Ion Channels, Smart Materials & Neuroscience Conference

22-23 Feb 2024
Auditorium, Centre for Life Science
National University of Singapore

Programme Booklet

FOREWORD

On behalf of the organising committee, John and I would like to welcome all to the "Ion Channels, Smart Materials and Neuroscience" Conference. We hope that we have, in some small ways, created a collegial and conducive environment for all to come together to share and discuss their latest research, and to stimulate and nudge each other to greater achievements and more startling discoveries.

As the conference is held within the Chinese Lunar New Year, may we wish each and everyone good health, prosperity and fulfilment in the Year of the Dragon. For our foreign guests, please visit Chinatown to soak in the festivities and enjoy the dish called "Yu Sheng" in the hope that in 2024 you and your loved ones will be blessed abundantly, lacking nothing.

Soong Tuck Wah (chairman)
John Chua (Co-chair)

TABLE OF CONTENT

PROGRAMME

Day 1: 22nd Feb 2024

0800	Registration
0900	Opening Remarks **Tuck Wah SOONG**
	Session 1 Chair: Hua HUANG
0915	Sudden Unexpected Death in Epilepsy – Searching for an underlying Mechanism **Terrance SNUTCH, University of British Columbia**
0945	Altered mRNA translation drives social deficits in a mouse model of Cacna1c (Cav1.2) deficiency **Anjali M RAJADHYAKSHA, Cornell University**
1015	Tea
	Session 2 Chair: Sanjay KHANNA
1100	T-type calcium channels, cannabinoids and their roles in pain **Gerald ZAMPONI, University of Calgary**
1130	α2δ mutations linked to brain disorders affect synaptic functions **Gerald OBERMAIR, Karl Landsteiner University of Health Sciences**
1200	Epigenetic mechanisms underlying trigeminal neuropathic pain **Jin TAO, Medical College of Suzhou University**
1230	Lunch

	Session 3 Chair: Sajikumar SREEDHARAN
1400	Catecholamines increase the heart rate via L-type Cav1.3 (alpha1D) and 'funny' f-(HCN) channels **Matteo MANGONI, Institut de Génomique Fonctionnelle**
1430	Same, yet different: gating-modifying CACNA1D (Cav1.3) variants in human disease **Nadine J. ORTNER, University of Innsbruck**
1500	Altered glucose-induced electrical activity and insulin release during pancreatic β-cell postnatal development **Petronel TULUC, University of Innsbruck**
1530	Tea
	Session 4 Chair: Andrew TAN
1615	Synaptic architecture of remote memory recall **Jai Santosh POLEPALLI, National University of Singapore**
1645	The role of Importin-β1 in synapse to nucleus transport of proteins during transcription-dependent plasticity **Toh Hean CHNG, Lee Kong Chian School of Medicine, Nanyang Technological University**
1715	End of Day 1

Day 2: 23rd Feb 2024

0800	Registration
	Session 5 Chair: Chian Ming LOW
0900	Living Materials for Wound Healing **Bin LIU, National University of Singapore**
0930	Ionic channels in artificial membranes for healthcare applications **Daria ANDREEVA-BAEUMLER, National University of Singapore**
1000	Tea
	Session 6 Chair: Ping LIAO
1045	How ion channel alternative splicing varies with neuronal activity and cell type **Richard TSIEN, New York University**
1115	Diverse mechanisms underlying the pathogenesis of calcium channelopathies **Ivy E. DICK, University of Maryland**
1145	Identification of the $Ca_V1.1$ voltage-sensing domain controlling skeletal muscle excitation-contraction coupling **Bernhard Flucher, Medical University of Innsbruck**
1215	Lunch
	Session 7 Chair: Esther WONG
1345	Shaping Neuronal Networks by FEZ1-mediated trafficking **John Jia En CHUA, National University of Singapore**
1415	Engineered depalmitoylases tune ion channel activity and neuronal function **Manu BEN-JOHNY, Columbia University**
1445	Deciphering TDP-43 functions in health and disease **Shuo-Chien LING, National University of Singapore**
1515	Tea

Session 8 Chair: Ajay MATHURU	
1600	Liver-brain axis in metabolic regulation **Sarah Xinwei LUO, Institute of Molecular and Cell Biology**
1630	Impaired synaptic vesicle recycling in Parkinson's disease **Mian CAO, Duke-NUS Medical School**
1700	Modeling Cav3.1 channelopathies in mice **Philippe LORY, Institut de Génomique Fonctionnelle**
1730	End of Day 2

EVENT SPEAKERS

Terrance SNUTCH

Michael Smith Laboratories, University of British Columbia
Djavad Mowafaghian Center for Brain Health, University of British Columbia

Sudden Unexpected Death in Epilepsy – Searching for an underlying Mechanism

Anjali M RAJADHYAKSHA

Weill Cornell Medicine, Cornell University

Altered mRNA translation drives social deficits in a mouse model of *Cacna1c* (Cav1.2) deficiency

Gerald ZAMPONI

Department of Clinical Neuroscience, Hotchkiss Brain Institute, Cumming School of Medicine, University of Calgary

T-type calcium channels, cannabinoids and their roles in pain

Erika K. Harding, Vinicius M. Gadotti, Ivana A. Souza, Maria A. Gandini, Sun Huang, Flavia T.T. Antunes, and Gerald W Zamponi.

Cav3.2 T-type calcium channels are known to be important pharmacological targets in chronic pain states. Chronic pain can also be treated with various cannabinoids and terpenes, and previous evidence from the Connor and Lory laboratories suggested that both phyto-cannabinoids and endocannabinoids mediate analgesic effects via actions on T-type channels. Electrophysiological studies indicate that cannabinoid receptors do not functionally modulate Cav3.2 channels, but instead inhibit the activity of Cav2.2 channels by a membrane delimited pathway. By contrast, several terpenes, CBD and THC directly block Cav3.2 channels, and mediate analgesia via actions on this channel subtype when delivered spinally. By contrast THC does not appear to mediate spinal analgesic actions via cannabinoid receptors. Our data support a key role of Cav3.2 channels in the pain relieving activities of cannabis constituents.

Gerald OBERMAIR

Division of Physiology, Department of Pharmacology, Physiology, and Microbiology, Karl Landsteiner University of Health Sciences

α2δ mutations linked to brain disorders affect synaptic functions

α2δ proteins serve as auxiliary subunits of voltage-gated calcium channels, which are essential components of excitable cells such as nerve and muscle cells. Over the recent years, α2δ proteins have been identified as critical regulators of synaptic functions. Moreover, the genes encoding for the four α2δ isoforms have been linked to neurological and neurodevelopmental disorders including epilepsy, autism spectrum disorders, schizophrenia, and depressive and bipolar disorders. Despite the increasing number of potentially disease-associated mutations, the underlying pathophysiological mechanisms are only beginning to emerge. Using heterologous and homologous expression and analyses of specific knockout and mutant mouse models, we show that mutated α2δ proteins can alter synaptic functions, both, via their role as calcium channel subunits and as independent regulatory entities.

Jin TAO

Department of Physiology and Neurobiology & Centre for Ion Channelopathy, Medical College of Suzhou University

Epigenetic mechanisms underlying trigeminal neuropathic pain

Matteo MANGONI

CNRS, Institut de Génomique Fonctionnelle, Montpellier University

Catecholamines increase the heart rate via L-type Cav1.3 (alpha1D) and 'funny' f-(HCN) channels

The role of ion channels in heartbeat quickening by catecholamines is not understood. We show that sinoatrial node L-type Cav1.3 and hyperpolarization-activated HCN4 channels are the ionic underpin of beta-adrenergic receptor activation of heart rate. Mutant mice carrying ablation of Cav1.3 and expressing dominant-negative cAMP-insensitive HCN4 subunits in the heart lack diurnal variation in heart rate and fail to increase heartbeat after administration of catecholamines, or during physical activity. Consistently, selective pharmacologic inhibition of Cav1.3 prevents catecholaminergic increase in pacemaker activity when cAMP-dependent regulation of HCN4 was abolished, or upon interference with cAMP-mediated molecular movement of HCN4 c-linker structure in the channel c-terminus. Phosphorylation of the small RGK G protein Rad was required for Cav1.3 to increase pacemaker activity under β-adrenergic activation. Or study identifies Cav1.3 and HCN4 channels as the key effectors of beta-adrenergic regulation of sinoatrial pacemaker explaining the ionic mechanism underlying the "flight-or-fight" response of the heartbeat.

Nadine J. ORTNER

Department of Pharmacology and Toxicology, Institute of Pharmacy, Center for Molecular Biosciences Innsbruck, University of Innsbruck

Same, yet different: gating-modifying *CACNA1D* (Cav1.3) variants in human disease

Nadine J. Ortner[1#], Ferenc Török[1], Lucia Zanetti[1], Yuliia Nikonishyna[1], Nadja T. Hofer[1], Jörg Striessnig[1]

Background: Tightly regulated Ca^{2+}-influx through voltage-gated Cav1.3 L-type Ca^{2+} channels (LTCCs) is indispensable for proper physiological functions. Missense variants of their pore-forming α1 subunit (*CACNA1D* gene) have been found in patients with neurodevelopmental and endocrine dysfunction and alter channel gating in a complex manner, promoting Ca^{2+}-influx at subthreshold potentials. Since the presence and severity of symptoms differs among affected individuals, we here aim at i) elucidating the underlying molecular mechanisms, ii) identifying factors that impact clinical manifestation, and iii) studying variant-specific responsiveness to clinically available dihydropyridine (DHP) LTCC inhibitors.
Method: Different splice variants of wildtype and mutant Cav1.3 α1 subunits (co-expressed with β3 or β2a and α2δ1) were transiently expressed in tsA201 cells. Biophysical properties and pharmacological modulation by the LTCC inhibitor isradipine were determined in whole-cell patch-clamp recordings (15mM Ca^{2+}).

Results: All investigated disease-associated Cav1.3 mutant variants showed typical gating changes, in particular a shift of the voltage-dependence of gating towards more hyperpolarized membrane potentials. The extent of this shift differed strongly among variants (voltage of half-maximal activation, $V_{0.5}$, shifted by -10 mV up to -30 mV). Moreover, tail currents were prolonged and kinetics of channel inactivation during 5-s long depolarizing stimuli to the voltage of maximal activation were either unaltered or affected differentially (de- or increased inactivation). Interestingly, mutation-induced gating defects were preserved in different splice variants of Cav1.3 channels. Perfusion with different concentrations of the DHP isradipine revealed mutation-specific changes of drug responsiveness, with most variants showing preserved or

even increased isradipine sensitivity at negative membrane potentials (IC_{50} decreased by 2 to 7-fold with β3).

Conclusion: The low number of 13 patients affected by such high-risk *CACNA1D* variants precludes the identification of a clear genotype-phenotype correlation to date. However, the complex and variant-specific gating changes likely contribute to the observed inter-patient variability, and larger shifts of $V_{0.5}$ seem to correlate with disease severity. In the absence of reliable Cav1.3-selective inhibitors, our findings of preserved or even increased DHP sensitivity justify off-label treatment attempts in affected individuals.

Petronel TULUC

Department of Pharmacology and Toxicology, Institute for Pharmacy, University of Innsbruck

Altered glucose-induced electrical activity and insulin release during pancreatic β-cell postnatal development

Tamara Theiner[1], Petronel Tuluc[1]

[1] Department of Pharmacology and Toxicology, Institute for Pharmacy, University of Innsbruck

Monogenic forms of diabetes indicate an early age incidence independent of the immune response. While many postnatal physiological changes could be the cause, we hypothesized that also age-dependent variations in pancreatic β-cell function and mass contribute.

In 1-day, 14-days and 3-month old mice the pancreatic islets are well formed but, adult islets show a higher β-cell count (~80%) compared to earlier developmental stages (~67-70%). Electrophysiological characterization demonstrates that β-cells of 1-day old mice have significantly smaller high voltage-gated calcium channel (HVCC) currents compared to 14-day or adult mice by ~41% and ~15% respectively. Additionally, HVCC calcium influx in 1-day old β-cells is conducted mostly by R-type (~33%) and P/Q-type (~42%) while L-type channels contribute only with ~25%. Conversely, 14-day old β-cells show the largest HVCC calcium influx compared to other ages. Nevertheless, the L-type channels contribution to whole-cell calcium influx is similar to adults (~44% vs 50%). The smaller L-type currents in β-cells of 1-day old mice causes a complete absence of β-cell specific glucose-induced electrical activity. Conversely, the higher HVCC currents in β-cells of 14-days old mice enhance the glucose sensitivity of the electrical activity (EC50 = 6.1 mM Glucose) compared to adults (EC50 = 8.9 mM Glucose). Nevertheless, despite the better glucose sensitivity and larger calcium influx, the islets of 14-days old mice show ~30% lower peak of glucose-induced insulin release compared to adults. Cumulative our data show extensive variability in β-cell mass, glucose sensitivity, HVCC calcium currents, and electrical activity that cause reduced insulin release during postnatal development.

Jai Santosh POLEPALLI

Department of Anatomy, National University of Singapore
LSI Neurobiology Programme, National University of Singapore

Synaptic architecture of remote memory recall.

The prefrontal cortex (PFC) is involved in the formation and retrieval of memories. The PFC circuits exhibit diversity in synaptic properties, enabling them to perform precise computations in a fool-proof manner that result in normal behavioural output. Neurexins and neurexin interacting proteins, including cerebellins play crucial role in determining synapse specificity. One member of the Cerebellin family, Cerebellin-4 (Cbln4) is enriched in the PFC. We show that Cbln4 in the PFC mediates long-term storage of memories. Deletion of Cbln4 in the PFC diminishes recall of remote contextual memory but not recall of recently formed memories. At the synapses, loss of Cbln4 leads to reduced numbers of GABAergic and glutamatergic synapses.

Toh Hean CHNG

Lee Kong Chian School of Medicine, Nanyang Technological University
School of Biological Sciences, Nanyang Technological University

The role of Importin-β1 in synapse to nucleus transport of proteins during transcription-dependent plasticity

Enduring changes in synaptic efficacy is associated with the encoding of long-term memories and this requires activity-dependent transcription of new genes and translation of new proteins. It has been demonstrated that various transcriptional modulators are localized at the synapse and are transported to the nucleus during neuronal activity and this activity-dependent translocation is critical for different aspects of long-term plasticity. The failure of this signal transmission is the underlying cause of numerous neuropsychiatric and neurocognitive disorders. Our lab has studied the transport of proteins and plasticity factors from the synapse to the nucleus by looking at the adaptor protein Importin-β1, a component of the classical nuclear import machinery. Here, we present evidence that Impβ1 is localized at different subcellular compartments and play an important role in different forms of long-term plasticity in hippocampal neurons. We also show evidence that importin β1 mRNA is localized in dendrites and synapses and undergoes robust local translation in stimulated synapses, suggesting that the transport machinery plays an active role in shuttling plasticity-associated proteins into the nucleus. Finally, we describe a novel method of isolating plasticity factors that bind to Impβ1 at the synapse and identify putative candidates that may undergo synapse to nucleus signaling.

Bin LIU

Institute for Functional Intelligent Materials, National University of Singapore
Department of Chemical and Biomolecular Engineering, National University of Singapore

Living Materials for Wound Healing

Chronic wounds that are hard to heal pose a significant global public health challenge due to their limited treatments caused by bacterial infections and microcirculatory disturbances. Recently, we have developed an artificial skin through a bioengineering approach that sandwiches bacterial cellulose between photosensitizers and functionalized living cells. Glucose-modified photosensitizer (TBG) and vascular endothelial growth factor (Vegf)-functionalized living cells (HCVegf) were respectively modified on opposite sides of bacterial cellulose (BC) through biological metabolism and bioorthogonal reaction. The TBG layer, as the outermost layer, efficiently generates reactive oxygen species upon illumination to combat bacterial infections. HCVegf layer, the inner layer near diabetic wound, serves as a living factory for continuous delivery of Vegf to promote fibroblast proliferation and angiogenesis, thereby accelerating wound repair. Both *in vitro* and *in vivo* results demonstrated that the administration of HCVegf-BC-TBG significantly enhanced the healing process of infected diabetic wounds. Moreover, our results confirmed that this artificial skin is non-toxic and immune compatible, rendering it a promising next-generation medical therapy for the management of infected chronic wounds.

Daria ANDREEVA-BAEUMLER

Institute for Functional Intelligent Materials, National University of Singapore
Materials Science and Engineering Department, National University of Singapore

Ionic channels in artificial membranes for healthcare applications

While highly selective and permeable ionic channels are key transport pathways in biological membranes, achieving similar efficiency in artificial membranes remains a considerable challenge in membrane science and technology. In our pursuit of achieving high efficiency in water and ionic transport within artificial materials, we have developed a technology combining graphene-family 2D materials and macromolecules, particularly polyelectrolytes. Our recent research involves the creation of 2D membranes using graphene-oxide and synthetic polyamines, chitosan, and cellulose derivatives, forming a network of ionic channels. These membranes demonstrate regulated permeability for water and ions, akin to biological membranes [1, 2]. They showcase functionalities such as pH-induced release/uptake quantum dosing for biodetection [3], regulated ionic transport for sustainable anticorrosion [4], and various other bio-inspired features [5]. Artificial membranes endowed with inherent intelligence do not only mimic cellular functions but also have fundamental implications across diverse scientific and technological domains. They find extensive applications in healthcare and biomedical fields, including drug delivery systems, bionic devices, and biosensors.

Reference

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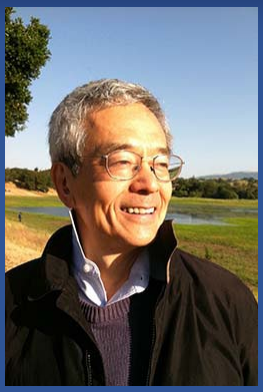

Richard TSIEN

Center for Neural Science, University of New York
NYU Neuroscience Institute and Department of Neuroscience and Physiology, NYU Langone Medical Center

How ion channel alternative splicing varies with neuronal activity and cell type

Y. Sun[1], Y. Qin[2], B. Li[2], X. Chen[3], R. W. Tsien[1]; [1]Neuroscience Institute, New York University Grossman School of Medicine, New York, NY; [2]Sun Yat-sen University, Guangdong, China; [3]Allen Institute for Brain Science, Seattle, WA

Neurons can regulate their excitability and firing properties through two processes: Hebbian plasticity, which uses positive feedback to amplify responses to changes in activity, and homeostatic plasticity, which utilizes negative feedback to maintain functional stability. These seemingly opposing processes allow incorporation of new information while stabilizing overall network excitability. Balancing these two forms of plasticity involves changes in ion channels that determine firing properties. One way ion channels can be altered is by regulation of alternative splicing, but how patterns of splicing vary across genes, cell types, and changes in activity is understudied and unclear. To investigate the activity-dependence of ion channel splicing, we analyzed RNAseq and collected PCR confirmatory results of alternative splicing in different ion channels. We found that splicing is regulated in distinct ways. For example, the inclusion of an NTD of Cavb4 increases under chronic inactivity and decreases under chronic depolarization. Expression of this splice variant has been shown to enhance current density of calcium channels, and its splicing changes suggest homeostatic regulation of neuronal excitability. On the other hand, Li et al. (2020) found that exclusion of an exon in BK channel is favored under both low and high activity, a non-monotonic pattern echoed by Nav1.2. For BK, exon exclusion widens the action potential, leading to homeostatic regulation under inactivity and Hebbian plasticity under depolarization. Thus, our results show exemplars of both monotonic and non-monotonic patterns of activity-dependent alternative splicing.

We next asked how the splicing changes we found might influence overall circuit function, a task that requires interrogation of individual cell types.

Cell types play distinct roles in neural circuits: splicing of an ion channel that increases excitability will have opposite circuit effects depending on whether it occurs in an excitatory or inhibitory neuron. Detecting cell type-specific splice variants requires distinguishing diverse neuronal types in the brain and simultaneously probing splice variants in those same neurons. To do this, we capitalized on BARseq, a high-throughput in situ sequencing method that can resolve neuronal types in brain slices (Sun et al. 2021). Adapting BARseq for exon detection allowed us to characterize differential expression of splice variants across brain regions and cell types. This paves the way for assaying activity-dependent splicing in intact circuits and investigating cell type-specific modifications underlying circuit plasticity.

Ivy E. DICK

Department of Physiology, University of Maryland School of Medicine

Diverse mechanisms underlying the pathogenesis of calcium channelopathies

$Ca_V1.2$ L-type Ca^{2+} channels are perhaps the most prevalent of the voltage-gated Ca^{2+} channels, existing in cardiac, neuronal and smooth muscle cell. Ca^{2+} entry through these channels is precisely controlled through multiple forms of regulation. A growing number of genetic mutations in $Ca_V1.2$ have been linked to a disruption of these regulatory processes, resulting in severe clinical phenotypes including cardiac arrhythmia and long-QT syndrome (LQTS). Interestingly, a subset of these mutations also produce neurological symptoms including autism spectrum disorder (ASD) and developmental delays. Here, we will probe the mechanisms underlying these tissue specific effects, identifying specific properties correlating to neurological phenotypes. Further, by evaluating these mutations using induced pluripotent stem cell derived neurons we can gain understanding into the pathogenesis of these $Ca_V1.2$ channelopathies.

Bernhard FLUCHER

Institute of Physiology, Medical University of Innsbruck

Identification of the $Ca_V1.1$ voltage-sensing domain controlling skeletal muscle excitation-contraction coupling

The skeletal muscle voltage gated calcium channel $Ca_V1.1$ functions as voltage sensor of excitation-contraction (EC) coupling as well as L-type calcium channel. Upon depolarization, $Ca_V1.1$ triggers the opening of the RyR1 in the sarcoplasmic reticulum, causing the calcium release essential for skeletal muscle contraction. Upon strong stimulation, $Ca_V1.1$ further elicits a calcium current; however, with kinetics and voltage-dependence different from those of EC coupling. We hypothesize that these distinct activation properties result from differential roles of the four $Ca_V1.1$ voltage-sensing domains (VSDs). Using site-directed mutagenesis and channel chimeras, we specifically altered the properties of individual VSDs and analyzed the effects of these operations on channel gating and the activation of EC coupling. Whereas mutations in all four VSDs affect the current properties, only mutations in VSD III reduce the amplitude and shift the voltage-dependence of depolarization-induced calcium release. Whereas all four VSD contribute to different aspects of channel gating, only a single VSD is sufficient for controlling EC coupling. Molecular dynamics simulations demonstrate that the pivotal role of VSD III in the EC coupling process is reflected by its rapid and comprehensive state transitions in response to membrane depolarization. Thus, our results demonstrate how the four VSDs of this voltage-gated ion channel divide physiological tasks among each other and reveal structural principles underlying the distinct physiological roles of the four VSD of this voltage-gated calcium channel.

John Jia En CHUA

Department of Physiology, National University of Singapore
LSI Neurobiology Programme, National University of Singapore
Healthy Longevity Translational Research Programme, National University of Singapore

Shaping Neuronal Networks by FEZ1-mediated trafficking

The myriad functions of the human brain is endowed by its networks of neurons. During brain development, neuronal projections sent out by billions of neurons navigate, with help from guidance cues, to target neurons and form trillions of synaptic connections to establish neuronal networks. Molecular motors of the Kinesin superfamily and their adapters play critical roles in supporting the growth and maturation of these networks by delivering essential biological materials to extending neuronal projections and developing synapses. We previously uncovered FEZ1 as a Kinesin-1 adapter involved in the delivery of synaptic cargoes. I will share how our recent findings have shed further light on the adapter's involvement in shaping the development of central and peripheral neuronal networks, and how perturbation of its function contributes to neuropsychiatric and neurodegenerative disorders.

Manu BEN-JOHNY

Department of Physiology and Cellular Biophysics,
Columbia University

Engineered depalmitoylases tune ion channel activity and neuronal function

S-Palmitoylation is a crucial post-translational modification that tunes the function and localization of various proteins including ion channel complexes and synaptic proteins. Palmitoylation is a reversible process mediated by zDHHC family of palmitoyl-transferases and acyl-protein thioesterases that attach and excise palmitic groups, respectively. Altered protein palmitoylation has been linked to a wide range of ailments including neurodevelopmental and neurodegenerative diseases. As such, strategies to selectively manipulate protein palmitoylation with enhanced temporal and subcellular precision are highly sought after to both delineate physiological functions and as potential therapeutics. Here, we develop a new approach to manipulate palmitoylation of target proteins by engineering the α/β-hydrolase domain containing protein 17 (ABHD17) with a chemically inducible dimerization. We further demonstrate that this strategy is programmable, allowing selective depalmitoylation in specific organelles and of individual protein complexes. Application of this approach revealed multifaceted modulation of presynaptic voltage-gated calcium channels. Overall, this strategy represents a versatile and powerful method for dissecting the dynamics of protein palmitoylation in live cells, providing valuable insights into their regulation in distinct physiological contexts

Shuo-Chien LING

Department of Physiology, National University of Singapore
Programs in Neuroscience and Behavioral Disorders, Duke-NUS Medical School
Healthy Longevity Translational Research Programme, National University of Singapore

Deciphering TDP-43 functions in health and disease

Common genetic loci and pathological signatures have unified two seemingly different adult-onset neurodegenerative diseases, amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD), which affect predominantly the motor system and cognition, respectively. In particular, mutations in TDP-43 are causal for both diseases coupled with the pathological TDP-43 inclusions present in the neurons and glia indicate that TDP-43 dysfunctions in these cells trigger ALS and FTD pathogenesis. Furthermore, TDP-43 aggregates, collectively known as TDP-43 proteinopathies, are common in aging human brains and in other neurodegenerative diseases, such as Alzheimer's disease (AD), underscoring the critical role of TDP-43 in brain health.

TDP-43 is ubiquitously expressed. Curiously, pathological TDP-43 also can be found in neurons, glia and other peripheral systems. Two key questions: the physiological functions of TDP-43 in different cell types, and whether the loss of TDP-43 in distinct glia contribute to ALS/FTD pathogenesis, remain unresolved. To this end, we systematically analyzed mice with TDP-43 deleted in distinct glia, including oligodendrocytes, Schwann cells and astrocytes. We uncovered that (1) TDP-43 is indispensable for oligodendrocyte survival and myelination by regulating SREBF2-mediated cholesterol metabolism, (2) TDP-43 is required for maximize conduction velocity by maintaining paranodal assembly in Schwann cells, and (3) TDP-43 maintains the protective status of astrocytes. Loss of TDP-43 function in each of the distinct glia results in motor deficits without apparent damage to motor neurons. These results highlight that TDP-43 participate in different physiological role in distinct glia, and TDP-43 dysfunction in different glia may be an integral part of ALS pathogenesis.

Sarah Xinwei LUO

Institute of Molecular and Cell Biology

Liver-brain axis in metabolic regulation

Maintaining energy homeostasis requires accurate sensing of incoming nutritional substrates and internal metabolic state, coupled with mechanisms to direct and utilize available resources. As a gateway between the gastrointestinal tract and the rest of the body, the mammalian liver is uniquely positioned to act as both metabolic and immune sensor and effector. Yet, the liver does not act in isolation and its functions are tightly regulated by the brain through innervation of the autonomic nervous system. The bidirectional connection between the central nervous system and hepatic neurocircuitry remains largely undefined, and presents a novel avenue for discovery. In this talk, I will present our findings of a sensory liver-brain neural circuit mediating communication of inflammatory state and the consequences of manipulating this circuit on feeding regulation. In addition, I will discuss preliminary findings on novel brain regions synaptically connected to the liver that may impact metabolic regulation. These studies further our understanding of brain communication with peripheral organs and may lead to novel strategies for managing inflammation and metabolic diseases.

Mian CAO

Neuroscience and Behavioural Disorders programme, Duke-NUS Medical School
Department of Physiology, National University of Singapore

Impaired synaptic vesicle recycling in Parkinson's disease

Parkinson's disease (PD) is the second most common neurodegenerative disorder characterized by selective loss of dopamine neurons in the midbrain and defective dopamine input to the striatum. Mutations in two genes encoding synaptically-enriched clathrin-uncoating factors, synaptojanin 1 (SJ1) and auxilin, which are involved in synaptic vesicle recycling, have been implicated in atypical Parkinsonism.

Here I will talk about several SJ1 and auxilin mutant mouse models we have generated and characterized. SJ1 knock-in (SJ1-KI^{RQ}) mice carrying a disease-linked missense mutation and auxilin knockout (Aux-KO) mice phenocopy each other and display neurological manifestations reminiscent of Parkinsonism, including dystrophic changes of nigrostriatal dopamine terminals. Furthermore, Aux-KO/SJ1-KI^{RQ} double mutant mice have shorter lifespan, more severe synaptic defects and dystrophic dopamine terminals than single mutant mice, as well as adaptive changes in striatal interneurons. In addition, selective and complete loss of SJ1 in dopamine neurons in SJ1 conditional KO (cKO) mice leads to similar dystrophic changes of dopamine terminals in a cell autonomous and gene dosage dependent manner.

In summary, the similar pathology and synergistic effect of SJ1 and auxilin mutations demonstrates a special lability of dopamine neurons to defects in clathrin uncoating, with implications for PD pathogenesis in at least some forms of this condition.

Philippe LORY

CNRS, Institut de Génomique Fonctionnelle, Montpellier University

Modeling Cav3.1 channelopathies in mice

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