology, 2022. 1: 153.
5. Ye X, Chen L, Wang H, Peng, S, Liu M, Yao L, Zhang Y, Shi Y, Cao Y*, Yang J*, Chen G*. Genetic inhibition of PDK1 robustly reduces plaque deposition and ameliorates gliosis in the 5×FAD mouse model of Alzheimer's disease. Neuropathology and Applied Neurobiology 2022: e12839.
6. Teng X, Hu P, Chen Y, Zang Y, Ye X, Ou J, Chen G*, Shi YS*. A novel Lgi1 mutation causes white matter abnormalities and impairs motor coordination in mice. FASEB Journal 2022 (36):e22212.
7. Wang H, Liu M, Ye Z, Zhou C, Bi H, Wang L, Zhang C, Fu H, Shen Y, Yang J, Hu Y*, Chen G*. Akt regulates Sox10 expression to control oligodendrocyte differentiation via phosphorylating FoxO1. Journal of Neuroscience 2021 (41): 8163-8180.
8. Hou J, Bi H, Ye Z, Huang W, Zou G, Zou X, Shi Y, Shen Y, Ma Q, Kirchhoff F, Hu Y*, Chen G*. Pen-2 negatively regulates the differentiation of oligodendrocyte precursor cells into astrocytes in the central nervous system. Journal of Neuroscience 2021 (41):4976-4990.
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10. Bi H Zhou C Zhang Y Cai X Ji M Yang J Chen G*, Hu Y*. Neuron-specific deletion of presenilin enhancer2 causes progressive astrogliosis and agerelated neurodegeneration in the cortex independent of the Notch signaling. CNS Neuroscience & Therapeutics 2021 (27): 174-185.
11. Wu J, Shao C, Ye X, Di X, Li D, Zhao H, Zhang B*, Chen G*, Liu H-K*, Qian Y* (2021) In vivo brain imaging of amyloid- aggregates in Alzheimer's disease with a near-infrared fluorescent probe. ACS Sensors 2021 (6):863-870.
12. Wang Q, Gong L, Mao S, Yao C, Liu M, Wang Y, Yang J, Yu B, Chen G*, Gu X*. Klf2-Vav1-Rac1 axis promotes axon regeneration after peripheral nerve injury. Experimental Neurology 2021 (343):113788.
13. Zhang T, Ding H, Wang Y, Yuan Z, Zhang Y, Chen G*, Xu Y*, Chen L*. Akt3-mTOR regulates hippocampal neurogenesis in adult mouse. Journal of Neurochemistry 2021:15441.

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Neuroinflammation, neurodevelopment, and neurodegeneration

To investigate what drives the decades-long neurodegeneration and disease progression of neurodegenerative diseases is urgent and important. Oxidative stress and chronic neuroinflammation are intertwined key pathologic factors in neurodegenerative diseases. NADPH oxidase (a key superoxide-producing enzyme complex during inflammation) activation and reactive oxygen species (ROS) production in activated microglia critically contribute to chronic neurodegeneration.

This study investigated expression patterns, regulatory mechanisms and pathological roles of neuronal NADPH oxidase in neurodegeneration. Both microglia and neurons showed persistent upregulation of NOX2 (the catalytic subunit of NADPH oxidase) in chronic models of Parkinson's disease (PD). Notably, NOX2 was found for the first time to exhibit a progressive and persistent upregulation in neurons during chronic neuroinflammation in both in vitro and in vivo models of PD (Fig. 1). While neurons displayed basal expression of NOX1, NOX2 and NOX4, significant upregulation only occurred in NOX2 but not NOX1 or NOX4 under inflammatory conditions. Neuronal NOX2 shared similar activation mechanisms with microglial NOX2. Importantly, neuronal ROS production, mitochondrial dysfunction and neurodegeneration induced by inflammatory mediators were blocked by pharmacological inhibition of neuronal NOX2. Specific deletion of neuronal NOX2 prevented LPS-elicited neurodegeneration in neuron-microglia co-cultures separately grown in the transwell system (Fig. 2). The attenuation of inflammation-elicited upregulation of NOX2 in neuron-enriched and neuron-glia cultures by ROS scavenger N-acetylcysteine indicated a positive feedback mechanism between excessive ROS production and NOX2 upregulation (Fig. 3).

Collectively, our findings uncovered crucial contribution of neuronal NOX2 upregulation and activation to inflammation-related neurodegeneration. This study reinforced the importance of developing NADPH oxidase-targeting therapeutics for neurodegenerative diseases.

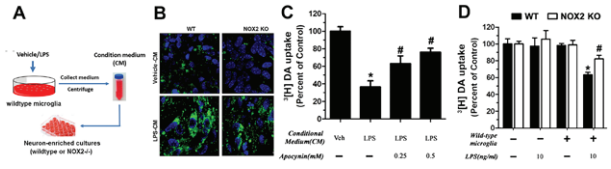

Figure 2. Neuronal NOX2 activation triggered by inflammatory factors induced neuronal NOX2-dependent ROS production and consequent dopaminergic degeneration.

A. Schematic diagram of the collection of conditional medium (CM) from vehicle-/LPS-treated microglia-enriched cultures and the treatment of neuron-enriched cultures with the CM. B. Intracellular ROS (iROS) production measured by intracellular CM-H2DCFDA oxidation in wildtype or NOX2-/- neuron-enriched cultures after incubation with the CM for 24 h. C. Midbrain neuron-enriched cultures were pretreated with apocynin for 30 min and then incubated with the CM from vehicle- or LPS-treated microglia. [3H]dopamine uptake assay was preformed to detect dopaminergic neurodegeneration 7 days after the addition of CM. D. Neuron-enriched cultures prepared from wildtype or NOX2-/- mice with or without co-culture with wildtype microglia and vehicle/LPS treatment. Neurodegeneration was determined by [3H] dopamine uptake assay at 7 days after the treatment. *p < 0.05 and #p <0.05 vs the corresponding neuronal cultures incubated with CM from vehicle-treated and LPS-treated wildtype microglia respectively (C). *p < 0.05 and #p < 0.05 vs the wildtype neurons co-cultured with wildtype microglia and treated with vehicle and LPS respectively (D).

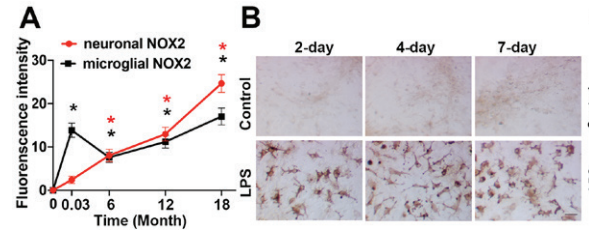

Figure 1. Persistent upregulation of NOX2 in both microglia and neurons in the substantia nigra of a chronic mouse model of PD with an i.p. injection of LPS (A) and in LPS-treated midbrain neuron-glia cultures (B & C).

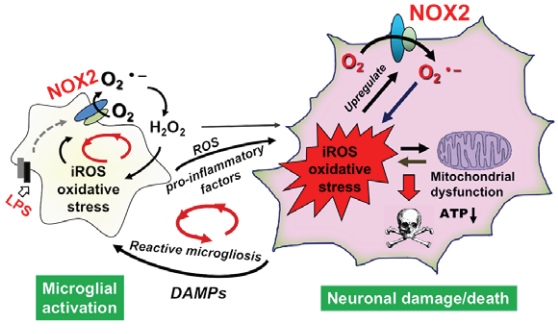

Figure 3. Multiple positive feed-back cycles sustained chronic neuroinflammation and NOX2-activation-dependent oxidative stress driving progressive neurodegeneration.

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

Selected publications(* Corresponding author)

1. 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
2. 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
3. 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
4. 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
5. Gao Y, Tu DZ, Yang R, Chu CH, Hong JS and Gao H-M* (2020) Through Reducing ROS Production, IL-10 Suppresses Caspase-1-Dependent IL-1 Maturation, thereby Preventing Chronic Neuroinflammation and Neurodegeneration. Int. J. Mol. Sci., 21, 465
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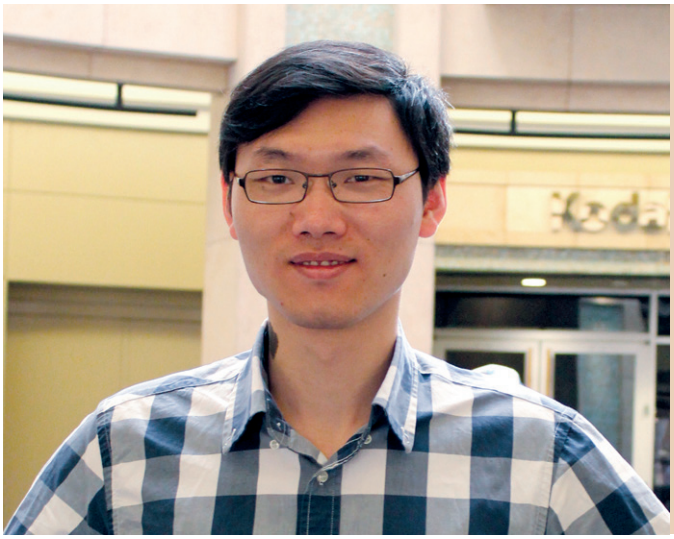

Guoqiang Wan, Ph.D.

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. In addition, even with the presence of intact sensory epithelia, hearing problems can also arise from irreversible loss of the synaptic connections between hair cells and SGNs, an auditory pathology termed as cochlear synaptopathy. Therefore, restoration of auditory functions requires not only preservation or regeneration of the sensory hair cells, neurons and non-sensory supporting cells, but also re-establishment of the cochlear synaptic connections (Figure 1). Our lab aims to identify novel molecular targets and pathways for the development and regeneration of cochlear sensory cells and synapses and to explore therapeutic potentials of these targets for treatment of sensorineural hearing loss.

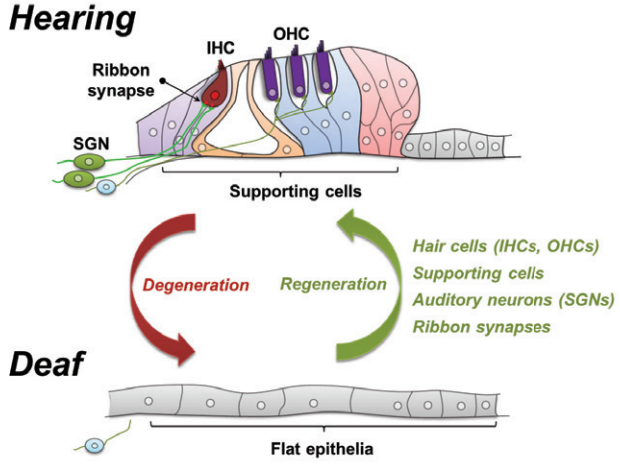

Figure 1. Research overview. In mammalian cochlea, sensory hair cells (IHC and OHC), neurons (SGN), supporting cells and the auditory ribbon synapses are required for normal hearing, damage of these cells and synapses results in deafness.

We recently identified a novel deafness gene from a Chinese family affected by autosomal dominant nonsyndromic hearing loss. This gene, names CINGULIN, was required for the hair cell cuticular plate morphology and for hearing in human and mouse models (Figure 2).

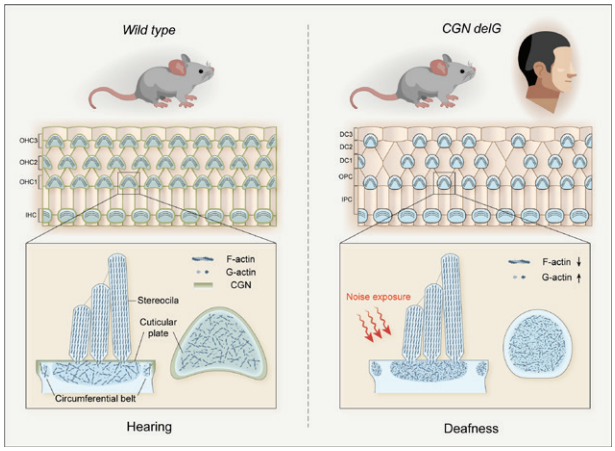

Figure 2. The tight junction-related protein Cingulin (CGN) is a novel deafness gene required for maintenance of cochlear hair cell cuticular plates and hair bundles. A frameshift mutation in CGN results in progressive hearing loss in human and mouse model.

Selected publications(* Corresponding author)

1. Zhu, G.J.*, Huang, Y.*, Zhang, L.*, Yan, K.*, Qiu, C., He, Y., Liu, Q., Zhu, C., Morín, M., Moreno-Pelayo, M.Á., Zhu, M.S., Cao, X., Zhou, H., Qian, X., Xu, Z.#, Chen, J.#, Gao, X.#, Wan, G.# (2023). Cingulin regulates hair cell cuticular plate morphology and is required for hearing in human and mouse. EMBO Molecular Medicine, e17611.
2. Liu, Q., Zhang, L., Zhu, M.S., and Wan, G. (2021). High-throughput screening on cochlear organoids identifies VEGFR-MEK-TGFB1 signaling promoting hair cell reprogramming. Stem Cell Reports, 16:2257-2273.
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6. Du, H.*, Ye, C.*, Wu, D.*, Zang, Y.Y., Zhang, L., Chen, C., He, X.Y., Yang, J.J., Hu, P., Xu, Z., Wan, G.# and Shi, Y.S.# (2020). The cation channel TMEM63B is an osmosensor required for hearing. Cell Reports, 31(5):107596.

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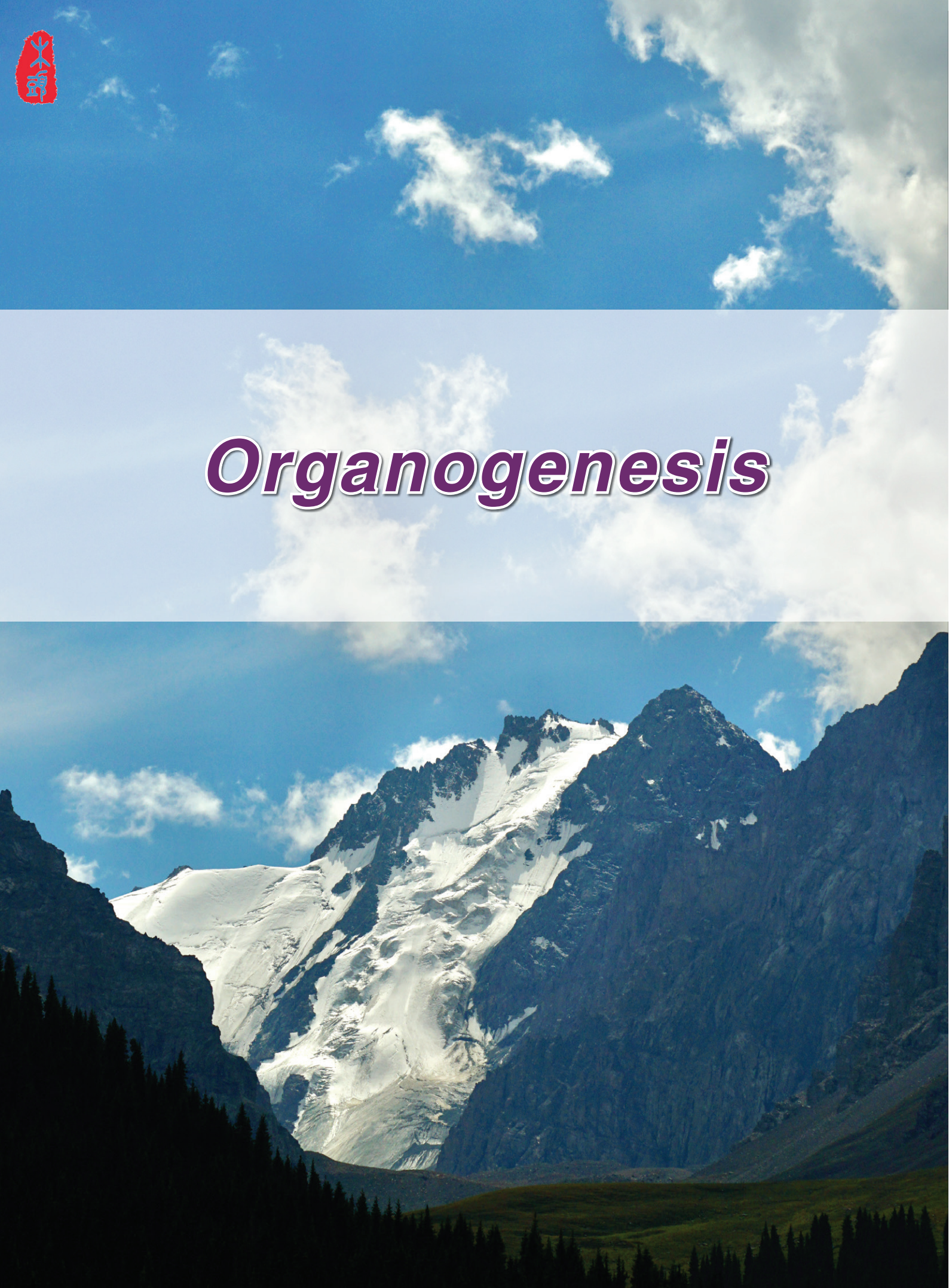
Organogenesis

Jiong Chen Ph.D.

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

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Understanding the driving forces underlying collective cell Migration

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

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

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

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

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

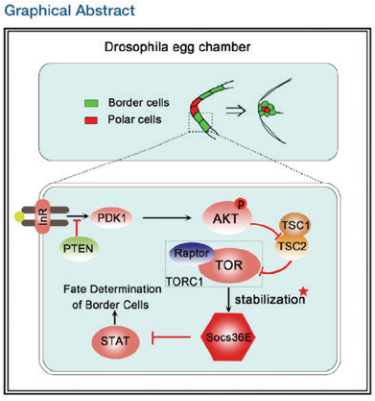

Figure 1. The growth promoting InR/Akt/TORC1 pathway attenuates migratory cell fate of border cells by down-regulation of JAK/STAT and destabilization of Socs36E. (from Kang et al., 2018)

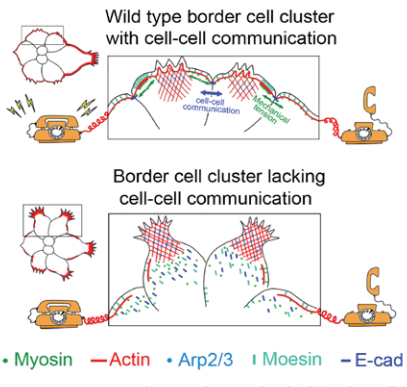

Figure 2. Diagram showing how individual border cells communicate with each other via supracellular actin-myosin network. Disruption of the supracellular network results in lack of cell-cell communication and defects in collective cell migration (from Wang H. et al., 2020)

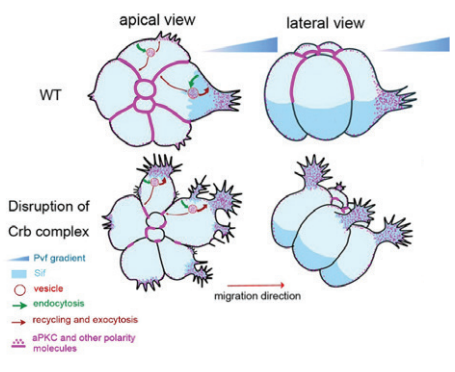

Figure 3. Diagram showing WT and Crb complex-deficient border cells in apical and lateral views. The model proposes how the two pools of aPKC and three distinct cell polarities are established by the Crb and Par complexes and endocytic recycling machinery. (from Wang et al., 2018)

Selected Publications

1. 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)
2. 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)
3. 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)
4. Wang, H. *, Guo, X., Wang, X., Wang, X. and Chen, J. * Supracellular actomyosin mediates cell-cell communication and shapes collective migratory morphology. Iscience (2020)
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9. Zhang, L., Luo, J., Wan, P., Wu, J., Laski, F. and Chen, J.* Regulation of cofilin phosphorylation and asymmetry in collective cell migration during morphogenesis. Development 138, 455-64. (2011)

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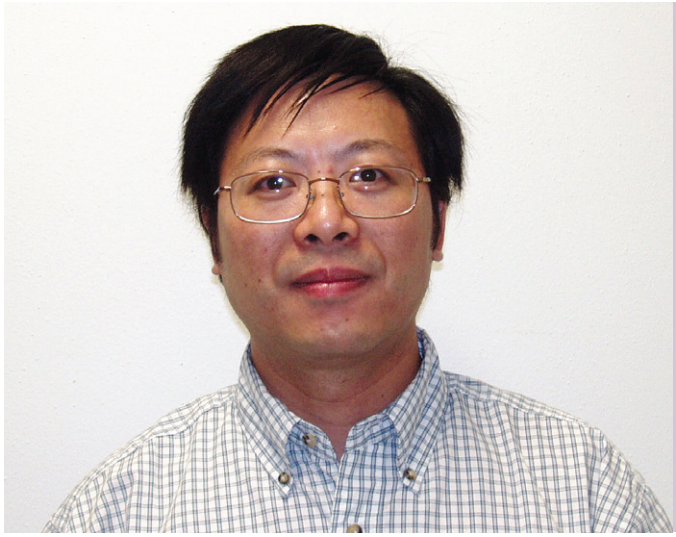

Qing Zhang, Ph.D

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

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Regulation of hedgehog signaling

Hedgehog signaling plays critical role in embryonic development and adult tissue homeostasis in species ranging from insects to human. Aberrant Hh signaling activity is associated with many human disorders including birth defects and cancers.

In Drosophila, Hh tansduces signal through binding its receptor, a 12-transmembrane protein Patched (Ptc), that alleviates suppression of ptc on Smoothened (Smo) a GPCR-like seven-transmembrane protein. Active Smo as the Hh signal transducer triggers a largely conserved signaling cascade that culminates at the activation of latent transcription factors Cubitus interruptus (Ci) which controls Hh targets decapentaplegic (dpp), ptc and engrailed (en) expression.

Based on Hh pathway is conserved among species, we take advantage of Drosophila as a model to investigate the mechanism of Hh signaling. Our work mainly focuses on getting the whole picture of around 7000 conserved genes on Hh signaling regulation and trying to answer the long-standing questions, for example, how does Ptc, the membrane receptor of Hh, inhibit Smo activity? how is hyperactive Ci degraded? and so on.

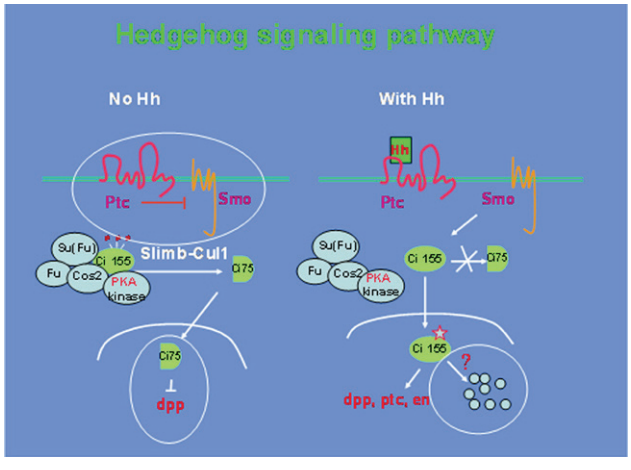

Fig1. Hedgehog signaling pathway in Drosophila.

HIB/SPOP inhibits Ci/Gli-mediated tumorigenesis by modulating the RNA Polymerase II components stabilities

Hedgehog (Hh) signaling mediated by transcription factor Ci/Gli plays a vital role in embryonic development and adult tissue homeostasis in invertebrates and vertebrates, whose dysregulation leads to many human disorders, including cancer. However, till now, cofactors of Ci/Gli which can affect tumorigenesis are not well known. Here, through genetic screen, we find overexpression of active Ci alone is not sufficient to generate tumor-like eye phenotype in Drosophila, however, its overexpression combined with knockdown of hib causes a striking tumor-like big eye phenotype. Mechanistically, HIB/SPOP inhibits Ci/Gli-mediated tumorigenesis by modulating the RNA polymerase II (RNAPII) components Rpb3/Rpb7 stabilities in E3 ligase dependent manner. In addition, Ci/Gli can promote HIB/SPOP-mediated Rpb7/Rpb3 degradation. Taken together, our results indicate Ci/Gli needs to hook up with suitable RNAPII together to achieve the tumor-like eye phenotype and HIB/SPOP plays dual roles through controlling Ci/Gli and Rpb3/Rpb7 protein stabilities to temper Ci/Gli/RNAPII-mediated tumorigenesis.

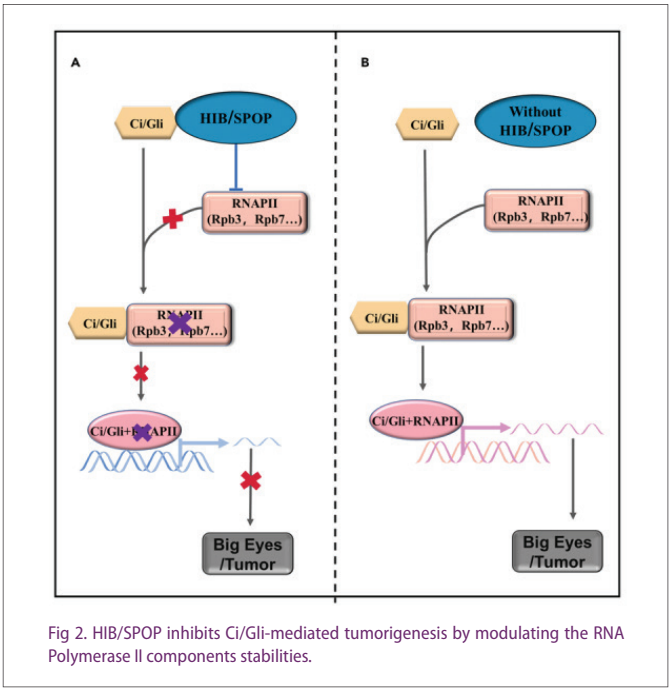

Fig 2. HIB/SPOP inhibits Ci/Gli-mediated tumorigenesis by modulating the RNA Polymerase II components stabilities.

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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 of Xenopus. In October 2008, he set up the laboratory in MARC for developmental biology and cancer biology. The results in his group suggest that the property of neural stemness is the key to understand tumorigenicity and pluripotent differentiation potential. He proposes novel conceptual paradigms that neural induction drives embryogenesis in gastrulating embryos but a similar process drives tumorigenesis in a postnatal animal. Tumorigenicity is by nature the manifestation of aberrant occurrence of pluripotent state in a postnatal animal. Pluripotency and tumorigenicity are both but different manifestations of neural stemness in pre- and postnatal stages of animal life, respectively

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Neural stemness unifies tumorigenicity and pluripotency.

My studies revealed that 1) most cancer promoting genes are neural stemness/embryonic neural genes, whereas a major part of cancer suppressor genes are non-neural gene during vertebrate embryogenesis, suggesting that cancer (tumorigenic) cells share regulatory networks with neural stem cells (NSCs) or embryonic neural cells; 2) different types of cancer cells exhibit the property of neural stem cells (neural stemness) and pluripotent differentiation potential; and 3) neural stemness determines and unifies tumorigenicity and pluripotency. The unique property of neural stemness might be predetermined by the evolutionary advantage of neural genes and neural cell state.

I proposed that tumorigenesis represents a process of progressive loss of original cell identity and gain of neural stemness, and consequently, gain of tumorigenicity and pluripotency, in cells of postnatal animals. This reminds of embryonic neural induction, a most fundamental process required for neurodevelopment and body axis formation during embryogenesis. Neural induction is that, in gastrulating embryos, the ectodermal cells lose their epidermal fate and assume the neural default fate and consequently, turn into neuroectodermal (primitive neural stem) cells. They differentiate into the nervous system and also non-neural cells. An ectopic neural induction event causes a conjoined twin formation during embryogenesis.

Both pluripotent and cancer cells can be induced to differentiate into normal cells and integrate into normal embryonic development within an embryo. They cannot integrate into tissues/organs in a postnatal animal because of lack of correct differentiation signals and thus form tumors. Pluripotency and tumorigenicity are both but different manifestations of the same cell property, i.e., neural stemness, in embryonic and postnatal stages of animal life, respectively. Neural induction drives body axis formation during embryogenesis, but a neural induction-like process drives tumorigenesis in postnatal animals (Figure 1). These findings might provide a comprehensive explanation of tumorigenesis and suggest neural stemness as the target for cancer therapy. For detailed information, see our papers listed below.

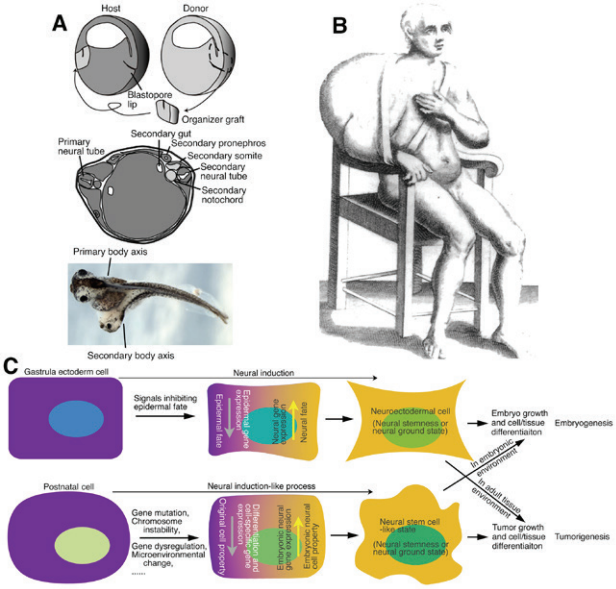

Figure 1. The unification of embryogenesis and tumorigenesis. Neural induction drives body axis formation (ectopically, a conjoined twin formation) during embryogenesis, but a neural induction-like process drives tumorigenesis in postnatal animals. A tumor represents a severely degenerated conjoined twin-like structure that is formed in postnatal stage of animal (including human) life.

Selected publications (*Correspondence author)

1. Cao Y*. Neural induction drives body axis formation during embryogenesis, but a neural induction-like process drives tumorigenesis in postnatal animals. Front Cell Dev Biol. 2023 May 9;11:1092667.
2. Zhang M, Liu Y, Shi L, Fang L, Xu L, Cao Y*. Neural stemness unifies cell tumorigenicity and pluripotent differentiation potential. J Biol Chem. 2022 Jul;298(7):102106.
3. 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.
4. Chen L, Zhang M, Fang L, Yang X, Cao N, Xu L, Shi L, Cao Y*. Coordinated regulation of the ribosome and proteasome by PRMT1 in the maintenance of neural stemness in cancer cells and neural stem cells. J Biol Chem. 2021 Oct 4;297(5):101275.
5. Yang X, Cao N, Chen L, Liu L, Zhang M, Cao Y*. Suppression of Cell Tumorigenicity by Non-neural Pro-differentiation Factors via Inhibition of Neural Property in Tumorigenic Cells. Front Cell Dev Biol. 2021 Sep 14;9:714383.
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7. Cao Y*. Tumorigenesis as a process of gradual loss of original cell identity and gain of properties of neural precursor/progenitor cells. Cell Biosci. 2017 Nov 7;7:61. (Review)
8. Zhang Z, Lei A, Xu L, Chen L, Chen Y, Zhang X, Gao Y, Yang X, Zhang M, Cao Y*. 2017. Similarity in gene-regulatory networks suggests that cancer cells share characteristics of embryonic neural cells. J Biol Chem. 292(31):12842-12859.
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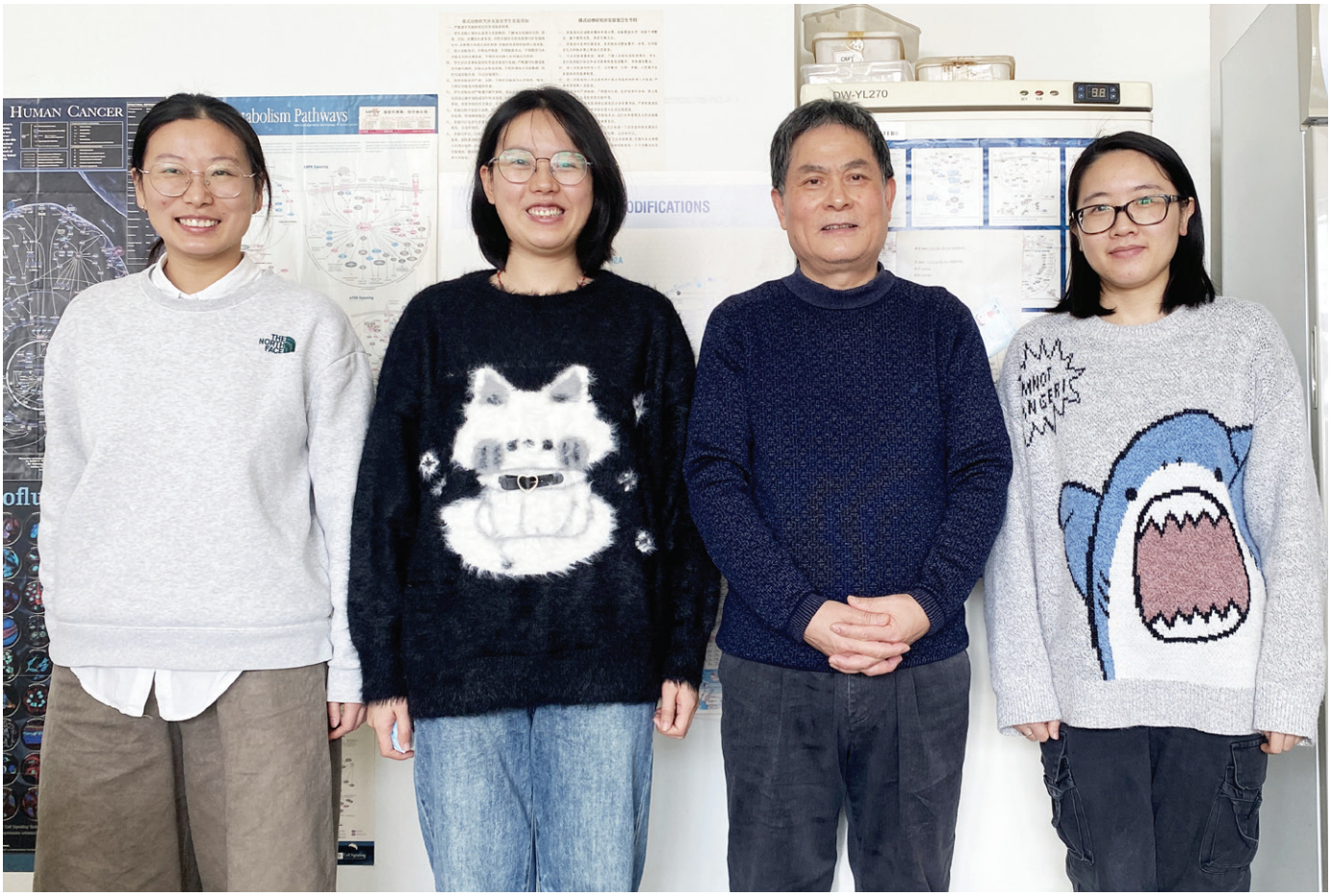

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Qingshun Zhao, Ph.D

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

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Zebrafish development

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

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

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

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

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

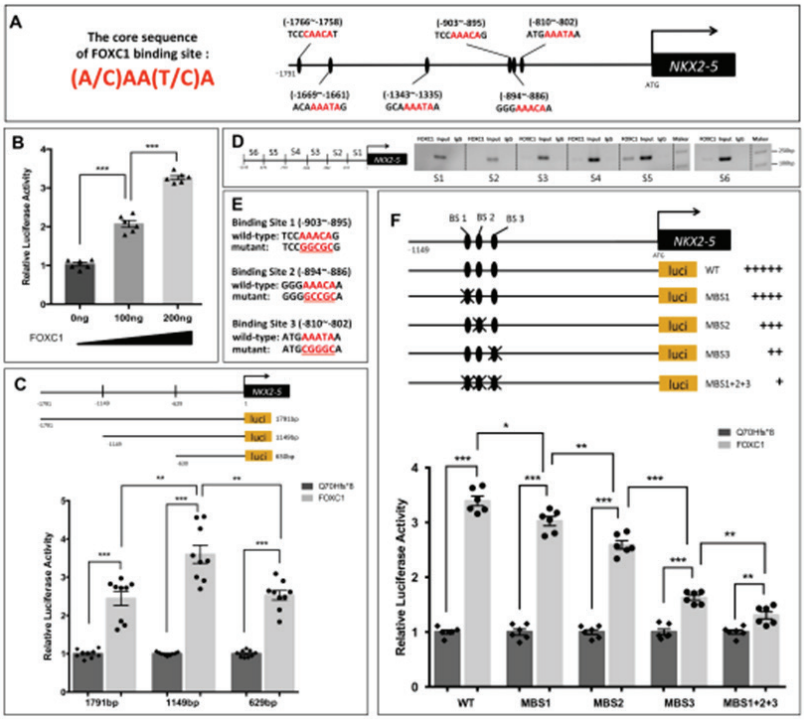

Figure 1. FOXC1 directly regulates the expression of NKX2-5 by binding to its proximal promoter in H9c2 cells.

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

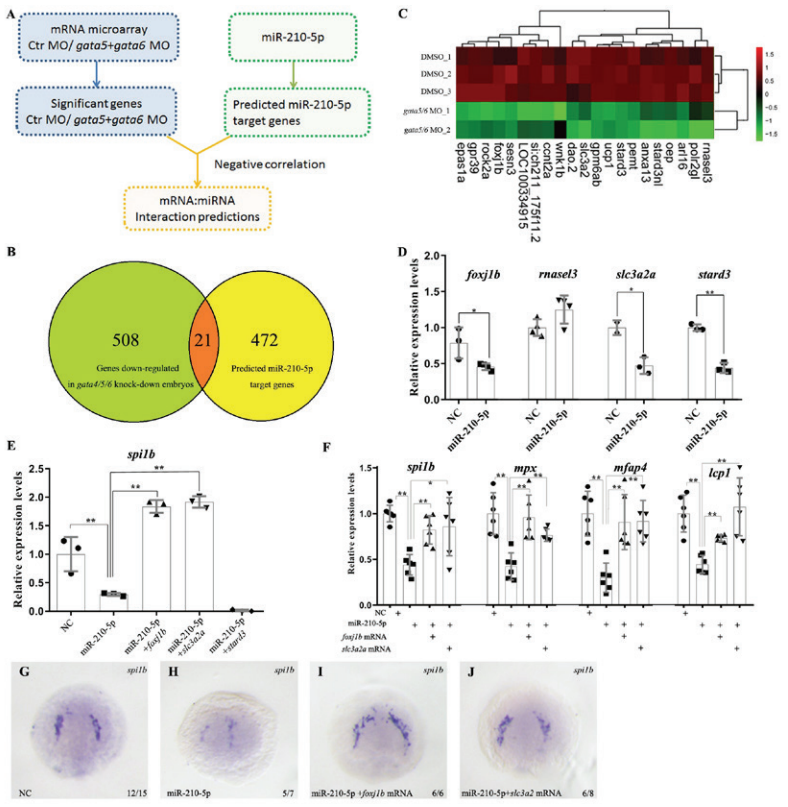

Figure 2. Both foxj1b and slc3a2a work downstream of miR-210-5p to mediate its role in inhibiting zebrafish primitive myelopoiesis.

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

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

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

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Dong Liang, PhD (2011)
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Yunyun Yue, PhD (2017)
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Chun Gu, PhD (2019)
Qinxin Zhang, PhD (2019)
Luqingqing He (2021)
Nan Li (2021)
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Yunfeng Zhang, MS (2021)
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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 is promising for the regeneration of failure organs. However, it's challenging and intractable to functionally regenerate large and complex organs in tissue engineering, which is hampered by insufficient seed cells, immune rejection, especially for the lack of theories and techniques for building mature vascular systems. What's exciting, harnessing the mature blood vessel network in existing dispensable organs might be one powerful approach to effectively and integrally overcome the obstacles. Spleen is a suitable transforming organ due to its unique advantages. After remodeled to be a pro-regenerative niche, the spleen can be transformed into another one with specific physiological functions, compensating for the latter's failed native functions.

We have successfully transformed the spleen into a liver-like organ, through translocating and remodeling the native spleen to make the niche therein easier to inject and more satisfactory for the hepatocytes' inoculation. The hepatized spleen exerts typical hepatic functions to rescue the host mice from severe liver damage. Besides, we developed another powerful and promising strategy -- organ reprogramming, which could not only solve the shortage of seed cells but also endow the organism with new functions. In this study, we restored the liver functions in the spleen through 3 steps. The number of fibroblasts was through silica particles (SiO_2) stimulation, the expanded fibroblasts were converted to hepatocytes (iHeps) by lentiviral transfection of three key transcriptional factors (Foxa3, Gata4 and Hnf1a), and the iHeps were further expanded with tumor necrosis factor-α (TNF-α) and lentivirus-mediated expression of epidermal growth factor (EGF) and hepatocyte growth factor (HGF). iHeps possessed hepatic functions – such as glycogen storage, lipid accumulation and drug metabolism – and performed fundamental liver functions to improve the survival rate of mice with 90% hepatectomy. Conversion of the spleen into a liver-like organ establishes fundamental hepatic functions in mice, suggesting its potential value for the treatment of end-stage liver diseases. In addition, functional tissues such as islets, thyroid, and thymus were also regenerated in the spleen (Figure 1). The above research breaks through the bottleneck of regeneration of large and complex organs through "organ function remodeling", which is a new exploration in the field of tissue engineering.

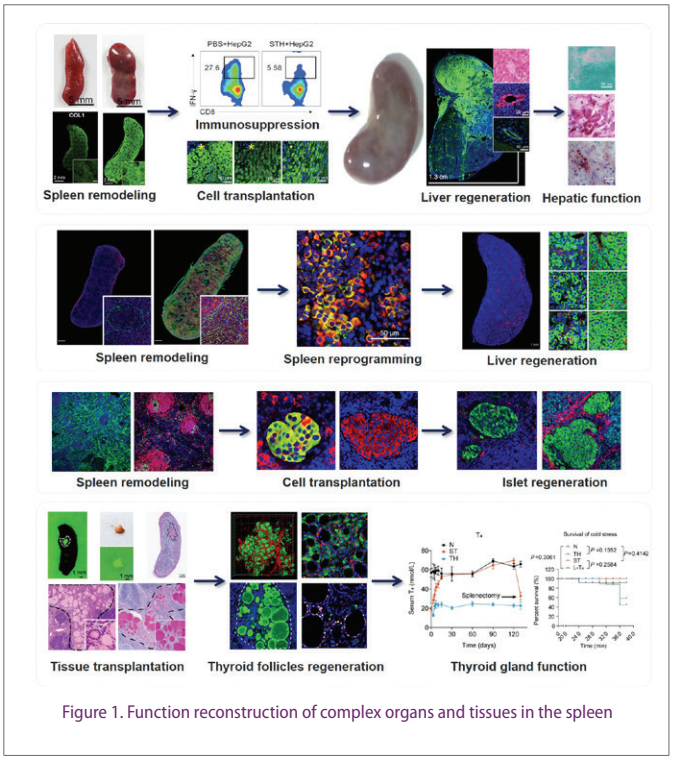

Figure 1. Function reconstruction of complex organs and tissues in the spleen

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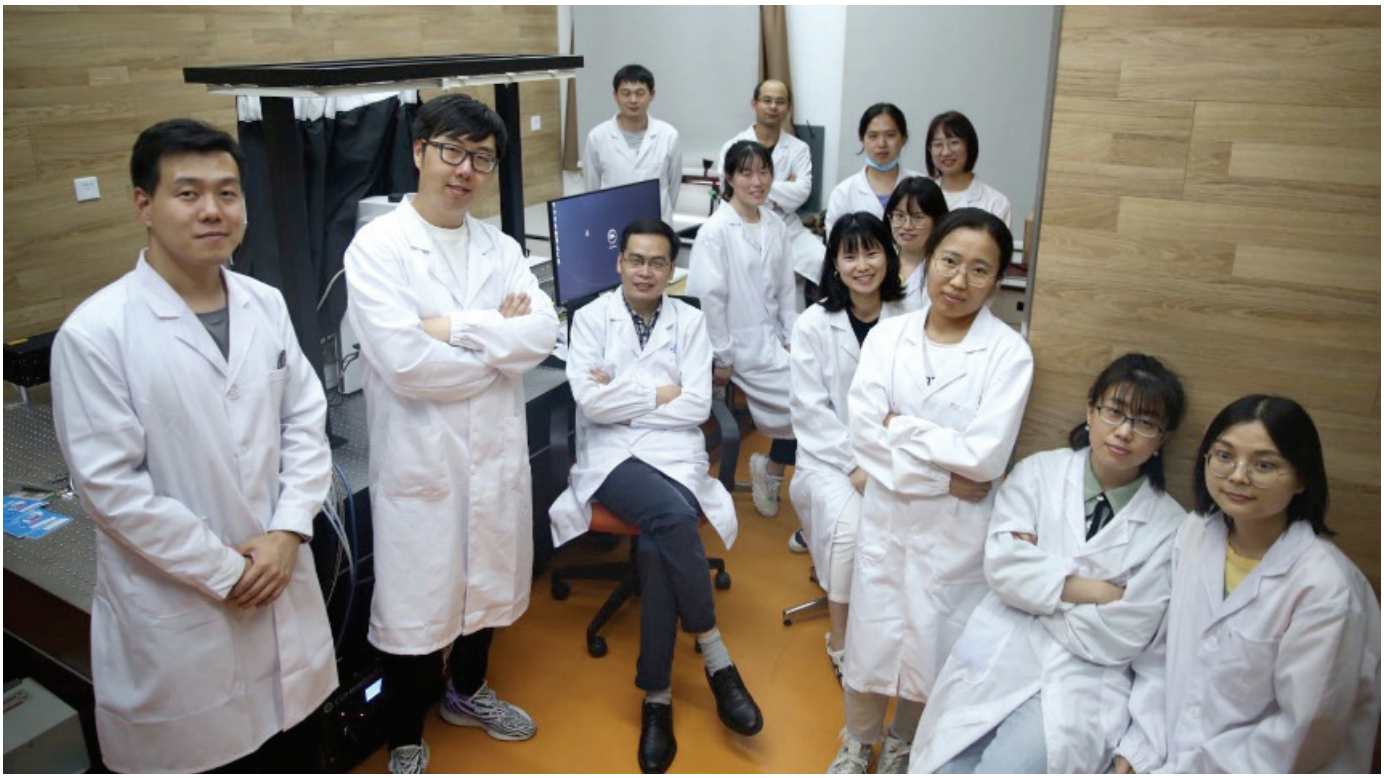

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Lifang Yang
Zhewei Yang
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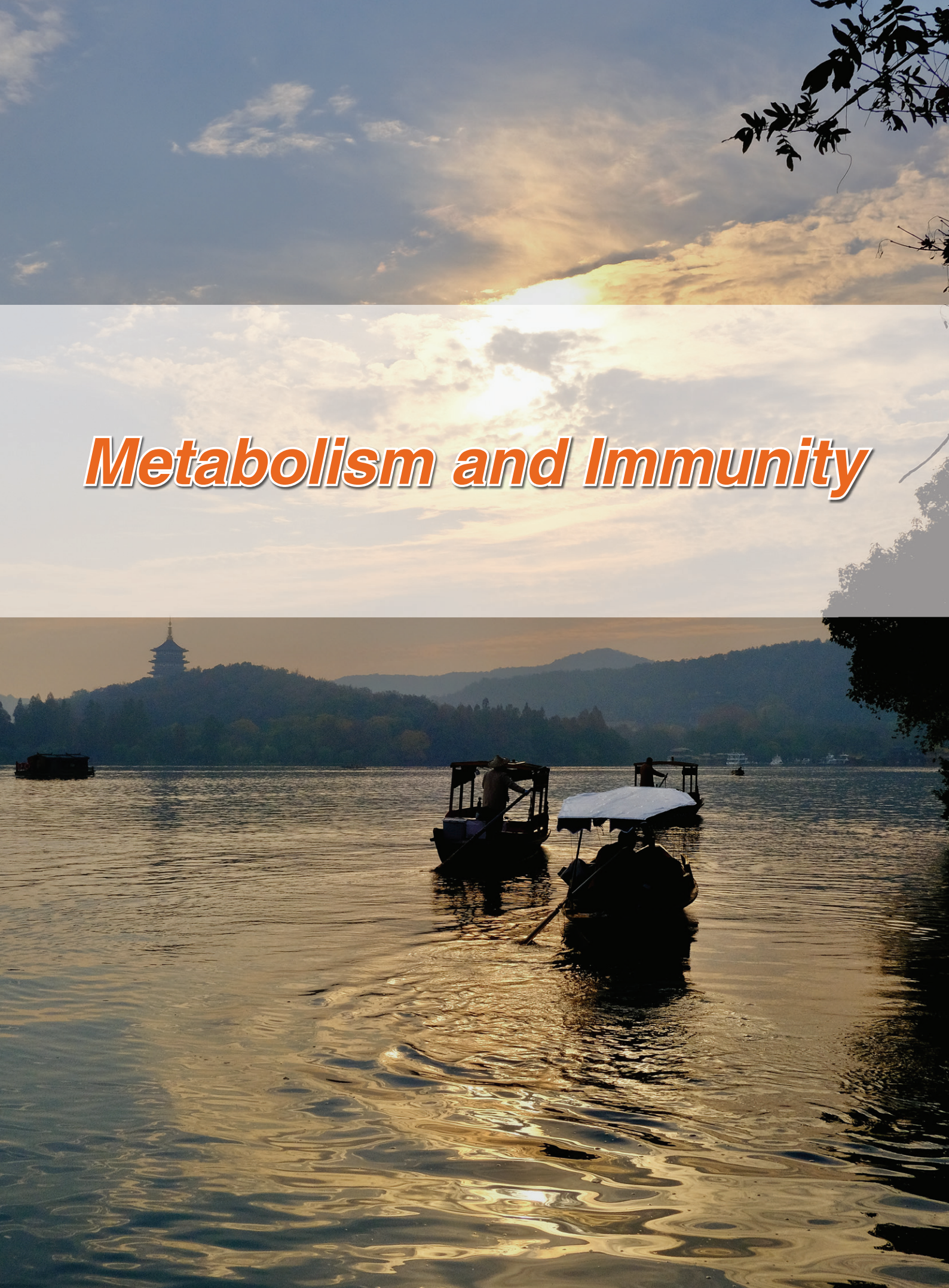

Metabolism and Immunity

Xiang Gao, Ph.D.

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

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Physiological regulation and metabolic homeostasis

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

1. The Deficiency of SCARB2/LIMP-2 Impairs Metabolism via Disrupted mTORC1-Dependent Mitochondrial OXPHOS (Figure 1)

Deficiency in scavenger receptor class B, member 2 (SCARB2) is related to both Gaucher disease (GD) and Parkinson's disease (PD), which are both neurodegenerative-related diseases without cure. Although both diseases lead to weight loss, which affects the quality of life and the progress of diseases, the underlying molecular mechanism is still unclear. In this study, we found that Scarb2(-/-) mice showed significantly reduced lipid storage in white fat tissues (WAT) compared to WT mice on a regular chow diet. However, the phenotype is independent of heat production, activity, food intake or energy absorption. Furthermore, adipocyte differentiation and cholesterol homeostasis were unaffected. We found that the impaired lipid accumulation of Adiponectin-cre; Scarb2(fl/fl) mice was due to the imbalance between glycolysis and oxidative phosphorylation (OXPHOS). Mechanistically, the mechanistic target of rapamycin complex 1 (mTORC1)/ eukaryotic translation initiation factor 4E binding protein 1 (4E-BP1) pathway was down-regulated in Scarb2 deficient adipocytes, leading to impaired mitochondrial respiration and enhanced glycolysis. Altogether, we reveal the role of SCARB2 in metabolism regulation besides the nervous system, which provides a theoretical basis for weight loss treatment of patients with neurodegenerative diseases.

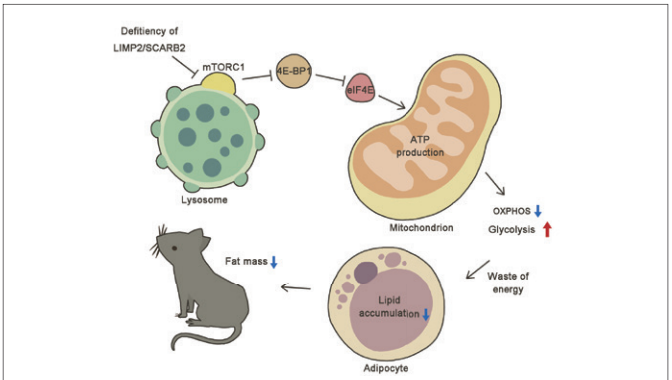

Figure 1. The Deficiency of SCARB2/LIMP-2 Impairs Metabolism via Disrupted mTORC1-Dependent Mitochondrial OXPHOS

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.

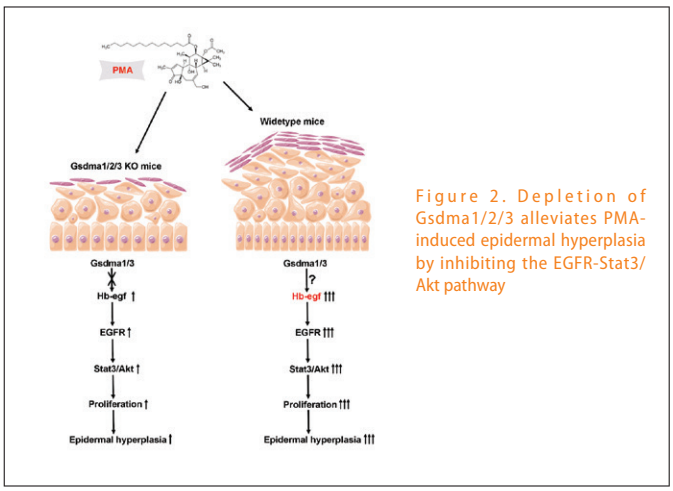

Figure 2. Depletion of Gsdma1/2/3 alleviates PMA-induced epidermal hyperplasia by inhibiting the EGFR-Stat3/Akt pathway

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1. Li, X., T. Zhang, L. Kang, R. Xin, M. Sun, Q. Chen, J. Pei, Q. Chen, X. Gao*, and Z. Lin*, Apoptotic caspase-7 activation inhibits non-canonical pyroptosis by GSDMB cleavage. Cell Death Differ, 2023. 30(9): p. 2120-2134.
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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. Rab8a as a mitochondrial receptor for lipid droplets in skeletal muscle

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

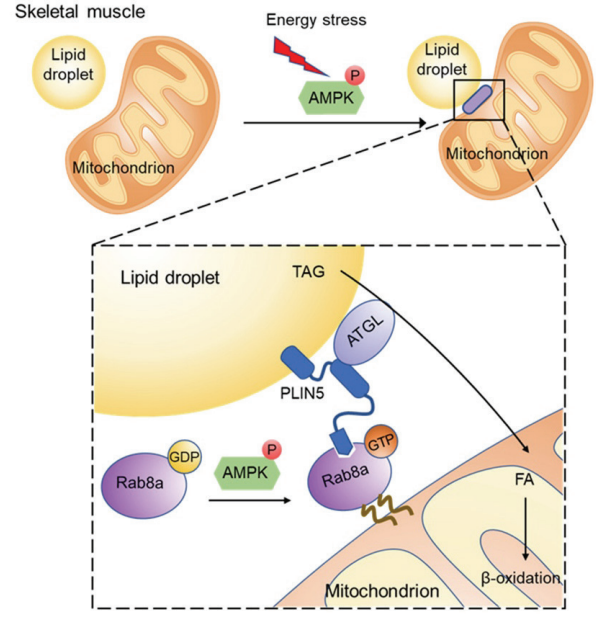

Figure 1 A model for Rab8a as a mitochondrial receptor for lipid droplets in skeletal muscle.

Selected Publications(* corresponding author)

1. Ouyang Q, Chen QL, Ke SY, Ding LF, Yang XY, Rong P, Feng WK, Cao Y, Wang Q, Li M, Su S, Wei W, Liu MJ, Liu J, Zhang X, Li JZ, Wang HY* and Chen S* (2023) Rab8a as a mitochondrial receptor for lipid droplets in skeletal muscle. Dev Cell 58, 289-305 (* corresponding authors)
2. Quan C, Zhu SS, Wang RZ, Chen JM, Chen QL, Li M, Su S, Du Q, Liu MJ, Wang HY* and Chen S* (2022) Impaired SERCA2a phosphorylation causes diabetic cardiomyopathy through impinging on cardiac contractility and precursor protein processing. Life Metabolism DOI: 10.1093/lifemeta/loac013 (* corresponding authors)
3. Zhu SS, Quan C, Wang RZ, Liang DR, Su S, Rong P, Zhou K, Yang XY, Chen QL, Li M, Du Q, Zhang JZ, Fang L, Wang HY* and Chen S* (2022) The RalGAPα1–RalA signal module protects cardiac function through regulating calcium homeostasis. Nat Commun 13: 4278 DOI: 10.1038/s41467-022-31992-z (* corresponding authors)
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9. Quan C, Li M, Du Q, Chen QL, Wang H, Campbell D, Fang L, Xue B, MacKintosh C, Gao X, Ouyang KF, Wang HY and Chen S* (2019) SPEG controls calcium re-uptake into the sarcoplasmic reticulum through regulating SERCA2a by its second kinase-domain. Circ Res 124(5): 712-726 (* corresponding author)

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Chao-Jun Li, Ph.D

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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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. Maternal and embryonic signals cause functional differentiation of luminal epithelial cells and receptivity establishment (Figure1)

Embryo implantation requires temporospatial maternal–embryonic dialog. Using single-cell RNA sequencing for the uterus from 2.5 to 4.5 day post coitum (dpc) and bulk sequencing for the corresponding embryos of 3.5 and 4.0 dpc pregnant mice, we found that estrogen-responsive luminal epithelial cells (EECs) functionally differentiated into adhesive epithelial cells (AECs) and supporting epithelial cells (SECs), promoted by progesterone. Along with maternal signals, embryonic Pdgfa and Efna3/4 signaling activated AECs and SECs, respectively, enhancing the attachment of embryos to the endometrium and furthering embryo development. This differentiation process was largely conserved between humans and mice. Notably, the developmental defects of SOX9-positive human endometrial epithelial cells (similar to mouse EEC) were related to thin endometrium, while functional defects of SEC-similar unciliated epithelial cells were related to recurrent implantation failure. Our findings provide insight into endometrial luminal epithelial cell development directed by maternal and embryonic signaling, which is crucial for endometrial receptivity.

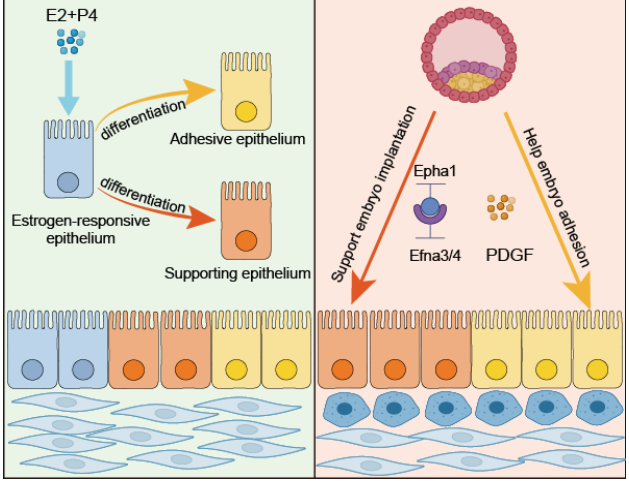

Figure1 The illustrated diagram showing maternal and embryo-derived signals in endometrium of mice during peri-implantation.

2. Ketone bodies promote epididymal white adipose expansion to alleviate liver steatosis in response to a ketogenic diet (Figure2)

Liver can sense the nutrient status and send signals to other organs to regulate overall metabolic homoeostasis. Herein, we demonstrate that ketone bodies act as signals released from the liver that specifically determine the distribution of excess lipid in epididymal white adipose tissue (eWAT) when exposed to a ketogenic diet (KD). An acute KD can immediately result in excess lipid deposition in the liver. Subsequently, the liver sends the ketone body β-hydroxybutyrate (BHB) to regulate white adipose expansion, including adipogenesis and lipogenesis, to alleviate hepatic lipid accumulation. When ketone bodies are depleted by deleting 3-Hydroxy-3-methylglutaryl-CoA synthase 2 (Hmgcs2) gene in liver, the enhanced lipid deposition in eWAT but not in inguinal white adipose tissue (iWAT) is preferentially blocked, while lipid accumulation in liver is not alleviated. Mechanistically, ketone body BHB can significantly decrease lysine acetylation of peroxisome proliferator-activated receptor gamma (PPARγ) in eWAT, causing enhanced activity of PPARγ, the key adipogenic transcription factor. These observations suggest that the liver senses metabolic stress first and sends a corresponding signal, that is, ketone body BHB, to specifically promote eWAT expansion to adapt to metabolic challenges.

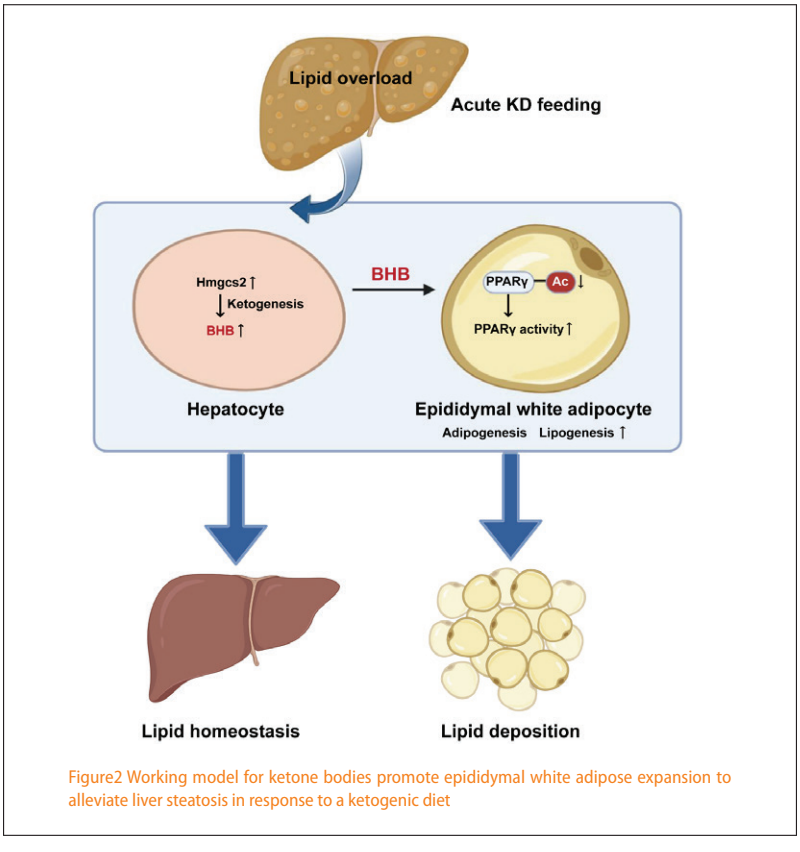

Figure2 Working model for ketone bodies promote epididymal white adipose expansion to alleviate liver steatosis in response to a ketogenic diet

3. Hepatic mevalonate pathway metabolite GGPP defineslipid metabolic difference between subcutaneous and visceral fatin MAO and MHO (Figure3)

Metabolically abnormal obesity (MAO) has a higher prevalence of hepatic steatosis, visceral fat (VISC) accumulation,cholesterol, and thus insulin resistance compared with metabolically healthy obesity (MHO). However, the mechanisms underlying such discrepancy between MAO and MHO have been unclear.By blood metabolome, fecal metabolome, and 16S gut microbiota sequencing, we found thatRuminococcus torques (R. torques) and mevalonolactone (MVL), a metabolitefrom the mevalonate pathway,as risk factors for insulin resistance, affect MAO occurrence. We found that MVL induces the nucleation of the transcription factor ZNF384, which binds as a transcription factor in the promoter region to initiate Ggps1 and Fdpsexpression. Overexpression of Fdps leads to elevated cholesterol in MAO. The aberrant overexpression of GGPS1 leads to the increasedisoprenoid geranylgeranyl pyrophosphate (GGPP)generation.In a protein prenylation-dependent manner, GGPP-dependent lipid droplet-associated protein-Perilipin4 prenylation enhances large lipid droplet formation, which augments hepatic lipid accumulation and insulin resistance. In a protein prenylation-independent manner, GGPP non-covalentlybinds and activatesacyl-CoA synthetase-ACSL1, inhibiting its translocation fromendoplasmic reticulumto mitochondrial to redirect the fate of fatty acids, which exaggerates lipid metabolic differences of VISC and SubQ followed by visceral fat accumulation.

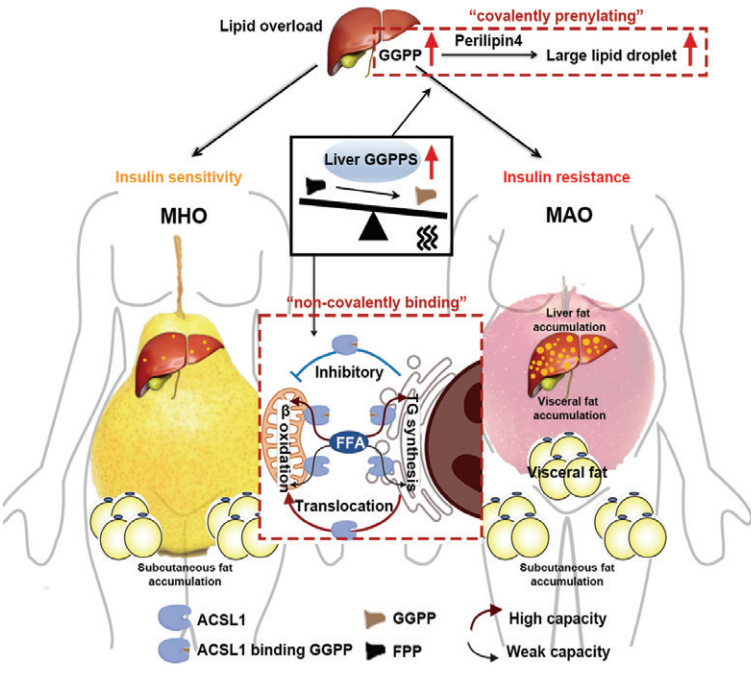

Figure3 Schematic for the contribution of the liver GGPP to MHO and MAO distinguishment via liver-adipose relay

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

1. Wu J, Bu D, Wang H, Shen D, Chong D, Zhang T, Tao W, Zhao M, Zhao Y, Fang L, Li P, Xue B, Li CJ. The rhythmic coupling of Egr-1 and Cidea regulates age-related metabolic dysfunction in the liver of male mice. Nat Commun. 2023 Mar 24;14(1):1634. doi: 10.1038/s41467-023-36775-8. PMID: 36964140; PMCID: PMC10038990.
2. Wang HQ, Liu Y, Li D, Liu JY, Jiang Y, He Y, Zhou JD, Wang ZL, Tang XY, Zhang Y, Zhen X, Cao ZW, Sheng XQ, Yang CF, Yue QL, Ding LJ, Hu YL, Hu ZB, Li CJ, Yan GJ, Sun HX. Maternal and embryonic signals cause functional differentiation of luminal epithelial cells and receptivity establishment. Dev Cell. 2023 Nov 6;58(21):2376-2392.e6. doi: 10.1016/j.devcel.2023.08.004. Epub 2023 Aug 28. PMID: 37643613.
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4. Jing J, Ouyang L, Zhang H, Liang K, Ma R, Ge X, Tang T, Zhao S, Xue T, Shen J, Ma J, Li Z, Wu J, Yang Y, Zhao W, Zheng L, Qian Z, Sun S, Ge Y, Chen L, Li C, Yao B. Omega-3 polyunsaturated fatty acids and its metabolite 12-HEPE rescue busulfan disrupted spermatogenesis via target to GPR120. Cell Prolif. 2023 Sep 24:e13551. doi: 10.1111/cpr.13551. Epub ahead of print. PMID: 37743695.
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6. Peng Wang#; Haifeng Sun#; GulisudumuMaitiabula#; Li Zhang;Jianbo Yang; Yupeng Zhang; Xuejin Gao; Jieshou Li; Bin Xue*; Chao-Jun Li*;Xinying Wang*.Total parenteral nutrition impairs glucose metabolism by modifying the gut microbiome. Nature Metabolism. 2023; 5(2):331-348; doi:10.1038/s42255-023-00744-8
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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.

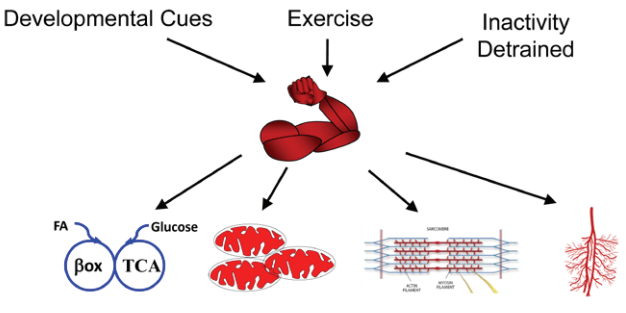

Fig 1. The muscle fitness is determined by developmental as well as physiological inputs. These inputs coordinately control the programs including fuel burning, mitochondrial ATP production, contraction, and angiogenesis.

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

Mitochondrial proteases are emerging as key regulators of mitochondrial plasticity and acting as both protein quality surveillance and regulatory enzymes by performing highly regulated proteolytic reactions. However, it remains unclear whether the regulated mitochondrial proteolysis is mechanistically linked to cell identity switching. Here we report that cold-responsive mitochondrial proteolysis is a prerequisite for white-to-beige adipocyte cell fate programming during adipocyte thermogenic remodelling. Thermogenic stimulation selectively promotes mitochondrial proteostasis in mature white adipocytes via the mitochondrial protease LONP1. Disruption of LONP1-dependent proteolysis substantially impairs cold- or β3 adrenergic agonist-induced white-to-beige identity switching of mature adipocytes. Mechanistically, LONP1 selectively degrades succinate dehydrogenase complex iron sulfur subunit B and ensures adequate intracellular succinate levels. This alters the histone methylation status on thermogenic genes and thereby enables adipocyte cell fate programming. Finally, augmented LONP1 expression raises succinate levels and corrects ageing-related impairments in white-to-beige adipocyte conversion and adipocyte thermogenic capacity. Together, these findings reveal that LONP1 links proteolytic surveillance to mitochondrial metabolic rewiring and directs cell identity conversion during adipocyte thermogenic remodelling (Fig. 2).

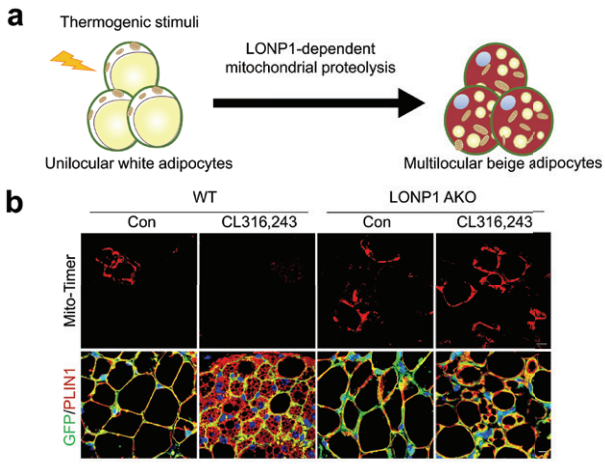

Fig 2. Proteolytic rewiring of mitochondria by LONP1 directs cell identity switching of adipocytes. LONP1 links proteolytic surveillance to mitochondrial metabolic rewiring and directs cell identity conversion during adipocyte thermogenic remodelling.

FNIP1 abrogation promotes functional revascularization of ischemic skeletal muscle by driving macrophage recruitment.

Ischaemia of the heart and limbs attributable to compromised blood supply is a major cause of mortality and morbidity. The mechanisms of functional angiogenesis remain poorly understood, however. Here we show that FNIP1 plays a critical role in controlling skeletal muscle functional angiogenesis, a process pivotal for muscle revascularization during ischemia. Muscle FNIP1 expression is down-regulated by exercise. Genetic overexpression of FNIP1 in myofiber causes limited angiogenesis in mice, whereas its myofiber-specific ablation markedly promotes the formation of functional blood vessels. Interestingly, the increased muscle angiogenesis is independent of AMPK but due to enhanced macrophage recruitment in FNIP1-depleted muscles. Mechanistically, myofiber FNIP1 deficiency induces PGC-1α to activate chemokine gene transcription, thereby driving macrophage recruitment and muscle angiogenesis program. Furthermore, in a mouse hindlimb ischemia model of peripheral artery disease, the loss of myofiber FNIP1 significantly improved the recovery of blood flow. Thus, these results reveal a pivotal role of FNIP1 as a negative regulator of functional angiogenesis in muscle, offering insight into potential therapeutic strategies for ischemic diseases (Fig. 3).

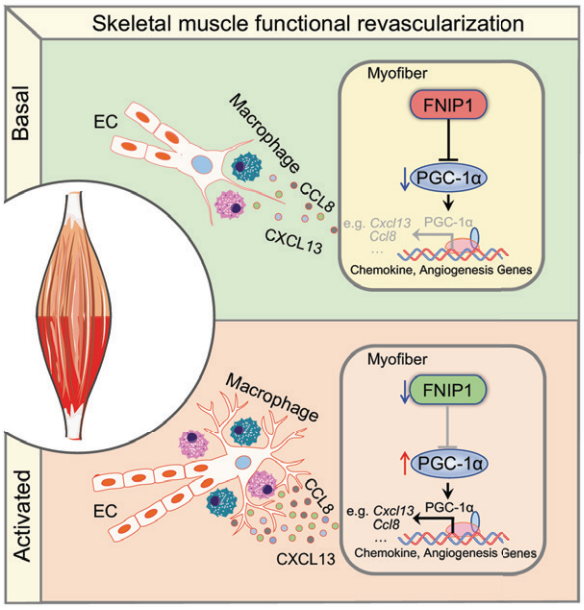

Fig 3. FNIP1 abrogation promotes functional revascularization of ischemic skeletal muscle by driving macrophage recruitment.

Myofiber FNIP1 deficiency induces PGC-1α to activate chemokine gene transcription, thereby driving macrophage recruitment and muscle angiogenesis program. FNIP1 as a negative regulator of functional angiogenesis in muscle, offering insight into potential therapeutic strategies for ischemic diseases.

Selected publications

1. Fu T #, Sun W#, Xue J#, Zhou Z#, Wang W, Guo Q, Chen X, Zhou D, Xu Z, Liu L, Xiao L, Mao Y, Yang L, Yin Y, Zhang XN, Wan Q, Lu B, Chen Y, Zhu MS, Philipp E. Scherer, Fang L, Piao HL, Shao M* and Gan Z*. Proteolytic rewiring of mitochondria by LONP1 directs cell identity switch of adipocytes. Nat Cell Biol. 2023; 25(6):848-864.
2. Sun Z#, Yang L#, Kiram Abdukahar#, Yang J#, Yang Z, Xiao L, Yin Y, Liu J, Mao Y, Zhou D, Yu H, Zhou Z, Xu D, Jia Y, Ding C, Guo Q, Wang H, Li Y, Wang L, Fu T*, Hu S* and Gan Z*. FNIP1 abrogation promotes functional revascularization of ischemic skeletal muscle by driving macrophage recruitment. Nat Commun. 2023;14(1):7136.
3. Yin Y#, Xu D#, Mao Y#, Xiao L, Sun Z, Liu J, Zhou D, Xu Z, Liu L, Fu T, Ding C, Guo Q, Sun W, Zhou Z, Yang L, Jia Y, Chen X, Gan Z*. FNIP1 regulates white adipose tissue browning and systemic glucose homeostasis by shaping intracellular calcium dynamics. J Exp Med. 2022; 219(5): e20212491.
4. Xu Z#, Fu T#, Guo Q#, Zhou D, Sun W, Zhou Z, Chen X, Zhang Z, Liu L, Xiao L, Yin Y, Jia Y, Pang E, Chen Y, Pan X, Fang L, Zhu M, Fei W, Lu B, Gan Z*. Disuse-associated loss of the protease LONP1 in muscle impairs mitochondrial function and causes reduced skeletal muscle mass and strength. Nat Commun. 2022; 13(1):894.
5. Guo Q#, Xu Z#, Zhou D, Fu T, Wang W, Sun W, Xiao L, Liu L, Ding C, Yin Y, Zhou Z, Sun Z, Zhu Y, Zhou W, Jia Y, Xue J, Chen Y, Chen XW, Piao HL, Lu B, Gan Z*. Mitochondrial proteostasis stress in muscle drives a long-range protective response to alleviate dietary obesity independently of ATF4. Science Advances. 2022; 8(30): eabo0340.
6. He S, Fu T, Yu Y, Liang Q, Li L, Liu J, Zhang X, Zhou Q, Guo Q, Xu D, Chen Y, Wang X, Chen Y, Liu J, Gan Z*and Liu Y*. IRE1α regulates skeletal muscle regeneration through Myostatin mRNA decay. J Clin Invest. 2021;131(17): e143737.
7. Xiao L, Liu J, Sun Z, Yin Y, Mao Y, Xu D, Liu L, Xu Z, Guo Q, Ding C, Sun W, Yang L, Zhou Z, Zhou D, Fu T, Zhou W, Zhu Y, Chen XW, Li J, Chen S, Xie X, Gan Z*. AMPK-dependent and -independent coordination of mitochondrial function and muscle fiber type by FNIP1. PLoS Genet. 2021; 17(3):e1009488.
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9. Liu L, Cai J, Wang H, Liang X, Zhou Q, Ding C, Zhu Y, Fu T, Guo Q, Xu Z, Xiao L, Liu J, Yin Y, Fang L, Xue B, Wang Y, Meng ZX, He A, Li JL, Liu Y, Chen XW*, Gan Z*. Coupling of COPII vesicle trafficking to nutrient availability by the IRE1a-XBP1s axis. Proc Natl Acad Sci USA. 2019;116(24):11776-11785.

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Mechanisms of metabolic disorder

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

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

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

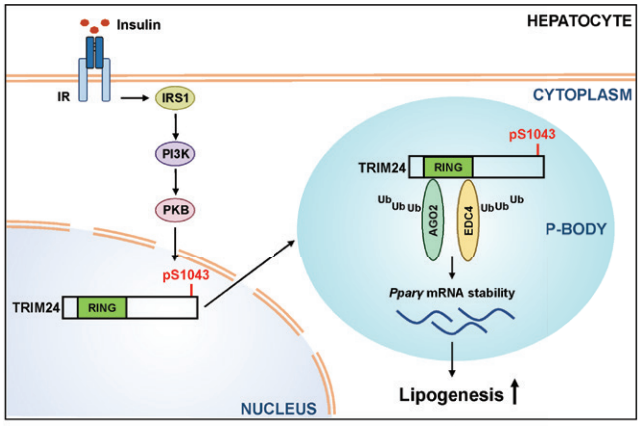

Figure 1 TRIM24 as an insulin-responsive regulator of P-bodies.

Selected publications:

1. Ouyang Q, Chen QL, Ke SY, Ding LF, Yang XY, Rong P, Feng WK, Cao Y, Wang Q, Li M, Su S, Wei W, Liu MJ, Liu J, Zhang X, Li JZ, Wang H-Y and Chen S*. (2023) Rab8a as a mitochondrial receptor for lipid droplets in skeletal muscle. Developmental Cell. 58 (4): 289-305 DOI:https://doi.org/10.1016/j.devcel.2023.01.007
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3. Zhu SS, Quan C, Wang RZ, Liang DR, Su S, Rong P, Zhou K, Yang XY, Chen QL, Li M, Du Q, Zhang JZ, Fang L, Wang H-Y* and Chen S* (2022) The RalGAPα1–RalA signal module protects cardiac function through regulating calcium homeostasis. Nat Commun 13: 4278 DOI: 10.1038/s41467-022-31992-z (* corresponding authors)
4. Wei W, Chen QL, Liu MJ, Sheng Y, OuYang Q, Feng WK, Yang XY, Ding LF, Su S, Zhang JZ, Fang L, Vidal-Puig A, Wang H-Y* and Chen S* (2022) TRIM24 is an insulin-responsive regulator of P-bodies. Nat Commun 13: 3972 DOI: 10.1038/s41467-022-31735-0 (* corresponding authors)
5. Yang XY, Chen QL, Ouyang Q, Rong P, Feng WK, Quan C, Li M, Jiang Q, Liang H, Zhao T-J, Wang H-Y* and Chen S*. Tissue-Specific Splicing and Dietary Interaction of a Mutant As160 Allele Determine Muscle Metabolic Fitness in Rodents. 2021 Diabetes Aug; 70(8): 1826-1842.
6. Chao Q, Qian D, Min L, Wang R, Ouyang Q, Su S, Zhu S, Chen Q, Sheng Y, Chen L, Wang H, Campbell DG, MacKintosh C, Yang ZZ, Ouyang KF, Wang H-Y* and Chen S*. A PKB-SPEG signaling nexus links insulin resistance with diabetic cardiomyopathy by regulating calcium homeostasis. 2020. Nature Comm. volume 11, Article number: 2186
7. Li M, Quan C, Chen S*, Wang H-Y*. The 14-3-3 protein is an essential component of cyclic AMP signaling for regulation of chemotaxis and development in Dictyostelium. https://doi.org/10.1016/j.cellsig.2020.109739
8. Chen Q, Rong P, Xu DJ, Chen L, Xie B, Sheng Y, Li P, Wang H-Y* and Chen S*. (2017) Muscle-specific Rab8a deletion impairs lipid uptake and storage in skeletal muscle and causes hyperlipidemia and hepatosteatosis in mice. Diabetes. 66(9):2387-2399. (*corresponding author)
9. Chen Q, Xie B, Zhu S, Rong P, Sheng Y, Ducommun S, Chen L, Quan C, Li M, Sakamoto K, MacKintosh C, Chen S* and Wang H-Y* (2016) A TBC1D1Ser231Ala knockin mutation partially impairs 5-aminoimidazole-4-carboxamide-1-ß-D-Ribofurano-side- but not exercise-induced muscle glucose uptake in mice. Diabetologia 60(2): 336-345 (*corresponding author)

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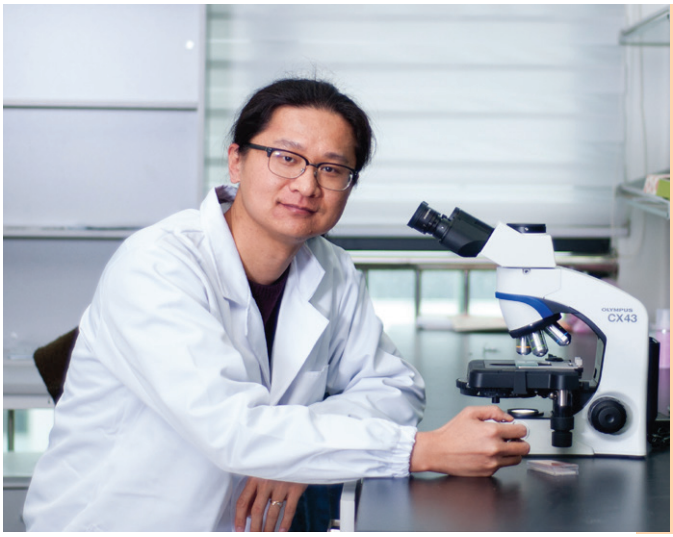

Yan LI Ph.D.

Dr. Yan Li received his Ph.D. degree from MIT in 2012 under the Singapore-MIT alliance program with supervision of Professor Jianzhu CHEN. From 2012 to 2016, he completed his post-doctoral training with Prof. James DI SANTO at Institute Pasteur, Paris. He worked as an assistant researcher at Institute Pasteur from 2016 to 2018. In 2018, he became a full professor of Nanjing University and a principal investigator at the State Key Laboratory of Pharmaceutical Biotechnology. In 2019, he was qualified as a doctoral advisor, also a principal investigator of the Chemistry and Biomedicine Innovation Center. He is awarded as Jiangsu Provincial "Innovative and Entrepreneurial Talent " and "Distinguished Professor", and received the grant support from the National Key R&D Program Youth Program (formerly the Youth 973 Program). In 2020, he was awarded the leading talent of Jiangsu Innovative and Entrepreneurial Team Program. In 2021, he was supported by National Science Fund for Excellent Young Scholars. In 2023, he assumed the position of director at Model Animal Research Center at Nanjing University, and is dedicated to advancing scientific research and facilitating the transformation of research findings by leveraging the institute's strengths in model animal research. His research has been published in prestigious journals such as Cell, Nature Methods, Nature Cancer, ACS Nano, Science Advances, Nature Communications, etc. He has been invited for presentation at international conferences for 10 times, and filed one international and 4 domestic patent applications. Dr. Yan Li is currently a member of the Immune Cell Branch of the Chinese Society of Cell Biology, a member of the Chinese Anti-Cancer Association, a board member of the Jiangsu Society of Cell and Developmental Biology. He is also an associate editor of the Frontiers in Immunology humanized mouse topic, and a member of the Scientific Committee of the International Workshops on Humanized Mice. In addition, he also reviews manuscripts for journals such as Nature Communications, Cellular and Molecular Immunology, PNAS, Science Bulletin, European Journal of Immunology, and Frontiers in Immunology.

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Next-generation humanized mouse models for translational medicine

900 million years ago, the primates and rodents diverged onto different branches of the evolutionary tree. Today, we still rely on rodents to model and understand human biology, despite the vast species differences leading to only a fraction of drugs designed and validated in mice passing clinical trials. Therefore, our lab is dedicated to constructing novel humanized mouse models to directly reveal the patterns of human disease occurrence and develop corresponding therapies. Our current research focuses on four main areas:

1.Development and function of the human hematopoietic system lineage

Upon transplantation of hematopoietic stem cells into immunodeficient mice, various human immune cell subgroups, including T cells and B cells, can be reconstituted in the host organism. However, certain human cell subgroups, such as red blood cells and granulocytes, do not effectively develop within humanized mice, preventing corresponding research on their development and function. To address this issue, we have developed new mouse strains and techniques to promote the development of these cells in mice and explore the similarities and differences between human and murine hematopoietic systems. For example:

1. We successfully reconstructed the largest human immune cell subgroup, neutrophils, in humanized mice and studied the nature and origin of tumor-associated immunosuppressive neutrophils using clinical samples, as well as their regulatory role in bone environment homeostasis.

2. By supplementing stromal cells, we improved human red blood cell development in humanized mice, leading to the creation of a humanized mouse model with high-level human red blood cell reconstitution. This model has been applied to research on diseases related to human red blood cells, such as malaria infection and thalassemia.

3. We discovered that immune cells resident in the fetal-maternal interface tissues have unique origins, spatiotemporal characteristics, and functions.

2.Drug and vaccine development evaluation for infectious diseases and tumors

Since the 20th century, scientists have discovered that tumor-infiltrating lymphocytes in cancer patients' tumors have the ability to kill tumors in vitro. When these cells were reintroduced into the bodies of some cancer patients, a partial alleviation of the disease was observed. Pioneering this approach, Professor Steven Rosenberg later developed TCR T-cell therapy, which showed promising results in melanoma patients. However, efforts to utilize humanized mice to screen for potent TCRs targeting different tumor antigens have not been successful due to low efficiency of antigen-specific immune responses. Similarly, although humanized mice possess a complete spectrum of human B cell development, antigen-specific humoral immune responses have consistently failed to reach levels similar to those in human. Consequently, obtaining human TCRs or full human antibodies still relies heavily on human sources or genetically humanized animals, which are highly limited. Therefore, we focus on identifying means to effectively activate antigen-specific responses in humanized mice, while improving the interaction between stromal and immune cells within their immune organs. This would enable humanized mice to serve as a platform for obtaining full human monoclonal antibodies and TCRs, as well as for evaluating treatment methods such as vaccines. Currently, our breakthrough research directions include:

1. Redesigning immunogens to effectively activate antigen-specific B cell responses in humanized mice, leading to the acquisition of monoclonal antibodies targeting specific antigens and establishing a platform for obtaining full human monoclonal antibodies.

2. Optimizing the cytokine environment and antigen presentation efficiency to facilitate expansion of TCRs targeting tumor antigens within humanized mice, thereby obtaining potent tumor-killing TCR T-cells.

3.Human disease modeling and treatment of tumors/autoimmune diseases

The combination of patient-derived xenografts (PDX or CDX) with humanized mice has been widespread used in tumor immunotherapy, particularly in the application of immune checkpoint antibodies and CAR-T cell therapy. However, for autoimmune diseases such as systemic lupus erythematosus (SLE), the lack of animal models that can simulate clinical disease manifestations and drug targets has been a hindrance to new drug development despite entering the era of immunotherapy. With our optimized novel humanized mouse models, we can:

1. Explore novel tumor immunotherapy methods and detection techniques, such as multi-specific antibody immunotherapy, novel oncolytic viruses, and in vivo cytokine probes.

2. Successfully establish a humanized model of SLE, fully reproducing clinical pathological features and developing new targeted treatment strategies.

4.Next generation of humanized mouse models: immune system + x

Not only the immune system, but research on various organ tissues is also limited by traditional mouse models. For example, several human viruses or bacteria cannot infect mouse stromal cells, or if they can infect, they may exhibit pathological features inconsistent with clinical observations. Additionally, the gut microbiota plays a crucial role in immune cell development and function, and both mice and humans have significant differences in their microbiota and immune systems. Based on this, the humanized mouse model of the immune system is just the beginning; we aim to continue engrafting human organs and microbiota into mice to reduce the use of traditional experimental animals and achieve the goal of simulating clinical responses more accurately. For instance:

1. Building an immunodeficient/human liver dual-sourced mouse model by transplanting human liver cells into mice with liver damage based on the humanized mouse model of the immune system. This will serve as a research platform for the pathology, vaccines, and drug development for liver diseases such as viral hepatitis.

2. Creating a lung/immune system dual-sourced mouse model by engrafting human fetal lung tissue into the humanized mouse model of the immune system for investigating respiratory pathogen infections, further enabling the screening of antiviral drugs and vaccine development and evaluation.

3. Investigating the regulation of the microbiota and its metabolites on human immune cell development and function by depleting or disrupting the gut microbiota of humanized mice, or by transplanting human microbiota.

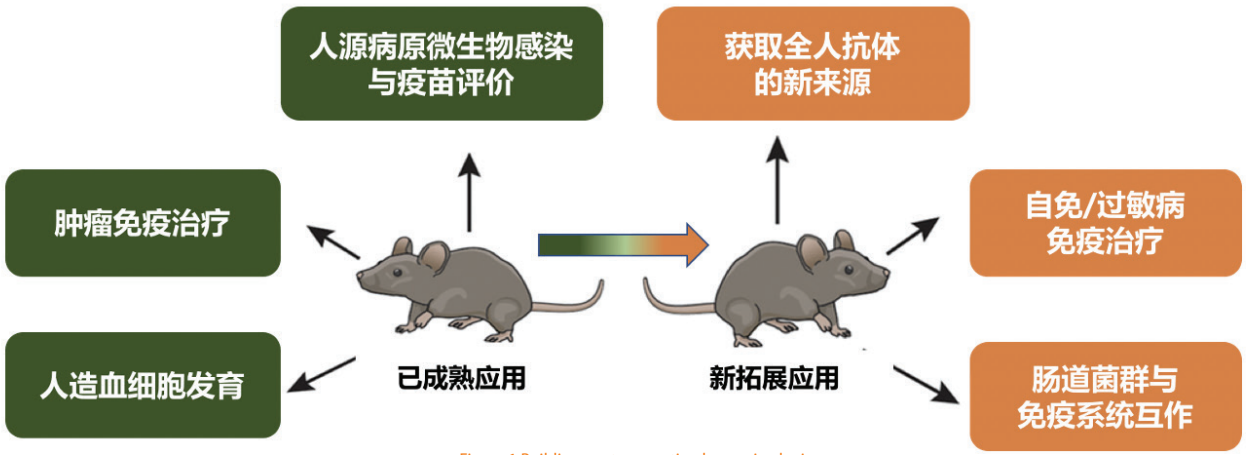

Figure 1 Building next generation humanized mice

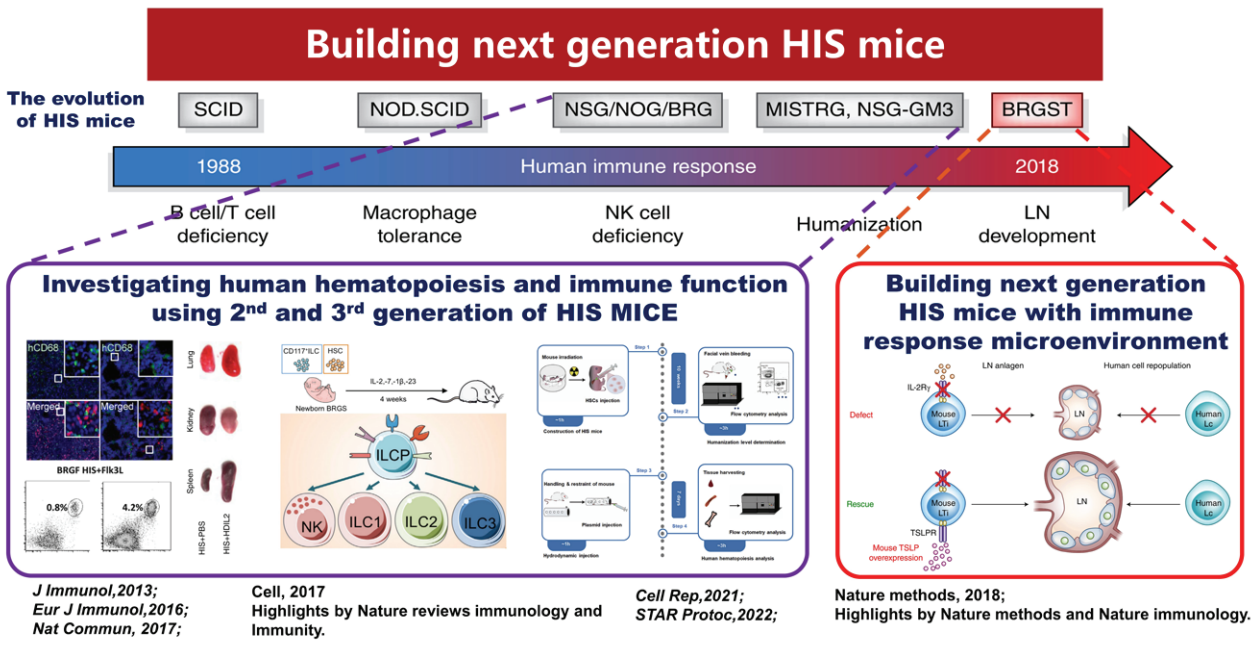

Figure 2 Current research fields in the laboratory

Selected Publications

1. Xiangyu Chen, Jing Zhao, Shuai Yue, Ziyu Li, Xiang Duan, Yao Lin, Yang Yang, Leiqiong Gao, Zhiwei Pan, Xiaofan Yang, Xingxing Su, Min Huang, Xiao Li, Ye Zhao, Xuehui Zhang, Zhirong Li, Li Hu, Jianfang Tang, Yaxing Hao, Qin Tian, Yifei Wang, Lifan Xu, Qizhao Huang, Yingjiao Cao, Yaokai Chen, Bo Zhu, Yan Li, Fan Bai, Guozhong Zhang, Lilin Ye (2023). Targeting tumor cells toward the antigenic specificity of bystander T cells in tumor microenvironment potentiates cancer immunotherapy. Nature Cancer. Accepted.
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Zhaoyu Lin, Ph.D.

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

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Immune and metabolic regulation of physical homeostasis

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

We focus on a new discovered immunoregulatory protein family-Gasdermin. Our lab analyzed the roles of Gasdermin family in physical status and autoimmune diseases. Gsdmd and Gsdme are demonstrated to be the executors of pyroptosis, which is a type of pro-inflammatory programmed cell death. We discovered that Gasdermin directly trigger cell death and inflammation in 2015. Our recent works are mainly about the regulation of Gsdmd in pyroptosis (Figure 1). We found that inhibition of ROS reduces

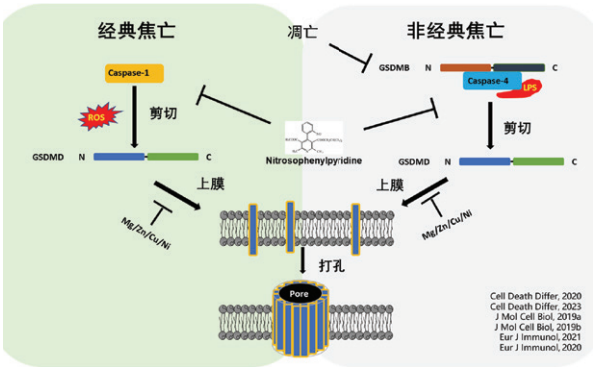

Figure 1. Gsdmd could be the target to block pyroptosis in autoimmune diseases

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 (Figure 2).

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

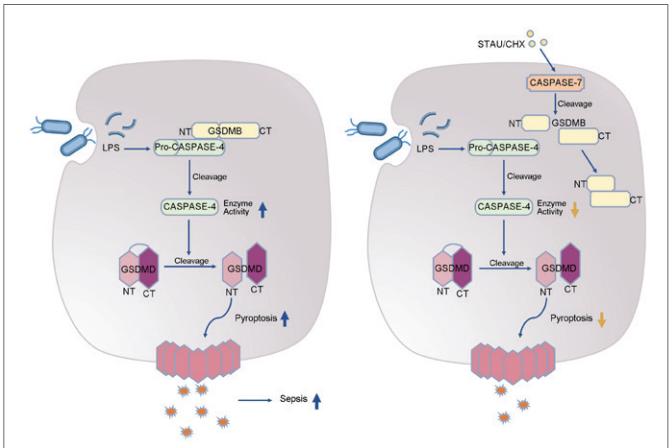

Figure 2. Apoptotic caspase-7 activation inhibits non-canonical pyroptosis by GSDMB cleavage

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 3).

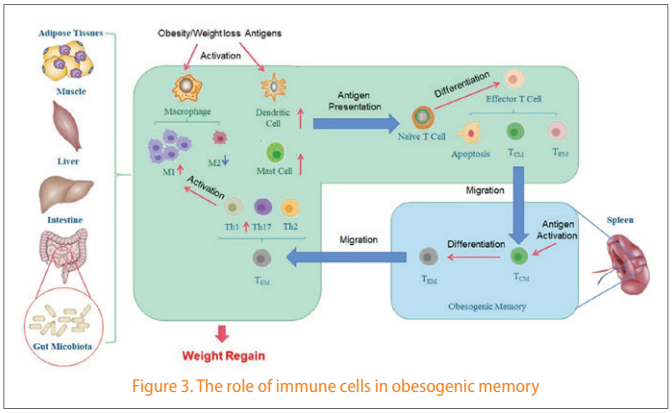

Figure 3. The role of immune cells in obesogenic memory

Selected Publications

1. Li, X., T. Zhang, L. Kang, R. Xin, M. Sun, Q. Chen, J. Pei, Q. Chen, X. Gao*, and Z. Lin*, Apoptotic caspase-7 activation inhibits non-canonical pyroptosis by GSDMB cleavage. Cell Death Differ, 2023. 30(9): p. 2120-2134.
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4. Chen, Q., J. Zheng, D. Wang, Q. Liu, L. Kang, X. Gao*, and Z. Lin*, Nitrosonisoldipine is a selective inhibitor of inflammatory caspases and protects against pyroptosis and related septic shock. Eur J Immunol, 2021. 51(5): p. 1234-1245.
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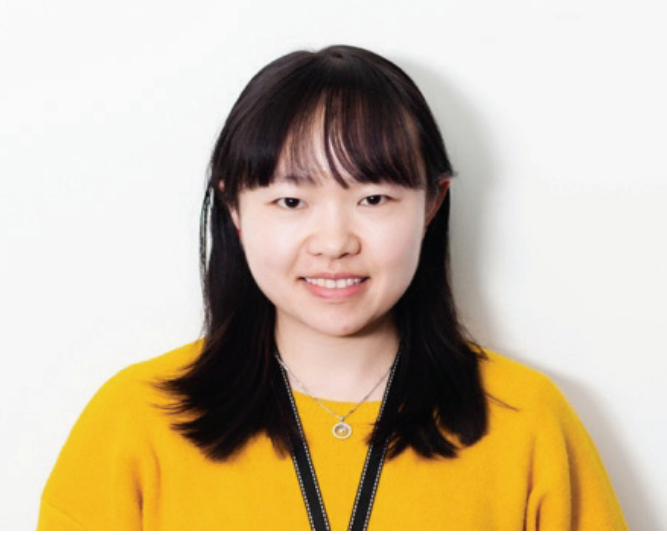

Qiaoli Chen, Ph.D.

Dr. Qiaoli Chen received her Ph.D. degree from Nanjing University in 2017. She joined MARC of Nanjing University as an associate researcher from 2018 to 2023. Dr. Chen established research group as a principle investigator and an assistant professor in Metabolic Physiology in 2023. She was selected as a "Double Creation Doctor" by Jiangsu Province in 2009. She currently serves as Director of the Technical Center at the Model Animal Research Institute, and also serves as Youth Director of the Metabolic Biology Society, Chinese Physical Society.

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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. 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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Tingting Fu, Ph.D.

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

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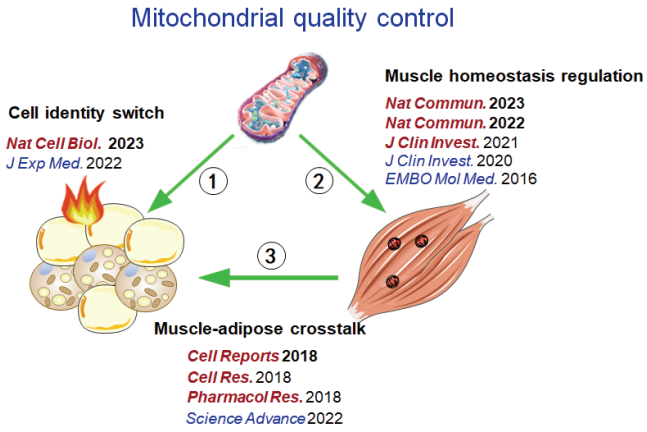
The physiological function and mechanism of mitochondrial quality control

Mitochondria are the essential organelles to generate energy and maintain the homeostasis of metabolic microenvironment. The quality of mitochondria is essential for maintaining metabolic homeostasis during adaptive stress responses. Dr. Fu's research focus on mitochondrial physiological relevance and molecular working mechanisms of mitochondrial quality control. Mitochondrial proteases serve as the first-line quality control by selective targeting and removal of damaged or dysfunctional mitochondrial protein to maintain proper function of mitochondria. Dr. Fu's group found that skeletal muscle LONP1-regulated mitochondrial protein homeostasis control muscle mass and function. Dr. Fu's recent work found that LONP1 links proteolytic surveillance to mitochondrial metabolic rewiring and directs cell identity conversion during adipocyte thermogenic remodelling.



Selected Publications

1. Fu T*, Sun W*, Xue J*, Zhou Z*, Wang W, Guo Q, Chen X, Zhou D, Xu Z, Liu L, Xiao L, Mao Y, Yang L, Yin Y, Zhang X, Wan Q, Lu B, Chen Y, Zhu M, Scherer PE, Fang L, Piao H, Shao M#, Gan Z#. Proteolytic rewiring of mitochondria by LONP1 directs cell identity switching of adipocytes. Nature Cell Biology. 2023; Jun;25(6):848-864.
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8. Liu L*, Ding C*, Fu T, Feng Z, Lee JE, Xiao L, Xu Z, Yin Y, Guo Q, Sun Z, Sun W, Mao Y, Yang L, Zhou Z, Zhou D, Xu L, Zhu Z, Qiu Y, Kai G, Gan Z#. Histone methyltransferase MLL4 controls myofiber identity and muscle performance through cooperating with MEF2. J Clin Invest. 2020; 130(9): 4710-4725.

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

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

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

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

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

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

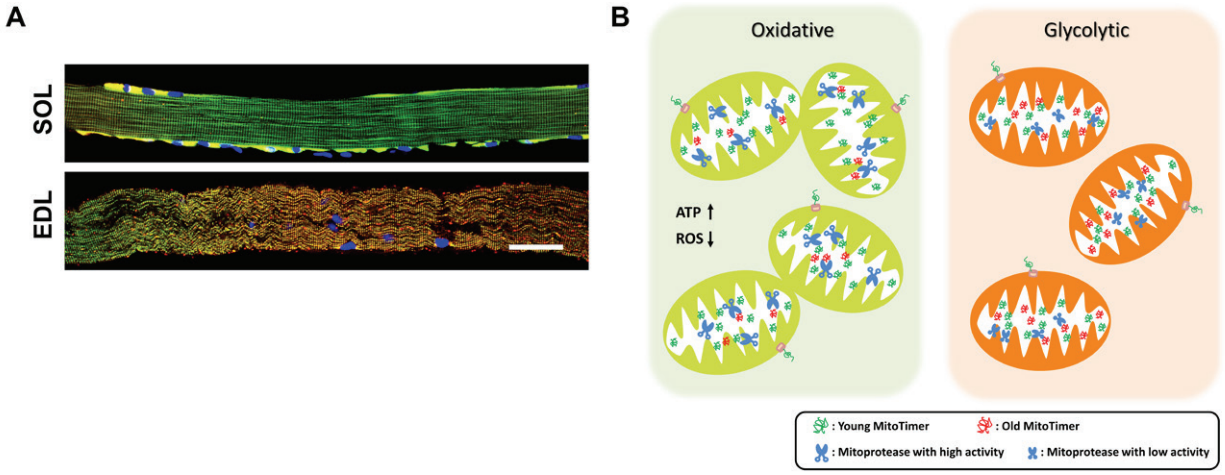

Figure 1. MitoTimer fluorescence reveals an active mitochondrial state tightly coupled with mitoproteolysis in the mouse oxidative skeletal muscle fibers.

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

Selected Publications

1. Xie YY#, Zhang YN#, Sun AN#, Peng YM, Hou WK, Xiang C, Zhang GX, Lai BB, Hou XS, Zheng FF, Wang F and Liu G*. The coupling of mitoproteolysis and oxidative phosphorylation enables tracking of an active mitochondrial state through MitoTimer fluorescence. Redox Biology 2022, 56,102447.
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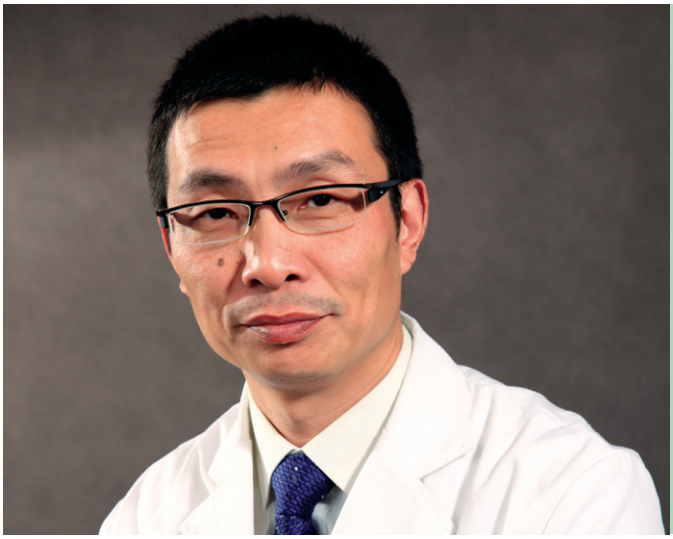

Qing Jiang Ph.D., M.D.

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

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

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Etiology and treatment of skeletal diseases

Tissue engineering scaffolds have presented effective value in bone repair. However, the integration of the diverse components, complex structures, and multifunction to impart the scaffolds with improved applicability is still a challenge.

Herein, a serial of macroscopic one-particle thick superlattice films generated by selfassembly of diverse size of gold nanoparticles (GNPs) were termed as SFGs and were considered as bioactive implant coatings for enhancing osseo-integration. Considering the universal applicability of SFGs for depositing on various substrates, these SFGs with enhanced osseo-integration capabilities could serve as a bioactive platform for surface modification of orthopedic implants, effectively addressing the issue of aseptic loosening (Zhuang, 2023). Furthermore, Sporopollenin exine capsules (SECs), extracted from plant pollen, are emerging as attractive and natural microcapsules for a wide range of bio-composite applications. We create SECs with increased surface hydrophilicity coated by polypeptide multilayer films using layer-by-layer (LbL) self-assembly technology. Our findings demonstrate that LbL modification of SECs improves their functional properties and has broad implications across bio-composite applications. (Zhou, 2023). In addition, we propose a novel fish-derived scaffold combined with photothermal therapy and mesenchymal stem cells (MSCs) to promote bone regeneration. The fish-derived scaffold is composed of the decellularized fish scale and gelatin methacrylate synthesized from fish gelatin (fGelMA), which can promote the proliferation and osteogenesis of MSCs with no obvious immunological rejection. Our study suggest that the fish-derived scaffold, photothermal therapy, and MSCs-based regenerative therapy is a promising clinical strategy in bone regeneration (Shen, 2023).

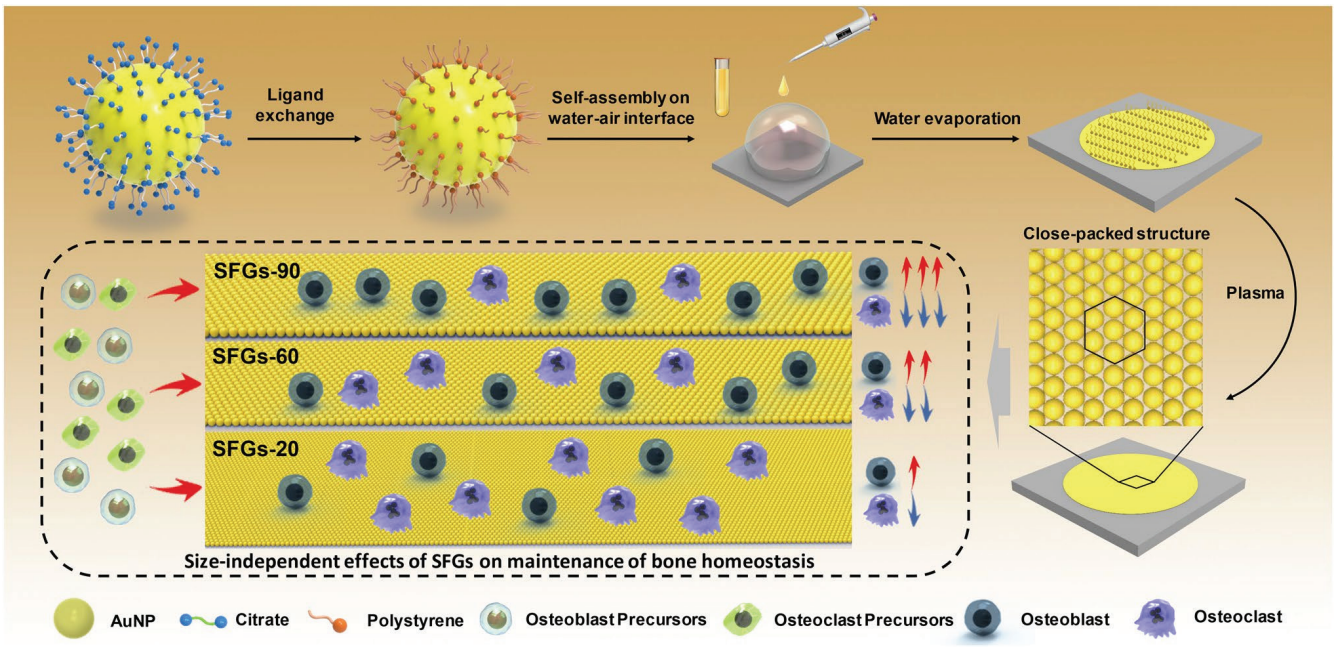

Figure 1. Schematic of the preparation of SFGs for positive maintenance of bone homeostasis

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1. Zhuang Z, Li Z, Gong G, Li Q, Zhang Y, Huang C, Huang Y, Tian L, Wang P*, Guo Z*, Jiang Q*: Two-dimensional superlattice films of gold nanoparticle-polystyrene composites: a bioactive platform for bone homeostasis maintenance. Advanced Composites and Hybrid Materials 2023, 6(5):166. (IF: 20.1, 中科院分区一区)
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Genetic rewiring of immune regulation

In recent years, our laboratory has been devoted to development of new genetic tools (based on the principle of synthetic biology and genome editing) to accurately reprogram cell functions. Owing to our past research background, we focus on the applications to rewire immune regulation.

The complex interface of tumor and immunity presents a highly dynamic system that is key to disease progression and cancer treatment. By currently focusing on developing novel genetic tools, we are hoping to later establish novel approaches to reinvigorate tumor-specific immune surveillance. 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. Synthetic immune rewiring:

Genetic rewiring of immune regulation holds great promise to improve cell-based therapies. For instance, in engineered T cells harboring the chimeric antigen receptor (CAR), such rewiring may aid CAR-T cells to mobilize other "helper" immune cells toward the eventual tumor eradication (Fig. 1A). The cutting-edge prime editing (PE) technology is well suited for enabling genetic rewiring. We and collaborators have recently developed a more efficient version of PE (xrPE). It can drive precise genetic modifications in a readily reversible manner (Fig. 1B, C). Furthermore, our collaborative team has also integrated the PE-specialized editing mechanism with Cas9's dsDNA nuclease activity, to establish a highly active uPEn platform. Attributed to the adoption of a regulatory protein module, the uPEn showed marked improvements in "copying" accuracies (Fig. 1D, E). In comparison to other state-of-the-art platforms, the uPEn features superior efficiencies for precise edits, despite also causing certain levels of undesirable indels (Fig. 1F, G). 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. Equipped with these recently developed toolkit, we will actively screen and install immune-regulatory genetic elements in cells.

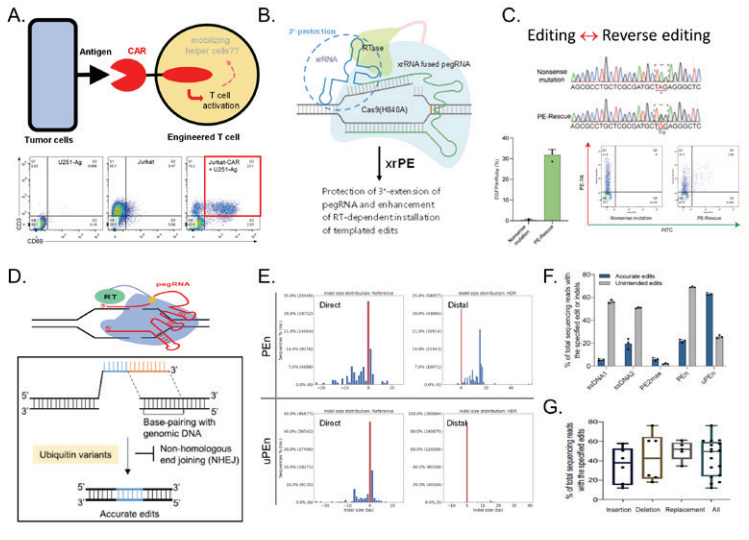

Figure 1: Synthetic immune rewiring.

(A) A scheme shows the notion of CAR-T functional potentiation by immune-rewiring. (B and C) The xrPE platform is further applied to precisely install primary and reverse mutations in cells. (D-G) The uPEn platform is based on the previous PEn tool that integrates DSB induction and the "copying" mechanisms to allow genetic knock-ins. The uPEn further adopts a protein regulator of DSB repair that drives more accurate installation of reverse-transcribed edits into the target site. For knock-in efficiencies, uPEn compares quite favorably to canonical PE, PEn, and the CRISPR/HDR approach.

2. Immune defense and tolerance:

This year marks our temporary conclusion of this topic due to non-scientific reasons. Type I IFNs are a family of ligands induced by a variety of innate immunity-activating stimuli (Fig. 2A). They act to fight against viral infections, to prevent "unscheduled" engagement of inflammatory response, and to participate in tumor immune surveillance. Nevertheless, IFN-Is are also known to drive several devastating immunopathologies. It was clear that our understandings to such pleiotropic cytokines were incomplete. Several years ago, we identified an IFN-I-induced immunotolerant axis operating along with its immunostimulatory actions (Fig. 2B). Such an axis requires IFN-I signaling in monocytes, the precursor to mature macrophages. An ensuing induction of IL-4/IL-6 in monocytes and their cooperative paracrine actions on the mature macrophages drive the latter cells into an M2-polarized state. In addition, we find that the IFN-I-to-IL-4/IL-6 axis thwarts the anti-tumor function by IFN-I in mice. Collectively, we believe that this immunotolerant axis underscores the double-faced immune actions by IFN-I.

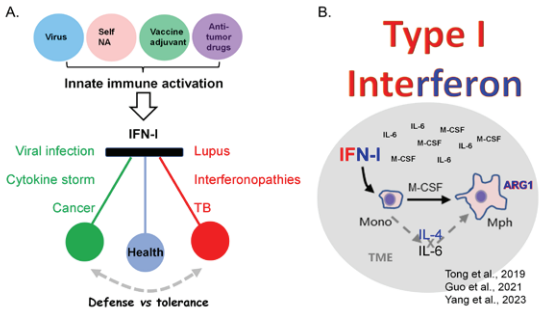

Figure 2: Immune defense and tolerance.

(A) The IFN-I family of ligands can be induced by a variety of stimuli. They drive anti-viral defense and tumor immune surveillance. On the other hand, they underlie a number of severe immunopathologies (B) We uncover an immune-tolerant axis by IFN-I that operates along with its immunostimulatory actions. Such axis thwarts the anti-tumor effects by IFN-I in mice.

Selected publications: (*corresponding author)

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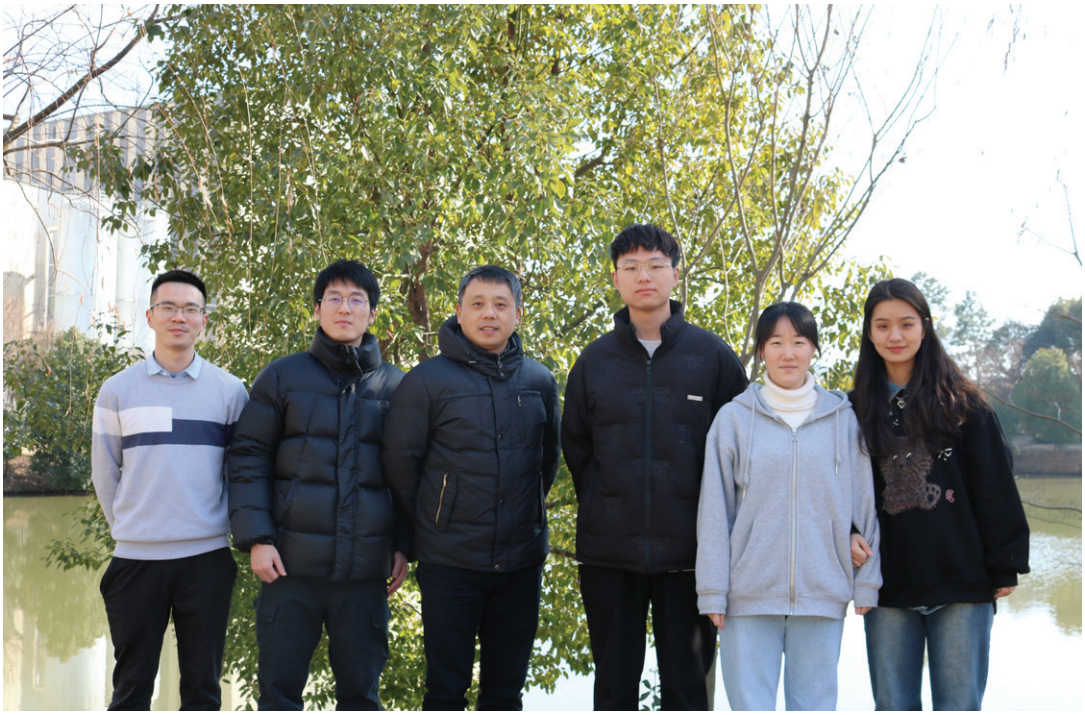

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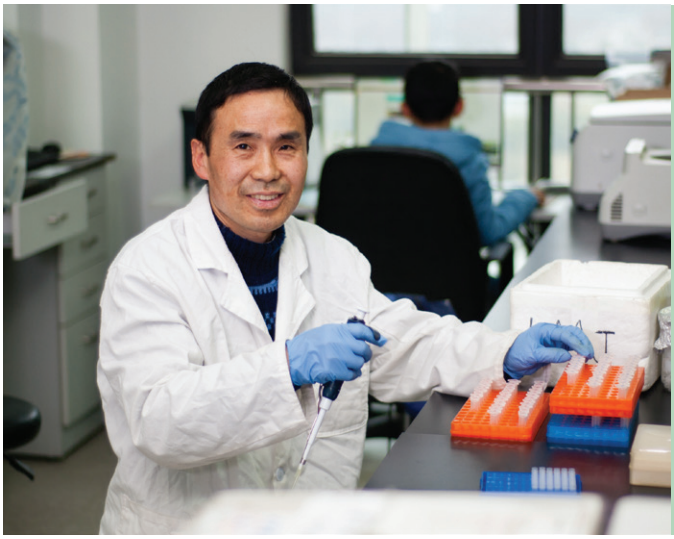

Jinzhong Qin , Ph.D.

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

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

1. Mga safeguards embryonic stem cells from acquiring extraembryonic endoderm fates.

Polycomb group (PcG) proteins form multiprotein complexes that affect stem cell identity and fate decisions by still largely unexplored mechanisms. Here, by performing a CRISPR-based loss-of-function screen in embryonic stem cells (ESCs), we identify PcG gene Mga involved in the repression of endodermal transcription factor Gata6. We report that deletion of Mga results in peri-implantation embryonic lethality in mice. We further demonstrate that Mga-null ESCs exhibit impaired self-renewal and spontaneous differentiation to primitive endoderm (PE). Our data support a model in which Mga might serve as a scaffold for PRC1.6 assembly and guide this multimeric complex to specific genomic targets including genes that encode endodermal factors Gata4, Gata6, and Sox17. Our findings uncover an unexpected function of Mga in ESCs, where it functions as a gatekeeper to prevent ESCs from entering into the PE lineage by directly repressing expression of a set of endoderm differentiation master genes.

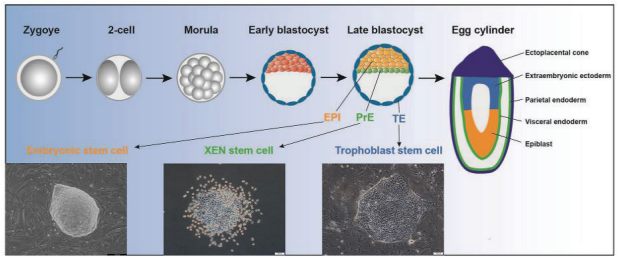

Figure 1. A process of progressive cell fate specification during mouse preimplantation development. Three distinct cell lineages are present in the implanting blastocyst: the extraembryonic trophectoderm (TE), the primitive endoderm (PE, also called the hypoblast), and the embryonic epiblast (EPI).

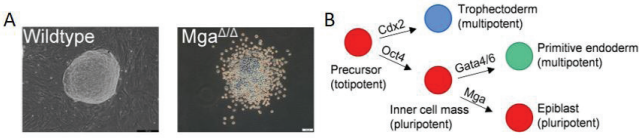

Figure 2. Mga is required for maintenance of the pluripotent state in ESCs.

(A) Mga deficiency results in dynamic changes in cell morphology and gene expression characteristic of Xen cells. (B) Mga blocks XEN lineage formation by repressing the expression of Gata4/6.

2. Rbbp4 suppresses premature differentiation of embryonic stem cells.

Polycomb group (PcG) proteins exist in distinct multi-protein complexes and play a central role in silencing developmental genes, yet the underlying mechanisms remain elusive. Here, we show that defificiency of retinoblastoma binding protein 4 (RBBP4), a component of the Polycomb repressive complex 2 (PRC2), in embryonic stem cells (ESCs) leads to spontaneous differentiation into mesendodermal lineages. We further show that Rbbp4 and core PRC2 share an important number of common genomic targets, encoding regulators involved in early germ layer specifification. Moreover, we fifind that Rbbp4 is absolutely essential for genomic targeting of PRC2 to a subset of developmental genes. Interestingly, we demonstrate that Rbbp4 is necessary for sustaining the expression of Oct4 and Sox2 and that the forced co-expression of Oct4 and Sox2 fully rescues the pluripotency of Rbbp4-null ESCs. Therefore, our study indicates that Rbbp4 links maintenance of the pluripotency regulatory network with repression of mesendoderm lineages.

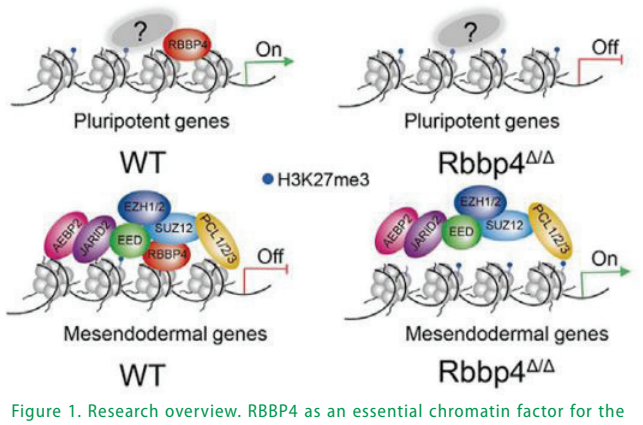

Figure 1. Research overview. RBBP4 as an essential chromatin factor for the maintenance of ESC pluripotency and it functions within the PRC2 complex to repress mesendoderm specifification.

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Inflammatory diseases and cell therapy techniques

Treatment of gastric cancer with the chimeric antigen receptor-modified human peritoneal macrophages

We developed a novel Chimeric Antigen Receptor-Macrophage (CAR-M) based on genetically modifying human peritoneal macrophages (PMs), expressing a HER2-FcεR1γ-CAR (HF-CAR). We tested HF-CAR macrophages in a variety of GC models in vitro and in vivo. HF-CAR-PMs specifically targeted HER2-expressed GC, and harboured the FcεR1γ moieties to trigger engulfment. Intraperitoneal administration of HF-CAR-PMs significantly facilitated the HER2-positive tumour regression in PC mouse model and prolonged the overall survival rate. In addition, the combined use of oxaliplatin and HF-CAR-PMs exhibited significantly augment anti-tumour activity and survival benefit.

An effective therapeutic strategy for intrahepatic cholangiocarcinoma by targeting CD44v5

In this study, we observed the specific expression of CD44 variant 5(CD44v5) in ICC tumors. CD44v5 protein was expressed on the surface of most ICC tumors (103 of 155). A CD44v5-targeted ADC, H1D8–DC (H1D8–drug conjugate), was developed that comprises a humanized anti-CD44v5 mAb conjugated to the microtubule inhibitor monomethyl auristatin E (MMAE) via a cleavable valine–citrulline-based linker. H1D8–DC exhibited efficient antigen binding and internalization in cells expressing CD44v5 on the cell surface. Because of the high expression of cathepsin B in ICC cells, the drug was preferentially released in cancer cells but not in normal cells, thus inducing potent cytotoxicity at picomolar concentrations. In vivo studies showed that H1D8–DC was effective against CD44v5-positive ICC cells and induced tumor regression inpatient-derived xenograft models, whereas no significant adverse toxicities were observed. These data demonstrate that CD44v5 is a bona fide target in ICC and provide a rationale for the clinical investigation of a CD44v5-targeted ADC-based approach.

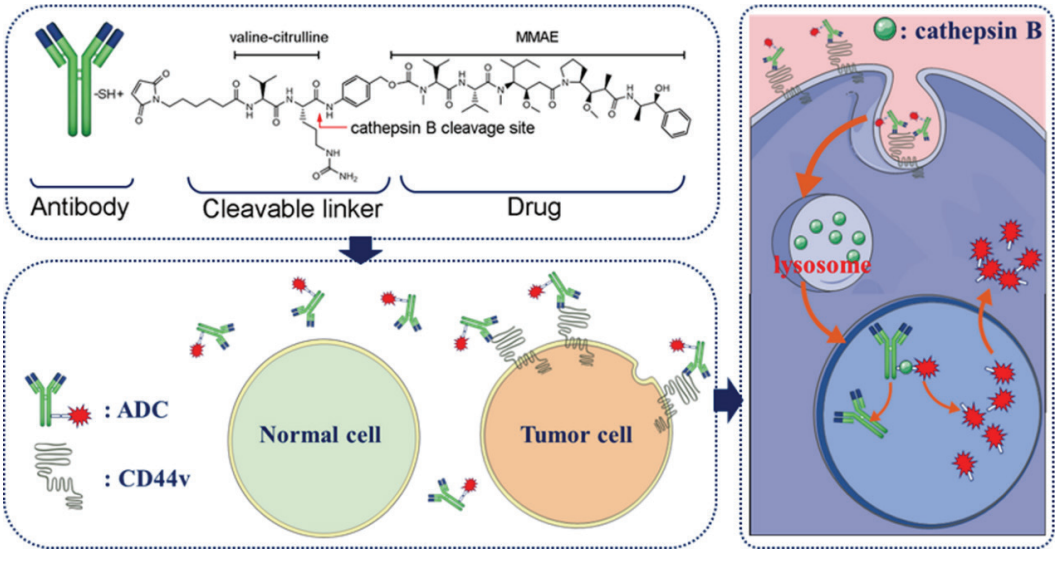

Figure 1. Therapeutic strategy for intrahepatic cholangiocarcinoma by targeting CD44v5

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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.

Transcriptional regulation of MAD2 promotor in rhabdomyosarcoma (RMS)

The chromosomes in rhabdomyosarcoma (RMS) are very unstable, and a high percentage of cells are tetraploid. It has been recently found that most RMS cells contain chromosome 2p24 amplification, in which MYCN is located, but the consequence of 2p24 amplification in the tumorigenesis and if it contributes to the chromosomal instability of RMS remains unknown. Mitotic arrest deficiency 2 (MAD2), a critical component of the spindle assembly checkpoint (SAC), is overexpressed in many cancer cells. It has been observed upon the inactivation of two major tumor suppressor (Rb and p53) pathways. However, the molecular mechanism is not yet clear to explain the relationship between oncogene activation, tumor suppressor activation, and chromosome instability.

Our group recently discovered that human rhabdomyosarcoma (RMS) cell lines implanted into mice showed the MAD2-MYCN double overexpression, suggesting that 2p24 amplification and MYCN overexpression link to the MAD2 overexpression in RMS. Our results showed that MYCN and MAD2 are overexpressed but not the other SAC proteins in these RMS cell lines. We found that MYCN binding sites (E-box) are frequently found in the vicinity of the E2F-binding elements that control the transcription of multiple mitotic regulators including MAD2. The results of our ChIP-qPCR and reporter assays using human skeletal muscle cells (HSkMCs) and RMS cell line Rh30 suggest that the binding of MYCN or E2F with the promotor region of MAD2 regulates MAD2 expression in an exclusive manner (Figure 1 and data not shown).

MYCN-MAD2 double-overexpression that synergistically regulates cancer development in rhabdomyosarcoma (RMS)

We established a system of zebrafish xenograft implanting different transfectants of human Rh30 cells with single or double overexpressing MAD2/MYCN or MDA2-MYCN (Figure 2A). Our results showed that MYCN-MAD2 double-overexpression synergistically promoted cancer development (Figure 2A), suggesting a transcriptional synergy of MYCN-MAD2 to activate MAD2 promotor (Figure 1 and data not shown). We are currently clarifying the mechanism behind, including the regulation of chromosome instability via MYCN-MAD2 double-overexpression to verify this hypothesis. We also established a system to assess the growth of Rh30 cells in zebrafish xenografts to test the inhibitory effect of MYCN-MAD2 depletion and MYCN inhibitor MYCi975 (Figure 2B). These results encourage us to perform efficiently drug screening targeting MYCN and/or MAD2 in the future.

Figure Legends

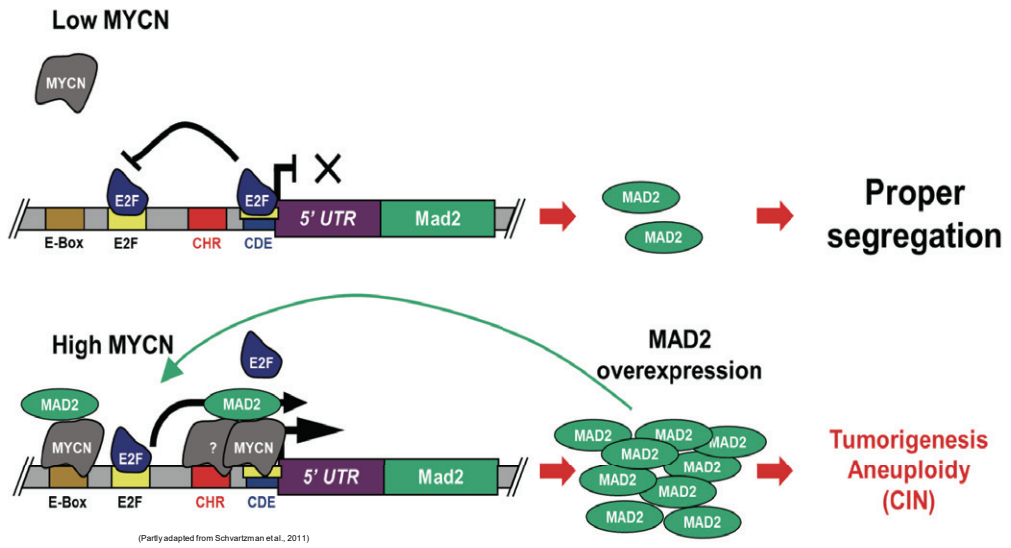

Figure 1. Hypothetical model of MAD2 regulation in both low MYCN or high MYCN conditions (This figure is partly adapted from Schvartzman et al., 2011).

In low MYCN condition, E2F binds to the inhibitory region of MAD2 promoter and the MAD2 is not overexpressed

and cell segregation can be properly regulated. But in high MYCN condition, MYCN binds to the promoter region in an exclusive manner with E2F and activate the expression of MAD2. Overexpressed MAD2 has positive feedback to synergize with MYCN to activate MAD2 promoter.

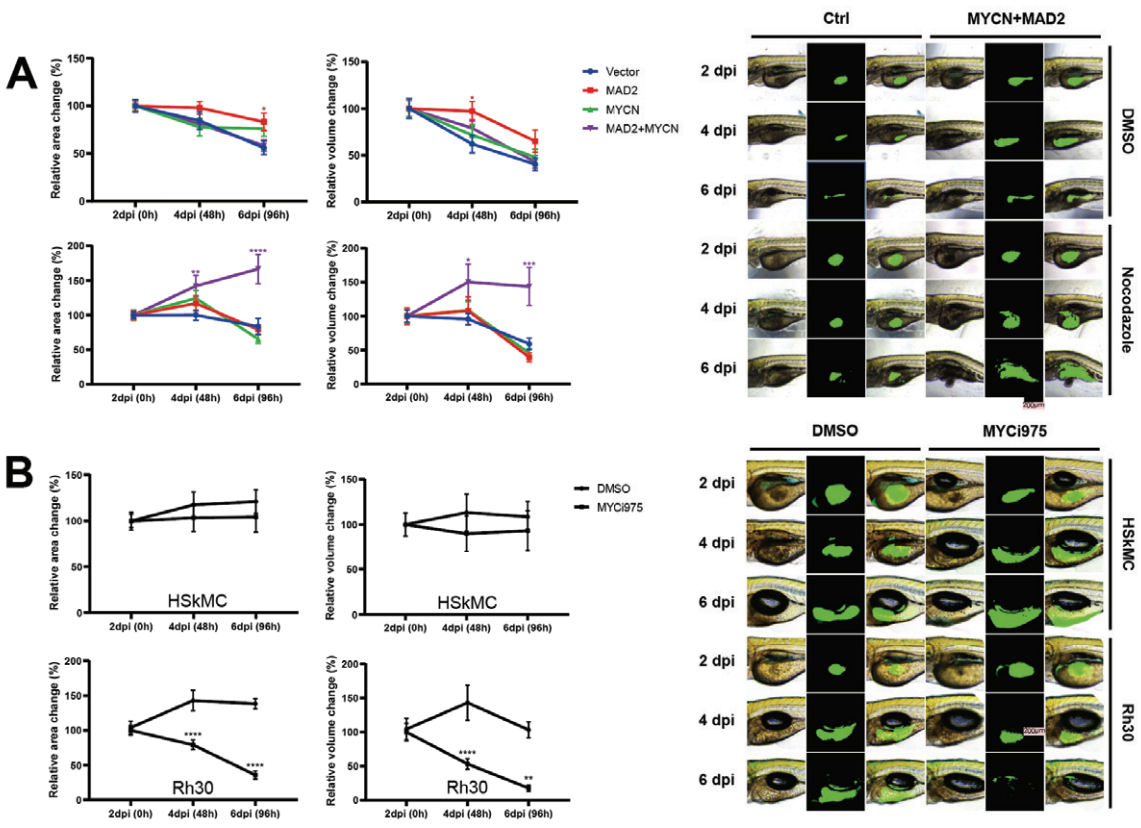

Figure 2. Transplanted human cell growth is synergistically enhanced by MAD2-MYCN double overexpression while reduced by the inhibition of MYCN in zebrafish xenograft.

Maximum plane images captured at 2 days, 4 days and 6 days post injection. Volume calculated by V=1/2 LxH^2 (L, Length; H, Height).

(A) HSkMCs overexpressing MAD2 and/or MYCN were transplanted into TU fish.

(B) HSkMCs or Rh30 cells were transplanted into TU fish. Fishes were treated with DMSO or MYCi975 at 2 days post injection (2dpi).

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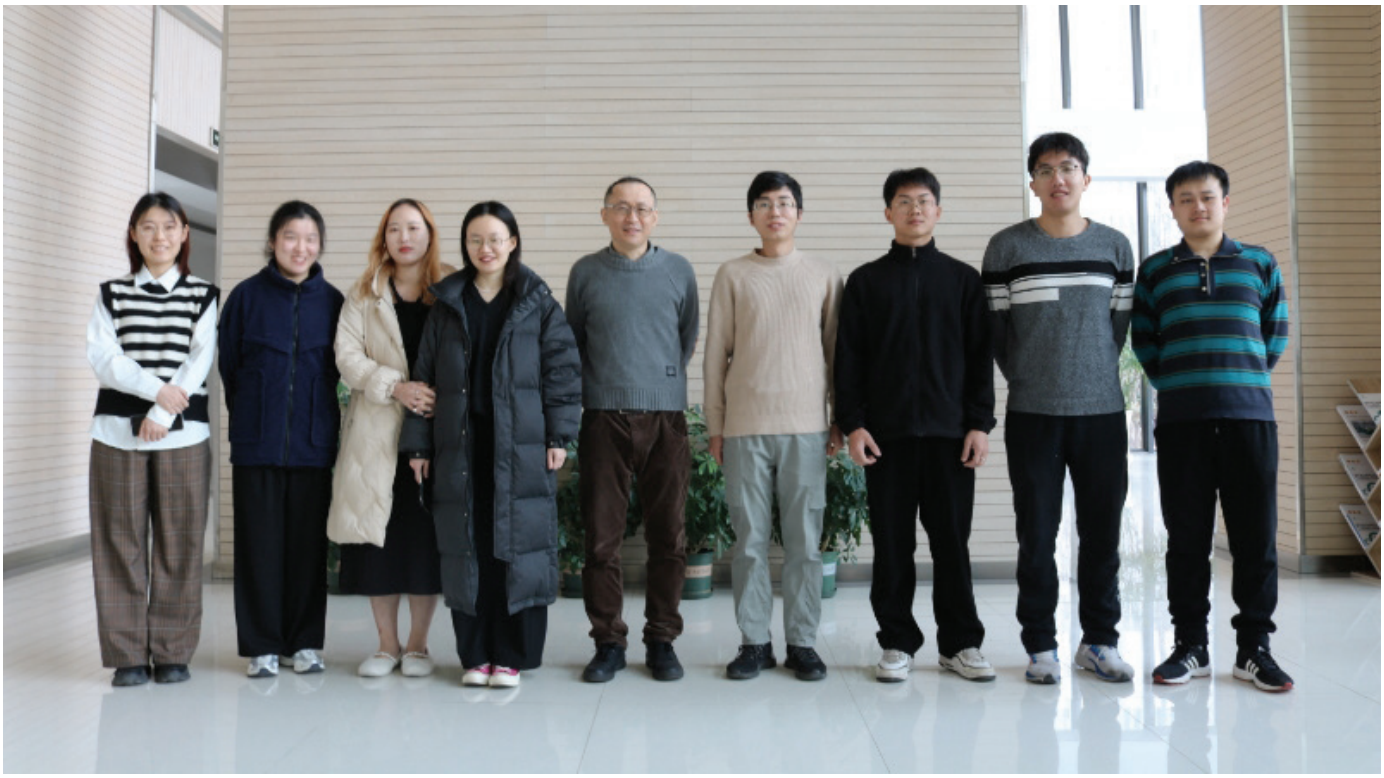

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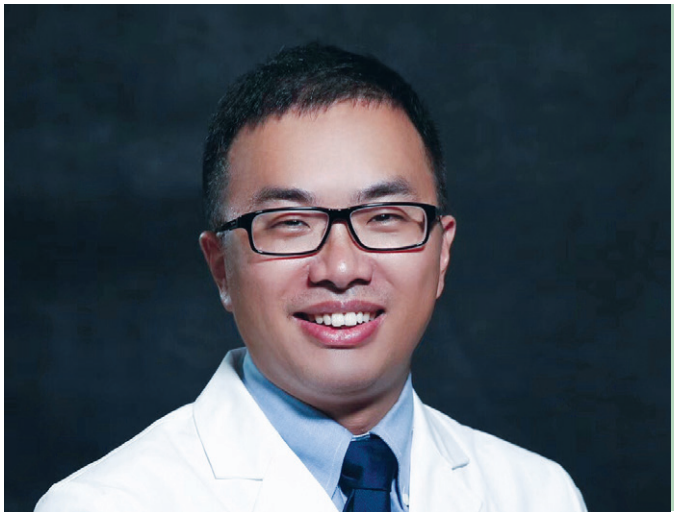

Dongquan Shi Ph.D., M.D.

Prof. Shi graduated from Medical School, Nanjing University (MD, PhD). He received training at Drum Tower Hospital Affiliated to Nanjing University Medical School, University of Pittsburgh and RIKEN Center for Integrative Medical Science in Tokyo. Now he is an experienced surgeon of Sports Medicine and Adult Reconstruction Department. He is serving as the Editor in Chief of Annals of Joint, Deputy Editor in Chief of BMC Surgery, Annals of Translational Medicine and Frontiers in Cell and Developmental Biology, and an editorial board member of Journal of Orthopedic Translation. Prof. Shi led the research team to study the genetics of bone, joint diseases, and regenerative medicine, and published 159 SCI articles. In 2023, Prof. Shi won the National Fund for Distinguished Young Scholars.

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Molecular classification and fibrocartilage hyalinization of osteoarthritis

Osteoarthritis (OA) is the most common disease that leads to serious physical and mental burden of patients. Our group focuses on fundamental mechanisms and intervention of OA as well as cartilage regeneration.

1. Molecular classification of knee osteoarthritis: reactive regeneration chondrocytes.

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. We focused on the cartilage degeneration-driven subtype and employed single-cell RNA sequencing to analyze chondrocytes from OA human femoral condyles. We identified two subpopulations (RPS4Y1+ subpopulation and CHI3L1+ subpopulation) associated with cartilage synthesis, maintenance and regeneration. Further transcriptomic analysis revealed a connection between CHI3L1+ subpopulation and microtubule (MT) stability-related processes. We used MT stabilizer to increase cartilage synthesis factor expression and upregulated TGF-β signaling.

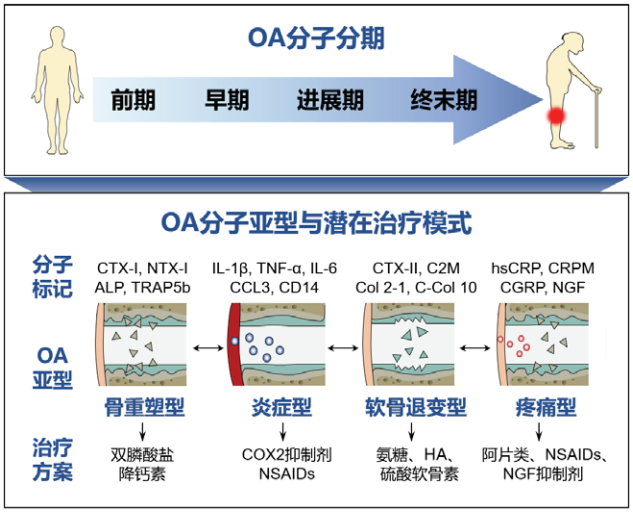

Figure 1. Schematic illustrations of OA Molecular classification

2. Schottky heterojunction-based biomedical nanoplatform.

Bone defects are one of the contributing factors to the development of knee osteoarthritis. Currently, the treatment for patients with bone defects often involves the use of grafts. However, autografts, derived from the patient's own tissue, have limited availability, and allografts, sourced from others, may elicit immune reactions. To address this clinical challenge, we focus on designing a piezoelectric material for the treatment of bone defects.

We designed a biomedical nanoplatform based on the Schottky heterojunction to enhance the accumulation of subcellular entities, facilitating electron transfer and activating the Wnt signaling pathway. This newfound understanding of the Schottky heterojunction expands its biomedical relevance, providing a promising material-based therapy for bone defect treatment.

In conclusion, these studies provide valuable insights for the treatment of osteoarthritis, highlighting the role of specific cell subtypes and innovative nanomaterials in addressing the challenges associated with cartilage regeneration and bone regeneration.

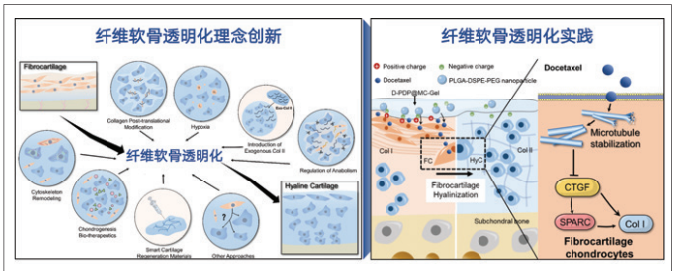

Figure 2. Schematic illustrations of concept and practice of fibrocartilage hyalinization

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NJU-MARC Experimental Animal Center

The Experimental Animal Center of the Model Animal Research Center at Nanjing University has an SPF (Specific Pathogen-Free) animal facility covering nearly 2000 square meters, with over 6000 cages for mice. There are 10 technical staff members. The Experimental Animal Center provides a conducive experimental environment for large instruments such as metabolic cages and small animal component analyzers. The center is rigorously managed to ensure that the experimental animals are at SPF level, supporting multiple laboratories both within and outside the university with experimental animal resources.

The Experimental 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





NJU-MARC Core Facilities

After 6 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 38 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 139000 hours service within or outside MARC research community.

So far, we have set up Microscopy and Imaging Core, Flow Cytometry Core, Proteomics and Metabonomics 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

Imaging

► 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

Mass Spectrometry

► Services

- Quantitative analysis of small molecules
- Identification of unknown metabolites
- Able to analyze various kinds of samples
- Metabolomics study

► Equipment

- Agilent 6550 iFunnel Q-TOF LC/MS System

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

► Services

- Cell sorting
- Able to analyze multiple fluorescent probes simultaneously

► Equipment

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

Cellular Metabolism

► Services

- Live cell energy metabolism

► Equipment

- Agilent Seahorse Xfe24 Extracellular Flux Analyzer

Single-cell sequencing library preparation systems

► Services

- Single cell 3' whole transcriptome amplification
- Analyze the TCR and BCR sequence information

► Equipment

- The MobiNova-100® single-cell sequencing library preparation system
- BD Rhapsody® single-cell sequencing library preparation system

Real time qPCR

► Services

- Gene expression detection

► Equipment

- ABI StepOne Plus
- Roche LightCycler 96

Others

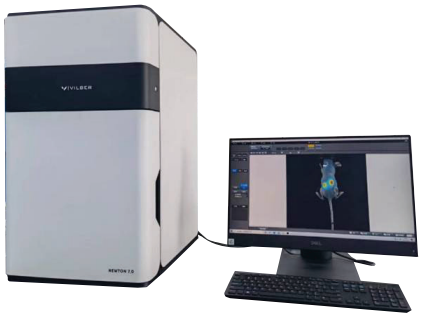
► Equipment

- BioTek synergy H1 plate reader
- Beckman OPTIMA XPN-100 centrifuge

New equipment

► Olympus SLIDEVIEW VS200

- Olympus SLIDEVIEW VS200 are suitable for quantitating large amounts of samples, including brain, cancer, stem cell, and drug discovery research.
- Quickly capture high-resolution,High-quality slide images and easy data analysis, sharing, and archiving.
- The VS200 system offers five imaging modes: brightfield, fluorescence,Darkfield, phase contrast, and simple polarization.
- Up to 6 slides can be loaded for automated scanning. High-resolution full glass in the range of 2x to 40x Piece imaging.
- Accommodates a wide range of slide sizes and observation methods, including manual brightfield scanning, AI recognition, and fully automated scanning and unique configurations in hardware.



► Vilber Newton 7.0 FT-500

- Equipped with a special thermostat for mice, compatible with the mouse anesthesia system, the throughput can reach 5 mice.
- It can be applied to in vivo fluorescence and bioluminescence imaging in mice, and cell migration tracking in vivo or in vitro. Signal overlays are possible to display multiple reporter genes simultaneously. It is used in the research of tumor development, stem cells, immune-related diseases, metabolic diseases, drug metabolism, and related molecular mechanisms of diseases.
- It can meet the detection needs of different fluorescent probes, such as bioluminescence(such as luciferase and fluorescence imaging of GFP, iRFP)and infrared dyes such as Cy5.5 and Cy7.

► Single-cell sequencing library preparation systems

- The MobiNova-100® single-cell sequencing library preparation system is designed and controlled by an optimized microfluidic chip. Cell separation and co-encapsulation of beads, reagents, and cells are stably realized during droplet generation to achieve a high cell capture rate.
- Analyze the TCR and BCR sequence information by identifying their CDR3 region (TCR/BCR assay) in combination with the single cell 3'whole transcriptome amplification(WTA) assay.

- BD Rhapsody® single-cell sequencing library preparation system is based on Microwell's monocellular separation technology, which Separate single cells using natural sedimentation method, the capture principle is gentle, and it has excellent capture ability for fragile cells (neutrophils, stem cells, CART cells, etc.), and the sample can be loaded with > 50% cell viability. Wide cell loading volume (100-40,000 cells/cartridge) and low multicellular rates.
- Run TCR/BCR assay(Analyze the TCR and BCR sequence information by identifying their full-length sequence or CDR3 region) in combination with RNA assays (WTA assay or the targeted immune response panel), BD® Single-Cell Multiplexing Kit and BD® AbSeq Kit to perform multiomic analyses.

National Resource Center for Mutant Mice

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

As of the end of 2023, NRCMM has accumulated 33,062 mouse and rat models, making it the resource bank with the most extensive mouse strain resources globally. It has served over 1,700 domestic and international institutions, providing more than 900,000 mouse models to hospitals, universities, research institutes, and national research centers, etc. NRCMM has also supported numerous national-level major projects, including “The establishment, implementation and quality control of standardized phenotyping analysis processes” and “The establishment and quality control of standardized mutant mouse strains". It has served more than 10 national labs in the field of life sciences, including Guangzhou Laboratory and the State Key Laboratory of Pharmaceutical Biotechnology. As a result, it has contributed to over 1,000 research papers with the Cumulative Impact Factor of 17,862.2.

In 2023, NRCMM continued its "Key Model for Research Project" (KMR Project), developing more than 80 new mouse models for anti-aging research and a total of over 300 innovative mouse models to support scientists in national-level research projects.

高校及科研院所
>500

三甲医院
>400

企业
>900

国内覆盖 34个省市自治区

Event in 2023

Laboratory Open Day

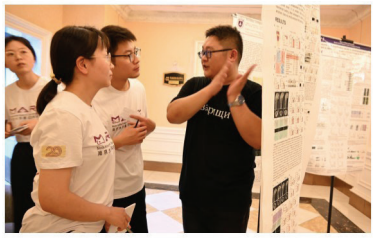
As a well-known biomedical research institution both domestically and internationally, MARC has held a special science popularization brand activity "Laboratory Open Day" in response to the call of the Chinese Society for Cell Biology for nine consecutive years, attracting nearly 1,000 primary and secondary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

On May 27th, MARC held the "2023 Laboratory Open Day" event with the theme of " The 'Lonely Heroes' Behind Scientific Experiments". More than 100 local primary and secondary school students and their parents from Nanjing, totaling more than 300 people, were invited to enter the center together to get up close and observe these "Lonely Heroes", aka. model animals, who have made great contributions to human health research.

On August 3rd, the CSCB awarded MARC the "2023 Excellent Laboratory for Science Popularization Activities" certificate.

The 20th Anniversary of MARC






From August 21 to 24, MARC held the "20th Anniversary Celebration of Model Animal Research Center of Nanjing University and the Academic Annual Meeting of 'MOE Key Laboratory of Model Animal for Disease Study' in Chizhou, Anhui Province. The meeting invited many senior experts at home and abroad from the Institute of Biophysics of the Chinese Academy of Sciences, Shanghai Zhongshan Hospital, Institute of Basic Medicine of the Chinese Academy of Medical Sciences, University of Cambridge, Pasteur Institute of France, etc., Bringing wonderful academic reports to all teachers and students of the institution.

Director Yan Li reviewed the experience and achievements accumulated by MARC in the past two decades in areas such as talent internationalization, scientific research internationalization, training mode internationalization, and characteristic activities internationalization , and stated that the Institute of MARC will continue to innovate and uphold its original intention of "promoting self-reliance and self-improvement in biomedical research in China" in the next two decades of development, inheriting the spirit of Nanjing University's "sincerity, grandeur, and inspiring learning and action", focusing on "national affairs" and shouldering "national responsibilities", promoting the progress of science and education, empowering the prosperity of industries, keeping pace with the pulse of the times, and creating new achievements.

In the " MARC Star" selection , Lulu Kang won the "MARC Star" award in 2022 with more than half of the votes, and 8 students won the Excellent Poster Award.

"Equality, learning, cooperation" are the core cultural values that MARC has continued to uphold over the past two decades of development. The development and future of MARC are closely related to the practical needs of every teacher and student. MARC has gone through storms for 20 years and still stands firm. We firmly believe that a more brilliant future is awaiting for MARC.











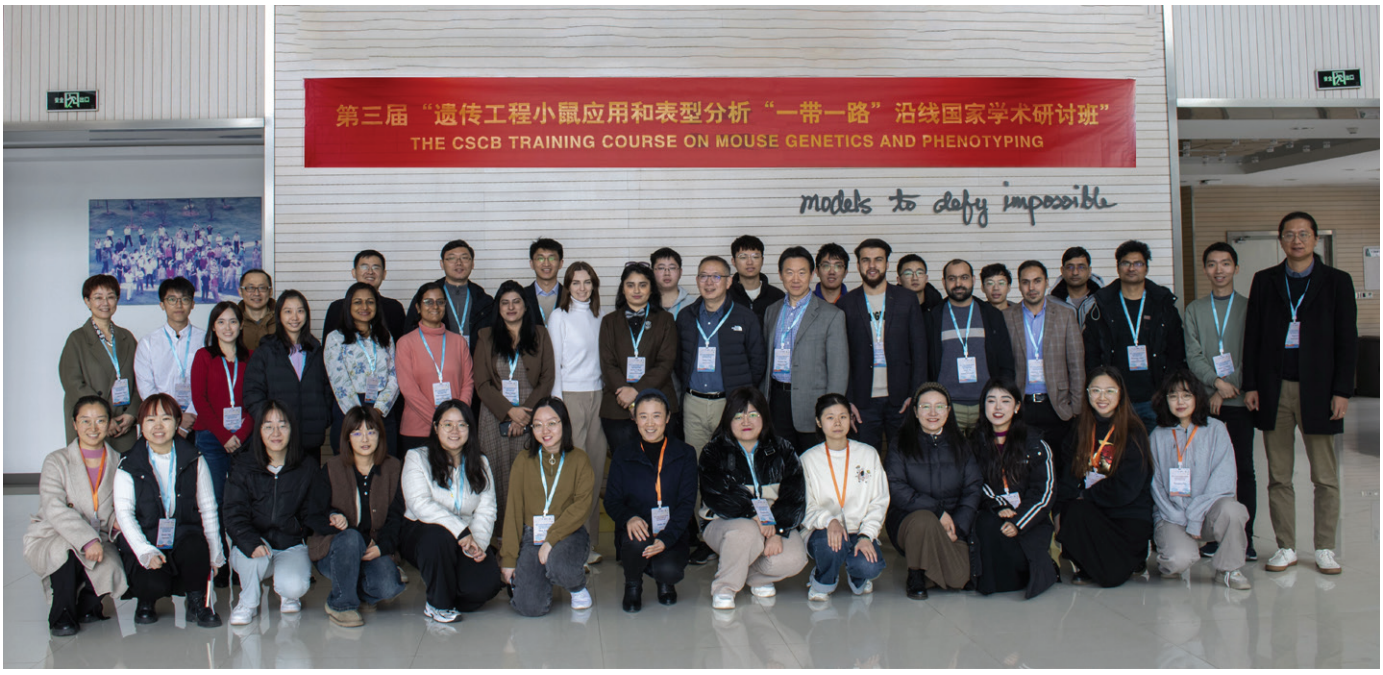

The 3rd CSCB training course on mouse genetics and phenotyping in the "One belt one road" initiative

In order to promote the concept of "building a community with a shared future for mankind",continue effectively promoting the in-depth development of people-to-people exchanges along the "One belt one road" initiative, in December 2023,the 3rd Chinese Society for Cell Biology (CSCB) training course on mouse genetics and phenotyping in the "One belt one road" initiative was held at the Model Animal Research Center of Nanjing University (MARC).

This training course,organized by CSCB and MARC, which gave full play to the advantages of MARC as the main scientific research and talent training base for developmental biology and genetics in China.

Nearly 20 experts and scholars from Malaysia, Singapore, Russia, Nepal, Pakistan, Sri Lanka and other "One belt one road" initiative countries participated in training course. During the meeting, MARC and some of the research institutes of the "One belt one road" initiative countries discussed the joint laboratory project.

Under the framework of "One belt one road" initiative, this training course facilitates the collaboration and innovation in biomedical advances using mouse models in the "One belt one road" initiative countries, promotes application and standardization of mouse genetics in international research community, and provides academic support for scientific research cooperation between domestic and foreign parties.



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Seminar

	Date	Speaker	Title	Unit
1	2023/2/23	Mengle Shao Ph.D.	Targeting Adipose Progenitors in the Treatment of Metabolic Disease	Institut Pasteur of Shanghai,Chinese Academy of Sciences
2	2023/3/17	Yan Chen Ph.D.	MCT1-mediated lactate transport in the regulation of metabolic homeostasis	Shanghai Institute of Nutrition and Health
3	2023/3/17	Yifu Qiu Ph.D.	The thermoporter couples mitochondrial calcium signaling with uncoupled respiration	College of Future Technology of Peking University
4	2023/6/20	Baidong Hou Ph.D.	Explore the innate B cell immune signaling in antiviral mechanism and application	Institute of Biophysics, Chinese Academy of Sciences
5	2023/7/20	Tim Sparwasser Ph.D.	Blocking metabolic checkpoints for the treatment of autoimmunity	University of Mainz
6	2023/7/21	Jianzhu Chen Ph.D.	Reprogram Macrophages for Disease Interventions	MIT
7	2023/8/4	Lei Jiang Ph.D.	Reductive carboxylation in redox homeostasis	Beckman Research Institute at City of Hope
8	2023/10/30	Bishoy Morris Faltas Ph.D.	APOBEC3 cytidine deaminases as evolutionary drivers of cancer	Weill Cornell Medical College
9	2023/11/1	Aibin He Ph.D.	Live imagenomics and single-cell multiomics for probing the history and future of cell fates	College of Future Technology of Peking University
10	2023/11/30	Lubin Jiang Ph.D.	Epigenetic studies of Plasmodium falciparum and their application to malaria prevention and control	Shanghai Institute of Immunology and Infection, Chinese Academy of Sciences
11	2023/12/28	Dahai Zhu Ph.D.	Utilizing multi-omics and DNA/RNA imaging techniques to re-understand the non-canonical functions and mechanisms of cell lineage-specific Pioneer TFs	Bioland Laboratory (Guangzhou Regenerative Medicine and Health Guangdong Laboratory)










Courses and Lecturers

The MARC, as an institute of the Nanjing University Medical School, is home to more than 100 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 2023, the following lecture series and courses were given by MARC staff at Nanjing University (unless indicated otherwise).

Principles, Methods and Techniques in Cell and Molecular Biology

Guoqiang Wan

Hongyu Wang

Zhenji Gan

Basic Concepts and Developments in Genetics

Qing Zhang

Jinzhong Qin

Geng Liu

Cellular and Molecular Mechanism of Development

Jiong Chen

Ying Cao

Basic Concepts and Frontiers in Immunology

Jianghuai Liu

Yan Li

Huiming Gao

Zhaoyu Lin

Medical Physiology

Shuai Chen

Guiquan Chen

Qiaoli Chen

Frontier of Cell Biology

Lubin Jiang(Shanghai Institute of Immunology and Infection, Chinese Academy of Sciences)

Jianzhu Chen(MIT)

Baidong Hou(Institute of Biophysics, Chinese Academy of Sciences)

Progress in Life Sciences

All PIs at MARC

PhD Theses

MARC students successfully defended the following PhD theses in 2023

Group Zhenji Gan

Wanping Sun
The Mechanistical and Physiological Function of Mitochondrial Protein Quality Control in Adipose tissue

Group Shuai Chen

Minjun Liu
The function and mechanistic actions of E3 ligase TRAF6 in proprotein convertase regulation

Qi Wang
The study of AMPK-TBC1D1 signaling pathway in the regulation of innate immunity and obesity development.

Wen Wei
Ubiquitylation regulates hepatic lipid metabolism via P-bodies

Qian Ouyang
Rab8a as a mitochondrial receptor for lipid droplets in skeletal muscle

Group Di Chen

Xiao Zang
Molecular mechanisms of cytochrome c deficiency-mediated delay of aging in C. elegans

GroupYun Shi

Yueying Wang
The role of ATRN and TMEM63A in myelin-related diseases

Group Geng Liu

Yannan Zhang
The study on the regulatory network of mitochondrial oxidative metabolism and metabolic fitness using a fluorescent probe indicating an active state of mitochondria

Group QingZhang

Yuxue Gao
HIB/SPOP inhibits Ci/Gli-mediated tumorigenesis by modulating the RNA polymerase II (RNAP II) components stabilities

Zhaoliang Shan
The rescue of the mitochondrial defects in Drosophila

Group Jun Yan

Meiqian Li
Downregulation of SPOP in bladder cancer promotes tumor-associated macrophage mediated cancer cell proliferation and stemness

2023 Summer Camp

As the primary task for MARC is to excel in scientific research and education, graduate students are the most valuable assets of our center. To attract more outstanding students to MARC, we held the 14th Summer Camp on July 5th this summer.

The summer camp was jointly held with the Medical School of Nanjing University, which attracted 69 college students from 34 universities. Dr Yan Li, director of the MARC, introduced the history, research directions and groups of the research center. The 2021 MARC Star winner Kun Zhou, along with outstanding graduates and PIs shared their experience and knowledge on scientific research and life at MARC. This year's summer camp activities also included the poster exhibitions from all research teams. The founder of MARC, Professor Xiang Gao, PIs and senior members of the research groups carried out face-to-face academic exchanges with the summer camp participants.

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

2023 Students Activities

As a bridge between teachers and students, the Student Union has organized many academic and extracurricular activities in 2023. In order to promote communication between laboratories, stimulate our critical thinking and creativity, we hold a seminar once a week. We invite professors from various experiments to share their scientific research, new ideas, and brainstorming with students from different laboratories. Students can ask questions and communicate with each other at any time. During the presentation between the professor and the students, we will also have a tea break where everyone can chat in a relaxed and pleasant atmosphere.

To help countries along the Belt and Road understand the versatility of mice, improve their experimental skills, and promote cooperation and innovation in biomedical progress in developing countries using mouse models. The Student Union also participated the 3rd CSCB training course, helping foreign students in this event to better participate in the event.

In addition to scientific research exchange meetings, we also held academic activities such as poster exhibitions and MARC Star selection. During the poster exhibition, students can showcase their research findings to others. All members of MARC can vote to select their ideal poster. Finally, the top three authors were selected as candidates for the 2021 MARC Star. The posters ranked third to eighth were selected as excellent posters. They all won awards for their outstanding research work.

We also participated in the "National Linkage 'Laboratory Open Day' Activity" to attract more people to pay attention to life sciences and gain a better understanding of related work in the field of life sciences,

In addition, our extracurricular activities are also diverse and colorful. In addition to learning and research, MARC students are also cultivated by a culture that promotes humanity, critical thinking, and social well-being. Thanks to the generous financial support provided by MARC and the government, we have sufficient resources to enrich our lives here. We called on students to participate in the badminton league organized by the School of Architecture and Urban Planning of Nanjing University. This allows us to savage our bodies and civilize our spirits, so that we can conduct scientific research in a more comprehensive mental state and live a happier life.

At the end of the year, we held a welcome party. The party went very smoothly, and everyone enjoyed this time in a happy and joyful atmosphere.

In the future, we will listen more to the voices of students and continuously improve our planning and organizational skills. On the one hand, we will organize more meaningful academic activities, such as inviting professors from different fields to give lectures and communicate with students. On the other hand, we will use limited space to organize more interesting activities, allowing students to relax and be full of vitality.

Marc Academy

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

In the past, we have held many activities which have received a wide and positive response. Table Tennis Competition held by the MARC Academy showed the athletic demeanor of MARC students. The Fun Games revealed the spirit of solidarity and fraternity for the honor of the school. The ¬First MARC Singer Contest displayed a healthy and civilized cultural atmosphere.

In this year, we completed the sorting of the new students and held a Fishing Contest, which was organized by the Dean of the Longwang Mountain Academy He Li and other deans or leaders of Academy. In order to foster a sense of teamwork, two students formed a team to participate in the competition. This competition attracted a lot of people, and everyone's enthusiasm was relatively high. All of us harvested happiness and a lot of fish. In particular, Qiaoli Chen, an assistant professor of MARC, also participated in the competition.

In addition to hosting above competitions, the deans and students of MARC Academy were actively involved in organizing MARC events. In the Summer Camp of 2023, students were divided into four groups. Each group was guided by a dean of MARC Academy to visit the environment of MARC. We also called on and participated in the Badminton League hosted by the School of Architecture and Urban Planning of Nanjing University. In the end of year, the deans of MARC Academy also participated in organizing 2023 MARC Welcome Party.

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NATIONAL RESOURCE CENTER FOR MUTANT MICE