The 8th International Ion Channel Conference

August 07-08, 2021 Online

PROGRAM

Contents

Conference Information

Introduction:

The International Ion Channel Conference is a academic conference jointly organized by scientists at home and abroad every two years. It aims to provide an international and high-level exchange and cooperation platform for experts, scholars and researchers in the field of ion channel research. The conference has been successfully held for seven consecutive sessions in Dalian (2007) , Haerbin (2009) , Shanghai (2011) , Shijiazhuang (2013) , Luzhou (2015) , Qingdao (2017). The scale of participants is constantly expanding, which is an important academic event with considerable international influence.

The 8th International Ion Channel Conference will be held at Hebei University of Technology, in August 7th to 8th. Many academicians, scientists and scholars from many countires are invited to attend the conference, and scholars at home and abroad who are active in biophysics, physiology, pharmacology, neuroscience and other fields will attend the conference. The conference will be conducted in the form of conference reports, keynote reports and posters. There will be many academicians and famous scientists giving wonderful special academic reports. The theme of the conference covers all aspects of ion channel research, it provides a multi-system and multi-level communication platform for scientists from all over the world, and a good communication environment for international and domestic scientific research cooperation.

We are sincerely invite you to participate in the conference.

Conference date: **August 07 - 08, 2021**

Conference Website: https://iicc2021.aconf.org/en-us/index.html

Sponsors & Organizers:

上海卓越脑科学发展基金会
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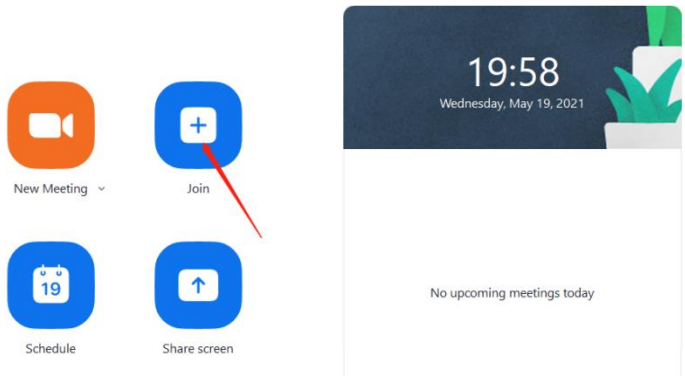

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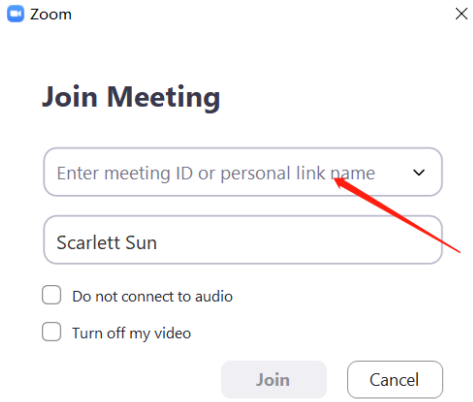

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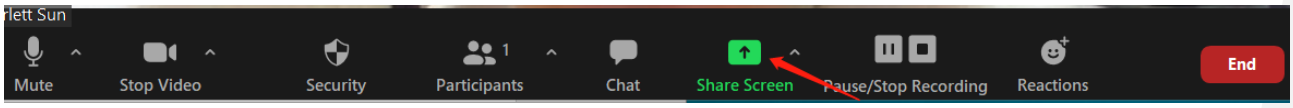

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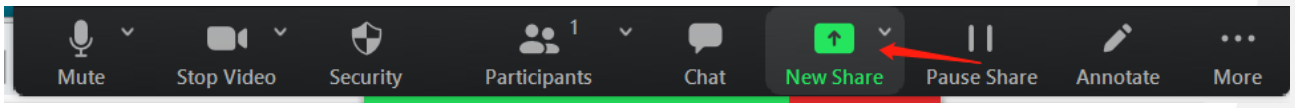

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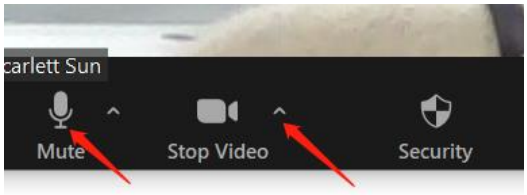

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Youxing Jiang	(USA)	Ming Lei	(Manchester, UK)
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Yong Zhan	(Tianjin, China)	Hailin Zhang	(Shijiazhuang, China)
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Agenda

August 7th 08:10-12:20 Opening Ceremony & Plenary Session 1

ZOOM: *851 8424 2634* **Password:** *681183* **ZOOM Link:** *https://zoom.com.cn/j/85184242634?pwd=NXo0cXFZQ1ZSU1dleW81UHV3eTdidz09*		
Chair: Hailong An		
August 7th	08:10-08:30	Opening Ceremony
	Time	**Speech**
	Chair: Kewei Wang/ Xiangyao Li	
August 7th	08:30-09:10	Voltage-gated Ca^{2+} channels: selectivity, permeation and synaptic modulation Richard W. Tsien, Professor (keynote) *NYU Neuroscience Institute, Department of Neuroscience and Physiology*
	09:10-09:40	Structural dynamics of HCN channels measured with tmFRET William N. Zagotta *University of Washington*
	09:40-10:10	tmFRET to measure conformational distributions Sharona E. Gordon, Professor *University of Washington*
	Chair: Lijun Kang/ Zhengyu Cao	
	10:10-10:50	Adaptivity of selectivity filter in TRPV1 Yifan Cheng Professor (keynote) *University of California San Francisco*
	10:50-11:20	Allosteric activation of the spicy sensor TRPV1 Jie Zheng, Professor *University of California Davis*
	11:20-11:50	Structural basis of CNG channel function and channelopathy Jian Yang, Professor *Columbia University*
	11:50-12:20	Breakout room talk Room1: Richard W. Tsien, Yifan Cheng, Jian Yang, Kewei Wang (Chair) Room2: William N. Zagotta, Sharona E. Gordon, Jie Zheng, Xiangyao Li (Chair)
	12:20-13:30	Lunch break

August 7th 13:30-18:10 Plenary Session 2

ZOOM: *851 8424 2634* **Password:** *681183*
ZOOM Link: *https://zoom.com.cn/j/85184242634?pwd=NXo0cXFZQ1ZSU1dleW81UHV3eTdidz09*

Time		Speech	
August 7th	Chair: Sheng Ye/Yutao Tian		
	13:30-14:10	T-type calcium channels as molecular targets for pain Gerald W Zamponi, FRSC, FCAHS, Professor and Senior Associate Dean (Keynote) *University of Calgary*	
	14:10-14:40	Structural and Functional Studies of Insect Ryanodine Receptors Zhiguang Yuchi, Professor *Tianjin University*	
	14:40-15:10	Blunting TRPML1 channels protects myocardial ischemia/reperfusion injury by restoring impaired cardiomyocyte autophagy Wuyang Wang, Professor *Xuzhou Medical University*	
	15:10-15:40	Physiological and pharmalogical modulation of CRAC channels Youjun Wang, Professor *Beijing Normal University*	
	15:40-16:10	cAMP binding and regulation of HCN channel function Lei Zhou, Senior Investigator *Shenzhen Bay Laboratory*	
	Chair: Yong Zhang/Wei Xiong		
	16:10-16:40	Link ER ion homeostasis maintained by an ER anion channel to ALS Yichang Jia Ph.D., Principal Investigator *Tsinghua University*	
	16:40-17:10	voltage gating and cytosolic Ca2+ activation mechanisms of Arabidopsis two-pore channel AtTPC1 Jiangtao Guo, Principal Investigator *Zhejiang University*	
	17:10-17:40	Structure of a mammalian sperm cation channel complex Dr. Jianping Wu, Assistant Professor *Westlake University*	
	17:40-18:10	Molecular Basis of Mechanosensory Transduction in Mammalian Hearing and Worm's Touch Yiquan Tang, Professor *Fudan University*	
	18:10-18:40	Breakout room talk	
		Room1: Gerald W Zamponi, Zhiguang Yuchi, Wuyang Wang, Youjun Wang, Lei Zhou, Sheng Ye (Chair)	Room2: Yichang Jia, Jiangtao Guo, Jianping Wu, Yiquan Tang, Yong Zhang (Chair)
	18:40-19:30	Dinner break	

August 7th 19:30-22:00 Plenary Session 3

ZOOM: *851 8424 2634* **Password:** *681183*
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Time		Speech
August 7th	Chair: Jing Yao/Chen Zhang	
	19:30-20:10	Acid-sensing ion channels: A quest of 20 Years Tianle Xu, Professor (keynote) *Shanghai Jiao Tong University School of Medicine*
	20:10-20:40	Lysosomal K+ Channels in Neurodegenerative Diseases Dejian Ren, Professor *University of Pennsylvania*
	20:40-21:10	From SWELL to PAC: Discovery of New Chloride Channels Zhaozhu Qiu, Associate professor *Johns Hopkins University*
	21:10-21:40	Optogenetic engineering of the calcium release-activated calcium (CRAC) channel Yubin Zhou, PhD, MD *Texas A&M University*
	21:40-22:00	Breakout room talk
		Room1: Tianle Xu; Dejian Ren; Zhaozhu Qiu; Yubin Zhou; Jing Yao (Chair)

August 8th 08:30-12:20 Plenary Session 4

ZOOM: *851 8424 2634* **Password:** *681183*
ZOOM Link: *https://zoom.com.cn/j/85184242634?pwd=NXo0cXFZQ1ZSU1dleW81UHV3eTdidz09*

Time		Speech	
August 8th	Chair: Tianle Xu/Yang Li		
	08:30-09:10	Neuronal Synaptic Plasticity and Postsynaptic Ion Channel Signaling Complexes in Health and Disease Mark L. Dell'Acqua, Professor (Keynote) *University of Colorado School of Medicine*	
	09:10-09:40	The N-linker region of hERG1a upregulates hERG1b Matthew Trudeau, Professor *University of Maryland School of Medicine*	
	09:40-10:10	Physiological Function of TRPV4 in Glia Cells Makoto Tominaga, professor *Div. Cell Signaling, National Institute for Physiological Sciences (NIPS)*	
	Chair: Yong Li/Ye Yu		
	10:10-10:50	Mechanogating mechanisms of the mechanosensitive Piezo channels Bailong Xiao (keynote) *Tsinghua University*	
	10:50-11:20	Voltage-clamp fluorometry analysis of structural rearrangements of ATP-gated channel P2X2 upon hyperpolarization Yoshihiro Kubo, Professor *National Institute for Physiological Sciences*	
	11:20-11:50	How are Voltage Signal and Enzyme Coupled? : S4 approaches the hydrophobic spine of the enzyme in voltage-sensing phosphatase, VSP Yasushi Okamura, MD, PhD, Professor *Osaka University*	
	11:50-12:20	Breakout room talk	
		Room1: Mark L. Dell'Acqua; Matthew Trudeau; Makoto Tominaga; Ye Yu (Chair)	Room2: Bailong Xiao; Yoshihiro Kubo; Yasushi Okamura; Yong Li (Chair)
	12:20-13:30	Lunch break	

August 8th 13:30-18:40 Plenary Session 5

ZOOM: *851 8424 2634* **Password:** *681183*
ZOOM Link: *https://zoom.com.cn/j/85184242634?pwd=NXo0cXFZQ1ZSU1dleW81UHV3eTdidz09*

Time		Speech	
August 8th	Chair: Xin Xie/Jianfeng Liu		
	13:30-14:10	Structures and Drug Discovery of Hormone Receptors H.Eric Xu (Keynote) *Shanghai Institute of Materia Medica, CAS*	
	14:10-14:40	Asymmetrical activation of Class C GPCR dimers Jianfeng Liu, Professor *Huazhong University of Science and Technology*	
	14:40-15:10	Ligand recognition and signal transduction of Angiotensin II type I receptor Jinpeng Sun, Professor *Shandong University*	
	15:10-15:40	Insights into Lipid Modulation of GPCR Signal Transduction Yan Zhang, Professor *Zhejiang University*	
	15:40-16:10	GPCRs in Oligodendrocyte Differentiation and Myelin Regeneration Xin Xie, Professor *Shanghai Institute of Materia Medica, CAS*	
	Chair: Wei Yang/Xiaona Du		
	16:10-16:40	Coupled activation of TRPV1 and ANO1 in sensory neurons Nikita Gamper, Ph.D. *University of Leeds*	
	16:40-17:10	Structural basis of rapid-antidepressant ketamine action on human NMDA receptors Shujia Zhu, Professor *Institute of Neuroscience, CAS*	
	17:10-17:40	De novo design of peptidic positive allosteric modulators targeting TRPV1 with analgesic effects Fan Yang, Professor *Zhejiang University*	
	17:40-18:10	Insights into the Gating Mechanism of ANO1 and Drug Screening Targeting ANO1 Hailong An, Professor *Hebei University of Technology*	
	18:10-18:40	Breakout room talk	
		Room1: H.Eric Xu; Jianfeng Liu; Jinpeng Sun; Yan Zhang; Xin Xie (Chair)	Room2: Nikita Gamper; Fan Yang; Shujia Zhu; Hailong An; Hailin Zhang (Chair)
	18:40-19:30	Dinner break	

August 8th 19:30-21:00 Plenary Session 6

ZOOM: *851 8424 2634* **Password:** *681183*
ZOOM Link: *https://zoom.com.cn/j/85184242634?pwd=NXo0cXFZQ1ZSU1dleW81UHV3eTdidz09*

Time		Speech
Chair: Bailong Xiao/ Chengfen Xing		
August 8th	19:30-20:10	To reveal the choreography of the Nav/Cav channels – something AlphaFold is incapable Nieng Yan, Professor (keynote) *Princeton University*
	20:10-20:40	Activation and inhibition of the taste channel TRPM5 Juan Du, Associate Professor *Van Andel Institute, Grand Rapids, Michigan*
	20:40-21:00	Breakout room talk
		Room1: Nieng Yan, Juan Du, Bailong Xiao (Chair)

Speakers

Richard W. Tsien, Professor

NYU Neuroscience Institute, Department of Neuroscience and Physiology
E-mail: Richard.tsien@nyumc.org

Abstract:

Voltage-gated Ca^{2+} channels: selectivity, permeation and synaptic modulation

We are studying how the location and identity of presynaptic calcium channels is regulated. Voltage-gated Ca2+ channels provide the critical link between the firing of a presynaptic nerve terminal and its release of neurotransmitter. The Ca2+ channels must be positioned very close to sites of vesicle fusion, and come in diverse forms with distinct activity-dependence, responsiveness to GABA, dopamine, acetylcholine and other neuromodulators, and susceptibility to neurological disorders such as migraine, ataxia or dystonia. Our working hypothesis involves molecular "slots" for particular types of channels. Slots regulate the mix of channel types and also help explain how defective channels might displace normal ones in genetically dominant disorders.

Our lab is particularly interested in studying multiple modes of synaptic vesicle fusion. The opening of Ca2+ channels drives at least two distinct forms of fusion. In the classical mode, the vesicle membrane fully merges with and flattens into the presynaptic membrane (full collapse fusion). In a newly characterized mode, termed "kiss-and-run," the connection between the vesicle interior and the external medium lasts long enough to allow passage of neurotransmitter, but the connection is severed before the identity of the vesicle is lost. We study the dynamic properties and functional implications of both fusion modes by loading single synaptic vesicles with single photoluminescent reporter particles?quantum dots. Sharp distinctions between full collapse fusion and kiss-and-run are now in hand. Experiments are underway to monitor the same fusion event optically and electrophysiologically.

One area of intense attention in our lab is the fundamental unit of cell-cell communication between brain neurons: quantal synaptic transmission. Presynaptic release of a packet of neurotransmitter, for example, glutamate, causes activation of postsynaptic receptors and a brief flow of current that promotes firing of the postsynaptic cell. We work on neuronal mechanisms that allow synapses to adapt to a sudden or long-lasting change in their level of activity. For example, blockade of impulses or of postsynaptic glutamate receptors causes a cascade of biochemical events that eventually leads to readjustment of critical molecular players on both sides of the synapse. We use state-of-the art methods to pin down the cell biology of changes in synaptic

strength, of importance for adaptation of brain networks in learning and memory. Ongoing work in cultures of isolated neurons and brain slices.

We study how synaptic transmission and depolarization cause changes in neuronal gene expression. Despite its importance, signaling from synapse or surface membrane to nucleus is only partly understood. One example of such signaling involves a local increase in Ca2+ concentration near a class of Ca2+ channels (L-type) different from those that trigger presynaptic transmitter release, subsequently leading to activation of an exemplar transcription factor, CREB, a regulator of transcription of many important neuronal genes. Our approach is to combine physiological approaches (how fast, how steeply voltage-dependent, how is signal transduced) and biochemical experiments using cDNA microarrays (which genes, in what context, what relationship to learning and memory).

William N. Zagotta, Professor

University of Washington
E-mail: zagotta@uw.edu

Abstract:

Structural dynamics of HCN channels measured with tmFRET

Ion channel proteins are the fundamental molecular elements for the control of membrane excitability and signaling in the nervous system. In response to one or more of a variety of stimuli, including neurotransmitters, voltage, and internal second messengers, ion channels open and allow the passage of certain selected ions across the cell membrane. In this way, channels can transduce these stimuli into changes in membrane potential and/or intracellular levels of calcium, the signals most used by the nervous system. The properties of each ion channel are highly specialized for its particular function. To this end, our long term goal is to determine the molecular mechanisms of the opening and closing conformational changes in ion channels. We have focused on a family of channels that is regulated by the direct binding of cyclic nucleotides, cAMP and cGMP. These channels play a fundamental role in the initial generation of an electrical signal in sensory receptors such as photoreceptors and olfactory receptors, and in the control of the pacemaker activity in cardiac and neuronal cells. To study the mechanism of gating by cyclic nucleotides, we employ a variety of approaches including electrophysiology, site-directed mutagenesis, protein chemistry, site-specific fluorescent labeling, and X-ray crystallography. By the combination of these approaches, we believe we will be able to gain new insights into the molecular mechanisms for channel function.

Sharona E. Gordon, Professor

University of Washington
E-mail: seg@uw.edu

Abstract:

tmFRET to measure conformational distributions

Yifan Cheng, Pfofessor

University of California San Francisco
E-mail: Yifan.Cheng@ucsf.edu

Abstract:

Adaptivity of selectivity filter in TRPV1

Jie Zheng, Professor

University of California Davis
E-mail: jzheng@ucdavis.edu

Abstract:

Allosteric activation of the spicy sensor TRPV1

Jian Yang, Professor

Columbia University
E-mail: jzheng@ucdavis.edu

Abstract:

Structural basis of CNG channel function and channelopathy

Gerald W Zamponi, Professor

University of Calgary
E-mail: zamponi@ucalgary.ca

Abstract:

T-type calcium channels as molecular targets for pain

Chronic pain can be a severely debilitating condition that reflects a long term sensitization of signal transduction in the afferent pain pathway. Among the key players in the afferent pain pathway are T-type calcium channels, whose activities are aberrantly enhanced under conditions of inflammatory and neuropathic pain. In this context, we discovered that the plasma membrane expression of the Cav3.2 T-type channel subtype is under dynamic control by ubiquitinating and deubiquitinating enzymes. Importantly, we were able to show that peripheral inflammation or nerve injury promotes the association of the deubiquitinase USP5 with the channel, leading to increased T-type channel activity in afferent fibers, and consequently pain hypersensitivity. Conversely, disruption of this process by decoy peptides alleviated pain hypersensitivity. The USP5 dependent process is activity dependent as evident from transcutaneous optogenetic stimulation of afferent fibers, and is regulated by interleukin 33. We developed a high throughput screen to identify novel small organic USP5 disruptors, leading to the discovery of a new class of analgesic molecules that are effective in mouse models of inflammatory and neuropathic pain. Finally, we describe preliminary data from a mouse model that harbors a pathogenic mutation in USP5 that has been linked to congenital insensitivity to pain in a pediatric patient.

Zhiguang Yuchi, Professor

Tianjin University
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Abstract:

Structural and Functional Studies of Insect Ryanodine Receptors

Diamide insecticides target insect ryanodine receptors (RyRs) and cause misregulation of calcium signaling in insect muscles and neurons, generating worldwide sales over 2 billion U.S. dollars annually. Several resistance mutations have been reported to reduce the efficacy of the diamides, but the exact binding sites and mechanism of resistance mutations are not clear. The recent breakthrough in the structural studies of mammalian RyRs has deepened our understanding of the channel, but the structural information about insect RyRs is still scarce. Recently we solved the cryo-electron microscopy (cryo-EM) structure of RyR in complex with the anthranilic diamide chlorantraniliprole (CHL). CHL binds to the pseudo-voltage-sensor domain (pVSD) of RyR, a site in proximity to the previously identified resistance mutations. Mutagenesis studies in silico, in mutant cell lines, and in transgenic drosophila strains reveal the key residues involved in diamide coordination and the molecular mechanism under species-selectivity and resistance mutations. We have also solved the crystal structures of several RyR domains from the diamondback moth and the bee, revealing insect-specific structural features which could be potentially targeted by novel insecticides. Interestingly, we found that the phosphorylation of insect RyR is temperature-dependent, facilitated by the low thermal stability and dynamic structure of the insect RyR. Our structures provide a foundation for developing novel pesticides to overcome the resistance crisis.

Wuyang Wang, Professor

Xuzhou Medical University
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Abstract:

Blunting TRPML1 channels protects myocardial ischemia/reperfusion injury by restoring impaired cardiomyocyte autophagy

Accumulating evidence suggests that autophagy dysfunction plays a critical role involved in myocardial ischemia/reperfusion (I/R) injury. However, the underling mechanism of malfunctional autophagy in the cardiomyocytes subjected to I/R has not been well defined. Here, we used an in vitro and an in vivo I/R model to monitor the autophagic flux in the cardiomyocytes, by exposing neonatal rat ventricular myocytes (NRVM) to hypoxia/reoxygenation (H/R) and by subjecting mice to I/R, respectively. We observed that autophagic flux in cardiomyocytes subjected to I/R was blocked in both the in vitro and the in vivo models, and down-regulating a lysosomal cationic channel, TRPML1, markedly liberated the blocked myocardial autophagic flux in I/R, demonstrating that TRPML1 contributes to the blocked autophagic flux in cardiomyocytes subjected to I/R. Mechanistically, a large quantity of reactive oxygen species (ROS) generated from the reperfusion process stimulated TRPML1 channels, activation of which in turn inhibited autophagic flux in cardiomyocytes presumably by disturbing the fusion between autophagosomes and lysosomes. As a result, the inhibited myocardial autophagic flux induced by TRPML1 damaged mitochondria turnover and resulted in mass accumulation of damaged mitochondria and detrimental ROS further release, which directly led to cardiomyocytes death. More importantly, pharmacological and genetic inhibition of TRPML1 channels greatly reduces infarct size and rescues heart function in mice subjected to I/R in vivo by restoring impaired myocardial autophagy. In summary, our study demonstrates that secondary to ROS elevation, activation of TRPML1 results in autophagy inhibition in cardiomyocytes subjected to I/R, which directly leads to cardiomyocytes death by disrupting mitochondria turnover. Therefore, targeting TRPML1 represents a novel therapeutic strategy to protect against myocardial I/R injury.

Youjun Wang, Professor

Beijing Normal University
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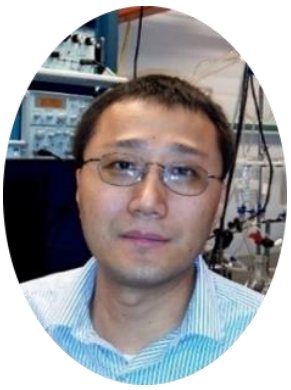
Abstract:

Physiological and pharmalogical modulation of CRAC channels

Constituted by STIM1 and Orai1, calcium (Ca2+) release activated Ca2+ (CRAC) channels mediate store operated Ca2+ entry (SOCE). Aberrant CRAC signaling is closely associated with immune-deficiency, many types of cancers neurodegenerative diseases. Thus it is crucial to unveil molecular mechanisms underlying its regulation, and to develop new pharmacological tools against CRAC channels. At pre-translational level, we identified a new spliced variant of STIM1 named STIM1β that could more efficiently engage and gate Orai1, resulting in enhanced SOCE responses. At post-translational level, we identified an interacting protein of STIM1, which could decrease SOCE by promoting lysosomal degradation of STIM1. Mostly based on virtual docking, we also obtained a new SOCE inhibitor that are more specific for STIM1-Orai1. Together, our findings may serve as potential targets or tools for treating CRAC related diseases.



Lei Zhou, Senior Investigator

Shenzhen Bay Laboratory
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Abstract:

cAMP binding and regulation of HCN channel function

Singlet oxygen (1O2) is the molecular oxygen in electronically excited state. 1O2 can be generated through photodynamic processes which require three elements: light, oxygen, and photosensitizer. Using the Xenopus oocyte expression system and the patch-clamp fluorometry setup, we discovered heterologously expressed hyperpolarization-activated cAMP-gated (HCN) channels on excised membrane patches are sensitive to the photodynamic modification (PDM) mediated by 1O2. 1O2 modification increased the voltage-insensitive current component and prolonged the deactivation of mouse HCN2 channel. Then we extended this study to native HCN channels in thalamocortical (TC) neurons in the brain. FITC-cAMP was chosen as the photosensitizer and was delivered into the recorded neuron via whole-cell patch-clamp recording pipette. After illuminating the brain slice with blue light pulses, we observed an increase in the voltage-insensitive, instantaneous Iinst component, accompanied by a long lasting decrease in the hyperpolarization-dependent Ih component. Both Ih and the increased Iinst after PDM could be blocked by the HCN blockers Cs+ and ZD7288. When FITC and cAMP were loaded into the neurons as two separate chemicals, light application did not result in any long-lasting changes of the HCN currents. Next, we investigated impacts of the PDM on the membrane excitability of TC neurons. Consistent with an upregulation of HCN channel function, PDM elicited a depolarization of the resting membrane potential. Importantly, Trolox-C, an effective quencher for singlet oxygen, could block the PDM-dependent increase in Iinst and depolarization of the RMP. Therefore, PDM of native HCN channels can be developed as a unique and novel biophotonics approach to modulate neuronal excitability.

Yichang Jia, Principal Investigator

Tsinghua University
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Abstract:

Link ER ion homeostasis maintained by an ER anion channel to ALS

Although anion channel activities have been demonstrated in sarcoplasmic reticulum/endoplasmic reticulum (SR/ER), their molecular identities and functions remain unclear. Here, we link rare variants of CLCC1 (Chloride Channel CLIC Like 1) to ALS (amyotrophic lateral sclerosis). We demonstrate that CLCC1 is a pore-forming component of an ER anion channel and that ALS-associated mutations impair the channel activity. CLCC1 unitary conductance is inhibited by luminal Ca2+ but facilitated by phosphatidylinositol 4,5-bisphosphate (PIP2). We identified a conserved lysine 298 (K298) in CLCC1 intraluminal loop as the critical PIP2-sensing residue. CLCC1 maintains steady-state [Cl-]ER and morphology and regulates ER Ca2+ homeostasis including steady-state [Ca2+]ER and efficiency of internal Ca2+ release. ALS-associated mutant CLCC1 increase steady-state [Cl-]ER and impair ER Ca2+ homeostasis. Phenotypic comparisons of multiple Clcc1 mutant alleles, including ALS-associated mutations, reveal a CLCC1 dosage-dependence in severity of disease phenotypes in vivo. Conditional knockout of Clcc1 cell-autonomously causes motor neuron loss and ER stress, misfolded protein accumulation, and characteristic ALS pathologies in the spinal cord. Thus, we argue that disruption of ER ion homeostasis maintained by CLCC1 underlies etiology of neurodegenerative diseases.

Jiangtao Guo, Principal Investigator

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E-mail: jiangtaoguo@zju.edu.cn

Abstract:

voltage gating and cytosolic Ca2+ activation mechanisms of Arabidopsis two-pore channel AtTPC1

Arabidopsis thaliana two-pore channel AtTPC1 is a voltage-gated, Ca2+-modulated, non-selective cation channel that is localized in the vacuolar membrane and responsible for generating slow vacuolar (SV) current. Under depolarizing membrane potential, cytosolic Ca2+ activates AtTPC1 by binding at the EF hand domain whereas luminal Ca2+ inhibits the channel by stabilizing the voltage-sensing domain II (VSDII) in the resting state. Here we present 2.8-3.3 Å cryo-EM structures of AtTPC1 in two states, one in closed state with apo EF hand domain and resting VSDII, and the other in open or partially open state with Ca2+-bound EF hand domain and activated VSDII. Structural comparison between the two different states allows us to elucidate the structural mechanisms of voltage gating, cytosolic Ca2+ activation, and their coupling in AtTPC1. This study also provides structural insight into the general voltage-gating mechanism among voltage-gated ion channels.

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Abstract:

Structure of a mammalian sperm cation channel complex

The cation channel of sperm (CatSper) is essential for sperm motility and fertility. CatSper comprises the pore-forming proteins CATSPER1–4 and multiple auxiliary subunits, including CATSPERβ, γ, δ, ε, ζ, and EFCAB9. Here, we report the cryo-electron microscopy (cryo-EM) structure of the CatSper complex isolated from mouse sperm. In the extracellular view, CATSPER1–4 conform to the conventional domain-swapped voltage-gated ion channel fold, following a counterclockwise arrangement. The auxiliary subunits CATSPERβ, γ, δ and ε—each of which contains a single transmembrane segment and a large extracellular domain—constitute a pavilion-like structure that stabilizes the entire complex through interactions with CATSPER4, 1, 3 and 2, respectively. Our EM map reveals several previously uncharacterized components, exemplified by the organic anion transporter SLCO6C1. We name this channel–transporter ultracomplex the CatSpermasome. The assembly and organization details of the CatSpermasome presented here lay the foundation for the development of CatSpermasome-related treatments for male infertility and non-hormonal contraceptives.

Yi-Quan Tang, Professor

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Abstract:

Molecular Basis of Mechanosensory Transduction in Mammalian Hearing and Worm's Touch

Mechanotransduction channels have been proposed as force sensors in various physiological processes such as hearing and balance. In particular, TMC1 has been shown to constitute the pore of hair cell mechanotransduction channels, but little is known about how force is sensed by TMC channels. We have recently used the genetic tractability of C. elegans to reveal a novel molecular mechanism by which TMC channels respond to force. Our study indicates that ankyrin, which provides enough extensibility and elasticity to serve as a gating spring, acts as a long-sought intracellular tether that transmits force to TMC mechanotransduction channels via the evolutionarily conserved calcium and integrin-binding protein (CIB) in the sensory cilia of C. elegans mechanoreceptor, and possibly at the dense bodies of body wall muscles. In addition, we also establish CIB2 and CIB3 as essential components of the mechanotransduction machinery in mouse auditory and vestibular hair cells. Our research has led to important discoveries that have advanced our understanding of the molecular basis of hearing and balance.

Tianle Xu, Professor

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Abstract:

Acid-sensing ion channels: A quest of 20 Years

Neuronal sensation of extracellular acidosis relies on acid-sensitive ion channels (ASICs) on the cell membrane surface. Unlike classical voltage- or ligand-gated ion channels, ASICs belong to a novel superfamily of ion channels whose biological functions and operating principles are unclear. In the light of this scientific frontier, our series of new functional, mechanistic and ligand studies suggest that ASICs may constitute new "low toxicity" neuroprotective targets for several major neurological diseases such as stroke and chronic pain. In addition, we have systematically elucidated the relationship between ASIC signaling and neuroplasticity, and resolved the neural circuitry basis and ion channel mechanisms underlying the dynamic regulation of sensory perception, learning and memory, which provides new ideas for understanding the brain cognitive neural network mechanism in normal and disease states.

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Abstract:

Lysosomal K+ Channels in Neurodegenerative Diseases

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Abstract:

From SWELL to PAC: Discovery of New Chloride Channels

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Abstract:

Optogenetic engineering of the calcium release-activated calcium (CRAC) channel

We describe herein a series of robust single-component Ca2+-selective ion channel or actuators tailored for remote control of Ca2+ signaling in mammals. Existing tools are either derived from engineered channelrhodopsin variants without strict Ca2+ selectivity or based on engineered GPCRs that might crosstalk with other signaling pathways. We introduce three different approaches to confer photosensitivity to STIM1 and ORAI as the two essential components for the calcium release-activated (CRAC) channel. These genetically-encoded calcium channels or actuators (GECAs) display biophysical features reminiscent of the ORAI1 channel, which enables precise optical control over Ca2+ signals and hallmark Ca2+-dependent physiological responses. GECAs can be further coupled with upconversion nanoparticles to enable wireless optogenetics in vivo. We demonstrate the use of GECAs to modulate anti-cancer immune response and intervene in neurodegeneration in a Drosophila model of amyloidosis. Similar approaches have been extended to photo-control immunogenic cell death (pyroptosis and necroptosis), as well as the design of photoswitchable chimera antigen receptor (CAR) T-cells for precision immunotherapy against both blood cancers and solid tumors.

Mark L. Dell'Acqua, Professor

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Abstract:

Neuronal Synaptic Plasticity and Postsynaptic Ion Channel Signaling Complexes in Health and Disease

Mark L. Dell'Acqua, PhD, Department of Pharmacology, University of Colorado School of Medicine, Anschutz Medical Campus, Aurora, CO, USA

Regulation of long-term potentiation (LTP) and depression (LTD) synaptic plasticity by the recruitment and removal of AMPA-type ionotropic glutamate receptors (AMPARs) from hippocampal CA1 excitatory synapses is crucial for normal learning and memory. In particular, Ca2+-permeable AMPARs (CP-AMPARs) assembled from GluA1 subunits are excluded from synapses under basal conditions but can be transiently recruited during the induction of NMDA-type glutamate receptor (NMDAR)-dependent LTP and LTD to rapidly modify synaptic strength. For changes in synaptic strength to be consolidated and maintained over longer periods of time following LTP/LTD, synapses must also signal distally to the nucleus to regulate gene expression in a process known as excitation-transcription (E-T) coupling. A-kinase anchoring protein (AKAP) 150 is a postsynaptic scaffold protein that recruits the kinase PKA and phosphatase Calcineurin (CaN) to NMDARs, AMPARs, and L-type voltage-gated Ca2+ channels to regulate both local changes in AMPAR trafficking during LTP and LTD and also distal E-T coupling to the nucleus through the CaN-regulated transcription factor NFAT. In Alzheimer's Disease (AD) synaptotoxic amyloid- (Aβ) oligomers are thought to impair LTP, enhance LTD, and promote synapse loss through disrupting these signaling pathways. Here we used knock-in mice with mutations that disrupt binding of PKA or CaN to AKAP150 to reveal that these enzymes oppose each other to regulate CP-AMPARs during LTP, LTD, and exposure to Aβ. In particular, we found that AKAP-PKA signaling is required for CP-AMPAR recruitment that facilitates LTP but also primes synapses for LTD and acute LTP impairment mediated by Aβ. Conversely, we found that AKAP-CaN signaling promotes CP-AMPAR removal that is required for both LTD and Aβ impairment of LTP. Finally, we found that aberrant activation of NFAT signaling to the nucleus downstream of AKAP-anchored CaN is required for subsequent Aβ-mediated synapse loss. These findings highlight the importance of postsynaptic ion channel signaling complexes in regulating both normal and aberrant synaptic plasticity.

Matthew Trudeau, Professor

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Abstract:

The N-linker region of hERG1a upregulates hERG1b

Makoto Tominaga, Professor

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Abstract:

Physiological Function of TRPV4 in Glia Cells

TRPV4 is a non-selective calcium-permeable cation channel with temperature sensitivity and widely expressed and activated in various neurons and glial cells in the nervous system. Schwann cells (SCs) are primary glia cells that wrap around axons to form the myelin sheath in the peripheral nervous system. Deletion of TRPV4 did not affect normal myelin development for SCs in sciatic nerves in mice. However, after sciatic nerve cut injury, TRPV4 expression levels were remarkably increased in SCs following nerve demyelination. Ablation of TRPV4 expression impaired the demyelinating process after nerve injury, resulting in delayed remyelination and functional recovery of sciatic nerves. These results suggest that local activation of TRPV4 could be an attractive pharmacological target for therapeutic intervention after peripheral nerve injury. Microglia maintain central nervous system homeostasis by monitoring changes in their environment and by taking protective actions to equilibrate such changes. We demonstrate that mouse microglia exhibit temperature-dependent movement in vitro and in vivo that is mediated by TRPV4 channels within the physiological range of body temperature. These findings may provide a new basis for future research into the potential clinical application of temperature regulation to preserve cell function via manipulation of TRPV4 activity.

Bailong Xiao, Professor

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Abstract:

Mechanogating mechanisms of the mechanosensitive Piezo channels

The mechanically activated Piezo channel plays a versatile role in conferring mechanosensitivity to various cell types. The homotrimeric Piezo channel resembles a gigantic three-bladed propeller-like structure, in which the non-planar transmembrane regions of 114 transmembrane segments in total are collectively curved into a unique nano-bowl shape. On the basis of the signature bowl-shaped feature of the Piezo channel-membrane system and previous electrophysiological characterizations, Piezo channels have been proposed to adopt a force-from-lipids gating mechanism to sense changes in local curvature and membrane tension. However, how it incorporates its intrinsic mechanosensitivity and cellular components to effectively sense long-range mechanical perturbation across a cell remains elusive. Here we show that Piezo channels are biochemically and functionally tethered to the actin cytoskeleton via the cadherin-β-catenin mechanotransduction complex, whose perturbation significantly impairs Piezo-mediated responses. Mechanistically, the adhesive extracellular domain of E-cadherin interacts with the cap domain of Piezo1 that controls the transmembrane gate, while its cytosolic tail might interact with the cytosolic domains of Piezo1 that are in close proximity to its intracellular gates, allowing a direct focus of adhesion-cytoskeleton-transmitted force for gating. Specific disruption of the intermolecular interactions prevents cytoskeleton-dependent gating of Piezo1. Thus, we propose a force-from-filament model to complement the previously suggested force-from-lipids model for mechanogating of Piezo channels, enabling them to serve as versatile and tunable mechanotransducers.

Yoshihiro Kubo, Professor

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Abstract:

Voltage-clamp fluorometry analysis of structural rearrangements of ATP-gated channel P2X2 upon hyperpolarization

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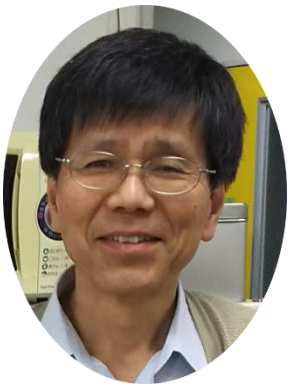
Gating of the ATP-activated channel P2X2 has been shown to be dependent not only on [ATP] but also on membrane voltage, despite the absence of a canonical voltage-sensor domain. We aimed to investigate the structural rearrangements of rat P2X2 during ATP- and voltage-dependent gating, using a voltage-clamp fluorometry technique. We observed fast and linearly voltage-dependent fluorescence intensity (F) changes at Ala337 and Ile341 in the TM2 domain, which could be due to the electrochromic effect, reflecting the presence of a converged electric field. We also observed slow and voltage-dependent F changes at Ala337, which reflect structural rearrangements. Furthermore, we determined that the interaction between Ala337 in TM2 and Phe44 in TM1, which are in close proximity in the ATP-bound open state, is critical for activation. Taking these results together, we propose that the voltage dependence of the interaction within the converged electric field underlies the voltage-dependent gating.

Reference:

Andriani RT, Kubo Y (2021) Elife 10: e65822



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Abstract:

How are Voltage Signal and Enzyme Coupled? : S4 approaches the hydrophobic spine of the enzyme in voltage-sensing phosphatase, VSP

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Voltage sensing phosphatase, VSP, contains four transmembrane helices that operates as a voltage sensor (VS) and a cytoplasmic catalytic region (CCR) with remarkable similarity to PTEN, a tumor suppressor phosphatase1. VSP is highly conserved from marine invertebrates to human, playing roles in the regulation of sperm maturation and epithelial functions. In contrast to voltage-gated ion channels where the VS regulates the transmembrane pore-gated domain, the VS of VSP activates the PI (4,5) P2 phosphatase, which is the C-terminal cytoplasmic region. We previously reported a hydrophobic structure within the CCR of Ciona intestinalis VSP (Ci-VSP) that protrudes into the membrane, and call this structure the “hydrophobic spine (HS).” The HS plays key roles in both the enzyme activity and coupling to the VS2. However, little is known on how the VS regulates the HS in VSP so far.

In this study, we found by mutagenesis screening that the hydrophobicity of two residues, I233 and F234, positioned just below the lowest arginine residue of S4, is critical for the coupling. Detailed motions of I233, F234 and the neighboring residues were studied using the method of incorporating Anap, a fluorescent unnatural amino acid. Voltage-induced fluorescence signals derived from Anap introduced at these sites were remarkably reduced when tryptophan was introduced at the HS. Furthermore, upon repeated membrane depolarizations, mutants with double cysteines on the S4 and HS showed remarkable reduction in sensing currents derived from the motion of the VS. This result provides evidence that the two regions come closer to each other with the upward motion of the VS. We propose a model of coupling between the VS and CCR where the lower hydrophobic part of the S4 forms a hydrophobic core with the HS at the membrane interface, activating the C-terminal enzyme region. Given that HS-like structure is conserved among many phosphoinositide phosphatases including PTEN, which does not contain a VS, moving the VS of VSP may perhaps “hijack” regulatory mechanisms innate to PTEN-like phosphoinositide phosphatases.

H.Eric Xu, Professor

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Abstract:

Structural and Drug Discovery of Hormone Receptors

Cell-cell communication and their functional coordination are a fundamental process of living organisms. Hormones, including small molecule neurotransmitters, peptides, and secreted proteins, are the most effective mediators of cell-to-cell signaling transduction. Hormone recognition by their receptors is the first step of hormone-mediated signal transduction. Two major classes of hormone receptors are nuclear receptors and G protein coupled receptors (GPCRs), which are also two major classes of drug targets. For the past few decades, our laboratory has been focusing on the structure and function of hormone receptors as well as structured based drug discovery targeting these receptors. In this meeting, I will first present our works in the areas of nuclear receptors by revealing the overall helical sandwiched fold of the nuclear receptor ligand-binding domain (LBD) and the topology of ligand binding pocket. Using the glucocorticoid receptor (GR) as an example, I will display how the ligand binding pocket will changes its topology to accommodate its bound ligands, and how this information was used to design a new generation of glucocorticoid drug with reduced side effects. I will then move on to our works in the area of GPCRs, which functions are mediated primarily through two pathways: G protein and arrestin. Biased ligands that selectively activated either G protein or arrestin pathways often display better safety profile than the balanced ligand that activated both pathways, thus biased ligands have become a new paradigm of GPCR drug discovery. Over the past 15 years, our laboratory have solved the structures of the first GPCR-arrestin complex as well as the first set of structures of GPCR in complex with the inhibitory G protein Gi.

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Abstract:

Asymmetrical activation of Class C GPCR dimers

Most GPCRs are cell surface proteins that can signal through G proteins in a monomeric state. These proteins can however influence each other through possible allosteric interaction within dimeric or even oligomeric entities. The discovery of the mandatory heterodimeric nature of the GABAB receptor, a class C GPCR, stimulated research on the allosteric interaction between GPCRs. Whereas GABAB agonists bind to the GB1 subunit, the GB2 subunit is solely responsible for G protein activation. Such an asymmetric activation process was then reported for other class C GPCRs, including the dimeric and heterodimeric mGluRs but also for many class A GPCRs homo and heterodimers including the LTB4, OT, D2, 5HT, Mu-a2A receptors.

As mandatory dimers, the class C GPCRs represent an excellent model to elucidate the structural basis for this asymmetrical activation process. We then first identified the dimer interfaces of the Class C mGlu and GABAB receptors in their inactive and active state and identified TM4 and TM5 as the interface of the inactive state, while TM6 is indeed the main component of the active interface. Indeed, cross-linking TM4 or TM5 between subunits prevents their activation by agonists, while cross-linking TM6 generates constitutively active receptors. These findings were largely confirmed by the cryo-EM structures of either the mGlu5, GABAB or CaSR in their antagonists and agonist+PAM stabilized states. Indeed, these structures revealed a close contact between the extracellular tip of TM6, leaving enough space for the possible outward movement of at least one TM6 within a dimer for a G protein activation by one subunit. Such a hypothesis could largely explain that only one subunit within such dimers could be active at a time.

The observation that the GABAB PAMs bind at the active GABAB dimer interface, to the intracellular side of TM6 shades some strong doubts about this idea, as the presence of the PAM made impossible any outward shift of either one of the TM6. This was confirmed by the cryo-E structure of the active GABAB heterodimer bound to the active Gi protein. Indeed, no outward shift of either TM6 was observed, revealing a mainly symmetric structure of the 7TM dimer. However, the structure revealed that, steric hindrance between the active nucleotide free G proteins largely explain why both subunits cannot bind a G protein at a time. Accordingly, the possible asymmetry within class C GPCR dimers may rather come from the action of the G protein on only one subunit, rather than from a direct allosteric interaction between the 7TMs. Such a process may be limited to class C GPCRs as the structural basis for the activation of the 7TMs from the other GPCR classes is different.

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Abstract:

Ligand recognition and signal transduction of Angiotensin II type I receptor

As the largest membrane protein family encoded by human genome, G protein-coupled receptors (GPCRs) regulate almost all known physiological processes and are considered the most important drug target. Angiotensin II receptor type 1 (AT1R), a key component of the renin-angiotensin system, plays a critical regulatory role in various physiological processes such as vasoconstriction and aldosterone secretion. The AT1R was known to sense the octapeptide angiotensin II (AngII), which is converted from angiotensin I by angiotensin-converting enzyme (ACE), to initiate Gq, Gi and arrestin signaling to regulate vascular resistance, cardiac output, inflammatory response and gastrointestinal functions. However, whether AT1R could sense other endogenous ligands and how specific downstream signaling of AT1R are organized to precisely regulate different physiological functions required further delineation.

Recently, we have identified homocysteine (hcy) and cartilage oligomeric matrix protein (COMP) as endogenous ligands of AT1R1,2. Whereas the hcy partially activates AT1R and synergistically increases AngII-induced vascular injury, the COMP acts as an endogenous allosteric biased modulator and counteracts the vascular injury by selectively blocking β-arrestin-2 pathway. We also found that β-arrestin-1 biased ligand stimulation promotes the direct coupling of AT1R to ion channel TRPC3 and regulates acute catecholamine secretion from chromaffin cells, which might be linked to higher risk of hypertension3. Moreover, by a combined computational and experimental framework, we unprecedently identified a cryptic allosteric site in AT1R, which might be targeted to develop allosteric modulators4.

Collectively, our results identified novel endogenous ligands of AT1R, delineated the molecular mechanism underlying AT1R biased signaling, and shed light on the development of selective modulators. These findings provide a deeper understanding of AT1R activation and might reveal novel therapeutic strategies for cardiovascular diseases.

Yan Zhang, Professor

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Abstract:

Insights into Lipid Modulation of GPCR Signal Transduction

Cholesterol, phospholipids, and lipid modifications play important roles in structural stability, ligand recognition, aggregation status, and signal transductions of GPCR and its downstream effector proteins. In recent years, although great progresses have been made in the study of GPCR structures and ligand-mediated activation mechanism, the understanding of membrane environment and membrane lipids on the regulation of GPCR function is still scarce.

In our recent papers, (1) the Go protein C351 site was modified by palmitoylation and mediated adhesion receptor GPR97 coupling with G protein; (2) phosphatidylinositol-4-phosphate (PI4P) is the molecular basis for the high constitutive activity of the 5-HT1A receptor. Our studies have shown that the 5-HT1A receptor has high constitutive activity and can form complexes with Gi proteins without the addition of an agonist. This discovery reveals the molecular mechanism of the high constituent activity of 5-HT1A receptor, which is of great significance for the functional study of 5-HT1A receptor; (3) phospholipid was first discovered as a structural molecule to enhance the stability of GABAB receptor. Phospholipids, as structural molecules, can enhance the stability of GABAB receptor. It was first found in the analysis of the structure of GABAB receptor under electron microscope that phospholipids are occupied in the TM domain of inactive and active GABAB, and recently determined GABAB-Gi complex, which is likely to be an essential structural molecule of GABAB receptor.

Xin Xie, Professor

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Abstract:

GPCRs in Oligodendrocyte Differentiation and Myelin Regeneration

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Our group is interested in the biological functions of G protein-coupled receptor (GPCR) and their roles in major diseases including autoimmune disease, neurodegenerative diseases, metabolic diseases and etc. In addition to the mechanism study, we also screen and develop drugs targeting GPCRs. In recent years, we also seek to study the mechanism of fate determination of stem cells with small molecule compounds.

One of the autoimmune diseases we're particularly interested is Multiple Sclerosis (MS). MS is an inflammatory disease that is characterized by immune-mediated demyelination and degeneration of the central nervous system. In the past few years, we've discovered that two GPCRs (CysLT1 and A2B) are critically involved in the development of MS by regulating the differentiation or function of immune cells. Blocking these receptors alleviates clinical symptoms of EAE, a mouse model of MS, indicating these receptors are potential drug targets for MS. Current drugs for MS all targets immune system. Although effective in reducing the relapse rate and the formation of new lesions, these drugs have very limited effects in preventing the progression of disability. Promoting oligodendrocyte progenitor cell differentiation, remyelination and subsequent functional recovery of the neurons have been proposed to be the new direction of MS therapy. Our recent study demonstrated that KOR, an opioid receptor, is important for oligodendrocyte-mediated remyelination in EAE, suggesting KOR might be a target to develop new MS therapies from a regenerative point of view.

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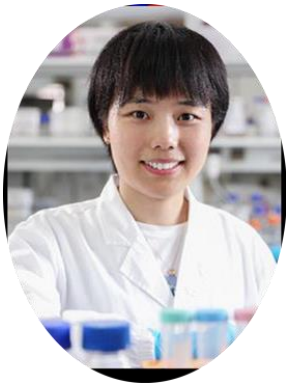
Abstract:

Coupled activation of TRPV1 and ANO1 in sensory neurons

ANO1 (TMEM16A) is a Ca2+ activated Cl- channel (CaCC) with functions ranging from epithelial transport to sensory transmission. ANO1 is expressed several tissue types, including epithelia, vasculature, as well as peripheral somatosensory neurons. These neurons also express the Ca2+ permeable heat sensor TRPV1 and functional coupling between TRPV1 and ANO1 has been demonstrated. ANO1 is also robustly activated by the Ca2+ release from the endoplasmic reticulum (ER) through inositol trisphosphate receptors (IP3R). Interestingly, TRPV1 was shown to induce Ca2+ release from the ER by activating phospholipase C (PLC). Thus, here we investigated Ca2+ sources coupling TRPV1 and ANO1 activation; we hypothesised that TRPV1 may be able to activate ANO1 through IP3R Ca2+ release as well. To this end, we developed a multi-wavelength live cell imaging approach to simultaneously monitor CaCC activity and Ca2+ dynamics in the dorsal root ganglion (DRG) neurons. We observed that activation of TRPV1 with capsaicin was indeed able to induce CaCC. Furthermore, CaCC activity produced by capsaicin application was attenuated after depletion of the ER Ca2+ load, suggesting that ER Ca2+ release contributed to TRPV1-induced CaCC activation. To confirm that this effect was induced by plasmalemmal and not ER-localised TRPV1 channels, we used a cell impermeable TRPV1 activator, a derivative of double knot spider toxin, in combination with an ER-Ca2+ sensor to demonstrate that ER depletion only occurs when membrane-localised TRPV1 are activated. To understand if there was a structural arrangement of channels that allowed this coupling, we used in situ Proximity ligation assay (PLA) and stochastic optical reconstruction microscopy (STORM) to show that ANO1, TRPV1 and IP3R receptors were often found in close proximity in DRG neurons. In summary, our findings demonstrate that functional coupling between ANO1 and TRPV1 in sensory neurons is facilitated by Ca2+ release through IP3R with the channels found in a nanodomain structure to enable efficient ANO1 activation.



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Abstract:

Structural basis of rapid-antidepressant ketamine action on human NMDA receptors

Ketamine is a non-competitive channel blocker of N-Methyl-D-Aspartate (NMDA) receptor. A single sub-anesthetic dose of ketamine produces rapid (within hours) and long-lasting antidepressant effects in patients who are resistant to other antidepressants. Ketamine is a racemic mixture of S- and R-ketamine enantiomers, with S-ketamine isomer as the more active antidepressant. Here we determined the cryo-EM structures of human GluN1-GluN2A and GluN1-GluN2B NMDA receptors in complex with S-ketamine, glycine and glutamate. Both electron density maps uncovered the binding pocket for S-ketamine in the central vestibule between the channel gate and selectivity filter. Molecular dynamics simulation revealed that S-ketamine displays motions between two distinct locations within the binding pocket. Two amino acids, L642 on GluN2A (homologous L643 on GluN2B) and N616 on GluN1, were identified as key residues forming hydrophobic and hydrogen-bond interactions with ketamine, and mutations at these identified residues led to the reduced potency of ketamine in blocking the NMDA receptor channel activity. These findings provide the structural basis of ketamine binding and action on human NMDA receptors, and pave the way for future development of ketamine-based antidepressants.

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Abstract:

De novo design of peptidic positive allosteric modulators targeting TRPV1 with analgesic effects

Transient Receptor Potential Vanilloid 1 (TRPV1) ion channel is a nociceptor critically involved in pain sensation. Direct blockade of TRPV1 exhibits significant analgesic effects but also incurs severe side-effects such as hyperthermia, causing failures of TRPV1 inhibitors in clinical trials. In order to selectively target TRPV1 channels that are actively involved in pain-sensing, we de novo designed peptidic positive allosteric modulators (PAMs) based on the high-resolution structure of the TRPV1 intracellular ankyrin-repeat like domain. We optimized the hot-spot centric approach (OHCA) for protein design; its usage in Rosetta increased the success rate in protein binder design. We demonstrated experimentally, with a combination of FRET imaging, surface plasmon resonance and patch-clamp recording, that the designed PAMs bind to TRPV1 with nanomolar affinity and allosterically enhance its response to ligand activation as we designed. We further demonstrated that the designed PAM exhibits long-lasting in vivo analgesic effects in rats without changing their body temperature, suggesting that they have potentials for developing into novel analgesics.

Hailong An, Professor

Hebei University of Technology

Abstract:

Insights into the Gating Mechanism of ANO1 and Drug Screening Targeting

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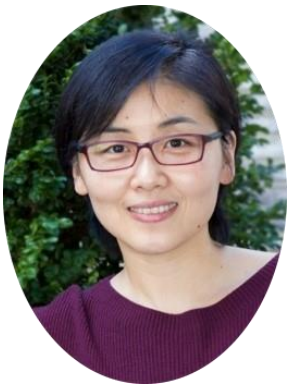
The calcium-activated chloride channel ANO1, also known as TMEM16A, shows calcium-dependent activation. The channel is expressed broadly and contributes to a variety of physiological processes. The mutation or abnormal expression of ANO1 channel is related to cancer and gastrointestinal dysfunction. Therefore, this channel is promising as a drug target for the above-mentioned diseases. Revealing the allosteric mechanism and the drug regulation mechanism of ANO1 is very important for understanding the relationship between channel structure and function. First, we explored the Ca2+-dependent gating mechanism of the ANO1 channel by molecular simulations. The results show that chloride ions remain semi-hydrated as they pass through the hydrophobic neck region and require the assistance of K645 and K588. Moreover, E705 in the TM7 plays a key role in Ca2+ dependent activation. It stabilizes the closed conformation of the pore in the Ca2+ unbound state, but swings 100o to serve as Ca2+ binding coordination in the Ca2+ bound state. Secondly, we identified the binding pocket of the ANO1 inhibitor, CaCCinh-A01, which is located at the extracellular entrance of the pore by molecular docking and targeted mutagenesis. To characterize the druggability of this binding pocket, we performed a virtual screen and found a highly potent inhibitor of ANO1, theaflavin. Molecular dynamics simulations revealed that theaflavin adopts a "wedge insertion mode" to block the ion conduction pore and induces pore closure. Moreover, the binding mode showed that the theaflavin pedestal plays an important role in pore blockade, and R515, R535, T539, K603, E623, and E633 were determined to be most likely to interact directly with the pedestal. Next, to confirmed that ANO1 can be used as an anticancer drug target, we obtained a natural product inhibitor of ANO1, arctigenin, based on the inhibitor binding pocket identified in the above study. Molecular biology experiments showed that arctigenin concentration-dependently inhibited the proliferation and migration of LA795, however, the inhibition effect can be abolished by knockdown of the endogenous ANO1 with shRNA. Further, we injected arctigenin on xenograft mouse model which exhibited significant antitumor activity with no adverse effect. Finally, to confirmed that ANO1 can be a drug target for the treatment of gastrointestinal motility disorders, we screened for several ginsenoside analogs (GRb1 GRg2 and GRf) that activate ANO1 channels. Isolated guinea pig ileum assay showed both GRb1 GRg2 and GRf increased the amplitude and frequency of ileum contractions. Therefore, GRb1 GRg2 and GRf can be considered a lead compound for the development of novel drugs for the treatment of diseases caused by ANO1

dysfunction. In summary, based on the study of a series of gating and drug regulatory mechanisms of ANO1 channels, we confirmed the feasibility of ANO1 as a drug target for diseases such as cancer and gastrointestinal dyskinesia, which will be useful for drug development of related diseases.



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Abstract:

To reveal the choreography of the Nav/Cav channels – something AlphaFold is incapable

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Abstract:

Activation and inhibition of the taste channel TRPM5

The Ca2+-activated TRPM5 channel plays an essential role in the perception of sweet, bitter, and umami stimuli in type II taste cells and in insulin secretion by pancreatic beta cells. Interestingly, the voltage dependence of TRPM5 in taste bud cells depends on the intracellular Ca2+ concentration, yet the mechanism remains elusive. In this talk, I will share our new findings on the structure and function of the TRPM5 channel. We determined cryo-electron microscopy structures of the zebrafish TRPM5 in an apo closed state, a Ca2+-bound open state, and an antagonist-bound inhibited state, at resolutions up to 2.3 Å. We defined two novel ligand binding sites: a Ca2+ binding site (CaICD) in the intracellular domain (ICD), and a binding site in the transmembrane domain (TMD) for a highly potent antagonist. The CaICD site is unique to TRPM5 and has two roles: shifting the voltage dependence toward negative membrane potential, and promoting Ca2+ binding to the CaTMD site that is conserved throughout Ca2+-sensitive TRPM channels. Replacing glutamate 337 in the CaICD site with an alanine not only abolished Ca2+ binding to CaICD but also reduced Ca2+ binding affinity to CaTMD, suggesting a cooperativity between the two sites. We have defined mechanisms underlying channel activation and inhibition. Conformational changes initialized from both Ca2+ sites, 70 Å apart, are propagated to the ICD–TMD interface and cooperatively open the ion-conducting pore. The antagonist wedges into the space between the S1-S4 domain and pore domain, stabilizing the TMD in an apo-like closed state. Our results lay the foundation for understanding the voltage-dependent TRPM channels and developing new therapeutic agents to treat metabolic disorders.

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