MEETING REPORT

Highlights for the 6th International Ion Channel Conference: ion channel structure, function, disease and therapeutics

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Abstract To foster communication and interactions amongst international scholars and scientists in the field of ion channel research, the 6th International Ion Channel Conference (IICC-2017) was held between June 23–27, 2017 in the eastern coastal city of Qingdao, China. The meeting consisted of 450 attendees and 130 speakers and poster presenters. The program consisted of research progress, new findings and ongoing studies that were focused on (1) Ion channel structure and function; (2) Ion channel physiology and human diseases; (3) Ion channels as targets for drug discovery; (4) Technological advances in ion channel research. An insightful overview was presented on the structure and function of the mechanotransduction channel Drosophila NOMPC (No mechanoreceptor potential C), a member of the transient receptor potential (TRP) channel family. Recent studies on Transmembrane protein 16 or Anoctamin-1 (TMEM16A, a member of the calcium-activated chloride channel [CaCC] family) were summarized as well. In addition, topics for ion channel regulation, homeostatic feedback and brain disorders were thoroughly discussed. The presentations at the IICC-2017 offer new insights into our understanding of ion channel structures and functions, and ion channels as targets for drug discovery.

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1. Introduction

Ion channels, present in membranes of all cells, are pore-forming membrane proteins that allow passage of ions, such as calcium, sodium and potassium, through the pore. The functions of ion channels include control of resting membrane potential, the shaping of action potentials and other electrical signals, controlling the flow of ions across secretory and epithelial cells, and regulating cell volume. The International Ion Channel Conference (IICC) is a conference series focused on ion channel research. The aim of the conference is to foster communications and interactions amongst ion channel researchers in the world, and to showcase the latest groundbreaking discoveries and technological break-throughs with a particular focus on ion channel structure, function and therapeutics. A brief conference history of IICC is summarized in Fig. 1. The IICC started in 2007 and is held in every two years at a city in mainland China. The number of participants of the IICC increased continually from less than 200 attendees in 2007 to 450 in 2017, indicating the growing interests and increasing impact of the conference in the field of ion channel research. This year, the 6th IICC, chaired by Dr. Kewei Wang at Qingdao University and Dr. Jian Yang at Columbia University, was held between June 23 to 27 in Qingdao, China.

The 2017 IICC was organized as a series of topical symposia, aiming at communicating updated findings from understanding of ion channel structures, molecular mechanisms, physiology and channelopathies to new perspectives for future research and therapeutics. At the meeting, leading scholars in the field such as Lily Jan, Yuh Nung Jan and Richard W. Tsien presented their keynote lectures. Lily Jan, a professor at University of California San Francisco, is an expert in physiological functions of potassium channels and calcium-activated chloride channels. The research topics of Dr. Yun Nung Jan (also a professor at UCSF) include: (1) molecular mechanisms underlying dendrite morphogenesis with an emphasis on the role of kinases, (2) regulators of axon and dendrite regeneration, and (3) mechanotransduction channels. Professor Richard W. Tsien, currently at New York University, studies calcium channel regulations, homeostatic feedback and brain disorders.

A roster and introduction of all invited speakers and symposium chairs are listed in the website of http://www.iicc2017.org. Four major themes were presented at IICC-2017: (1) Ion channel structure and function; (2) Ion channel physiology and human diseases; (3) Ion channels as targets for drug discovery; (4) Technological advances in ion channel research. In this report, we will briefly highlight the events of IICC-2017.

2. Highlights for symposium Session I: ion channel structure and function

In this session, Dr. Yuh Nung Jan first introduced the progress made by his group in the study of mechanotransduction channels, especially NOMPC (No mechanoreceptor potential C), a member of the transient receptor potential (TRP) family. In his talk, he pointed out that *Drosophila* turns out to be an excellent system for studying mechanotransduction channels. They have identified NOMPC as mechanotransduction channel for gentle touch, sound response as well as defecation behavior in *Drosophila*. Two models were revealed to interpret how force gates mechanotransduction channels. One is the membrane-tension model: force applied to the membrane generates a change in membrane tension that is sufficient to gate the channel. The other model is the tether model: force is transmitted via a tether to gate the channel. As ankyrin repeats (ARs) are essential for NOMPC mechano-gating, which requires the integrity of microtubules associated to the plasma membrane, a tethered mechanism for mechano-transduction channel activation of NOMPC was revealed. Furthermore, the

![Figure 1](image_url) A brief history of the International Ion Channel Conference from 2007 to 2017.
ARs of NOMPC can render voltage-gated potassium channels mechanosensitive, which highlights their functional sufficiency for mechano-gating for those normally mechano-insensitive channels. Structural analysis suggests that the ARs domain of NOMPC resembles a helical spring linking mechanical displacement of the cytoskeleton to the opening of the channel. The basis of translating mechanical force into an electrical signal within a cell is stressed by the NOMPC architecture. Moreover, Dr. Yifan Cheng at UCSF also presented his group's recent structural findings of NOMPC determined by single-particle cryo-electron microscopy (cryo-EM).

Dr. Bailong Xiao discussed the medium-resolution cryo-EM structure of the full-length mouse Piezo1, which forms a trimeric three-bladed, propeller-shaped structure with a putative central pore-module that resembles the pore architecture of other trimeric channels such as the acid-sensing ion channels, and three highly flexible peripheral propeller-resembling structures that might function as mechano-transduction modules. They have functionally identified the miniature ion-conducting pore-module formed by the last-two-TM-containing C-terminal region (residues 2189–2547), key pore-property-determining residues along the ion-permeating pathway, and the mechano-transduction module (residues 1–2190) by combining mutagenesis and electrophysiological characterization. The linker region between the mechanotransduction-module and the pore-module is critical for mechanotransduction and subject to protein interaction for modulating the mechanosensitivity of Piezo1.

Dr. Mark Dell’Acqua then presented the regulation of dendritic spine structural plasticity and synapse-to-nucleus signaling by L-type voltage-gated Ca\(^{2+}\) channel (LTCC) signaling complexes. LTCC is a Ca\(^{2+}\) signaling pathway, whose activity is regulated by multiple mechanisms, including positive regulation by the protein kinase PKA and negative regulation by the protein phosphatase calcineurin (CaN). Both regulatory enzymes are anchored to the channel by the scaffold protein A-kinase anchoring protein (AKAP) 79/150. In his talk, Dr. Dell’Acqua demonstrated another LTCC inhibition form in hippocampal neurons mediated by the endoplasmic reticulum (ER) Ca\(^{2+}\) sensor stromal interaction molecule 1 (STIM1), which is engaged by the neurotransmitter glutamate in a manner that depends on basal enhancement of LTCC function by AKAP-anchored PKA. The negative feedback mediated by STIM1 onto LTCCs results in regulation of both spine ER structure and nuclear signaling by the nuclear factor of activated T cells (NFAT) c3 that requires activation of AKAP-anchored CaN.

Dr. Xiaodong Liu from Tsinghua University presented the down- and up-regulation of LTCC. He mainly reported C-terminus-mediated inhibition (CMI) for Cav1.3 channels that multiple motifs coordinate to tune down Ca\(^{2+}\) current and Ca\(^{2+}\) influx toward the lower limits determined by end-stage Ca\(^{2+}\)-dependent inactivation (CDI). Spatial closeness of any two modules by constitutive fusion among preIQ3-IQ domain (IQV), proximal or distal C-terminal regulatory domain (PCRD and DCRD), facilitates the trio to form the complex, competes against calmodulin, and alters the gating. Acute CMI by rapamycin-inducible heterodimerization helps reconcile the concurrent activation/inactivation attenuations to ensure reduced Ca\(^{2+}\) influx.

3. Highlights for symposium Session II: ion channel modulation

Dr. Lily Jan began her presentation with identification of transmembrane protein 16, anoctamin-1 (TMEM16A) as the calcium-activated chloride channel (CaCC). During her talk, she also examined mechanisms that contribute to the hallmark feature of CaCC, named after the characteristic dependence of CaCC channel gating on calcium and membrane potential. The calcium-activated chloride channels (CaCCs) are heterogeneous groups of ligand-gated ion channels for chloride that have been first identified in salamander photoreceptors and *Xenopus* oocytes. They are present in many epithelial and endothelial cell types as well as in smooth muscle cells and mediate important physiological functions including epithelial secretion, sensory signal transduction as well as smooth muscle contraction.

Dr. Jan also discussed data from several papers of her group in which they first identified TMEM16A as the *Xenopus* oocyte CaCC using *Xenopus* oocytes as an expression system. Furthermore, they found that the TMEM16A expression pattern played significant roles in the physiological functions of CaCCs containing TMEM16A subunits as the rhythmic contraction of gastric smooth muscle diminished from TMEM16A KO mice. Furthermore, they show that TMEM16A modulates mucin secretion and airway smooth muscle (ASM) contraction as inhibition of TMEM16A-CaCC significantly impairs mucus secretion in primary human airway surface epithelial cells and reduces mouse and human ASM contraction. In the process of exploring how the functional TMEM16A-CaCC channel was regulated, they found TMEM16 family, *i.e.* TMEM16A, TMEM16A and TMEM16A shared a homodimeric architecture facilitated by their cytoplasmic N termini. This identified dimerization domain is important for channel assembly in eukaryotic cells. This group also identified four acidic amino acids as putative calcium-binding residues which are strong determinants of anion selectivity in the TMEM16A-CaCC channel. The presence of the positively charged side chains of these residues seem to underlie a more chloride-friendly open state of the channel because alterations of the charge, polarity, and size of amino acid side chains change the ability of different divalent cations to activate the channel.
but nor GIRK2 homotetramers or GIRK2/GIRK3 heterotetramers using transgenic animals.

4. Highlights for symposium Session III: channelopathy and drug discovery

Dr. Richard W. Tsien mainly discussed underlying mechanisms for neuropsychiatric disorders, especially the autism spectrum disorders (ASD). Ion channels selective for \( \text{Ca}^{2+} \), \( \text{Na}^+ \) and \( \text{K}^+ \) are prominent among hundreds of gene products implicated in ASD, along with numerous synaptic and nuclear proteins\(^\text{17} \). In uncovering signaling pathways lying downstream of \( \text{Ca}^{2+} \) channel opening, they found that \( \text{Ca}^{2+} \) rise is linked to the nucleus by a signaling pathway, where communication is initiated by a signaling complex near the dendritic \( \text{Ca}_V^1 \) channel, which sends a shuttle protein (CaMKII) to the nucleus upon activation. The phosphorylation of CaMKII at Thr287 by \( \beta \text{CaMKII} \) protects the \( \text{Ca}^{2+}/\text{CaM} \) signal, and CaN triggers its nuclear translocation. Once arriving in the nucleus, \( \text{Ca}^{2+}/\text{CaM} \) activates CaMKK, and the CREB kinase, CaMKIV\(^\text{18} \). Besides, nonionic \( \text{VA}\text{C} \) signaling is crucial for the function of \( \text{Ca}_V^1.2 \) in synaptic and neuropsychiatric processes as \( \text{Ca}_V^1.2 \) is fused to a ligand-gated \( \text{Ca}^{2+} \)-permeable channel, enabling independent control of localized \( \text{Ca}^{2+} \) and \( \text{VA}\text{C} \) signals. Dr. Tsien concluded that \( \text{Ca}^{2+} \) must first mobilize actin-bound \( \text{Ca}^{2+}/\text{CaM} \)-dependent protein kinase II, freeing it for subsequent \( \text{VA}\text{C} \)-mediated accumulation\(^\text{19} \).

Dr. Jian Payandeh from Genentech Inc. described a general protein-engineering strategy that has enabled the structural determination of the fourth voltage-sensor domain (VSD4) from human voltage-gated sodium 1.7 (Nav1.7) in complex with potent, state-dependent, isoform-selective small molecule antagonists\(^\text{20} \). Visualization of the isoform-selective inhibitor binding-site can help accelerate the development of new treatments for pain that selectively target Nav1.7.

Dr. Henggui Zhang at the University of Manchester discussed the development of the virtual heart for safety screening of anti-arrhythmic drugs \( \text{in silico} \). During his talk, he presented a virtual heart model which integrates ion channels, cells, tissues into a biophysically detailed model of human heart, providing an e-platform for testing the efficacy and safety of drugs\(^\text{21} \).

Dr. Zhuo Huang from Peking University School of Pharmaceutical Sciences presented their recent findings of epigenetic factor Chromodomain Y-like (CDYL) protein that binds to a regulatory element in the intron region of SCN8A (Nav1.6) gene and mainly recruits H3K27me3 activity for transcriptional repression of the gene. Injection of lentiviral CDYL shRNA to rat hippocampal neurons resulted in augmented Nav1.6-mediated sodium currents, lower neuronal threshold and increased seizure susceptibility, whereas transgenic mice over-expressing CDYL had higher neuronal threshold and were less prone to epileptogenesis. Further examination of human brain tissues revealed decreased expression of CDYL and increased expression of SCN8A in the temporal lobe epilepsy.

5. Highlights for symposium Session V: new frontiers in ion channel research

In this session, several young principal investigators presented the frontiers and technological advances in ion channel research. For example, to investigate ion channel in lysosome, Dr. Haoxing Xu from University of Michigan, developed a modified patch-clamp technique to directly record lysosomal membranes, and also established a fluorescence imaging method to specifically measure \( \text{Ca}^{2+} \) release\(^\text{22} \). Dr. William Koberst (University of Massachusetts Medical School) discussed this group’s efforts to fluently visualize ion-existing cells using glycan engineering to install chemical handles into the cell’s glycocalyx that directly abuts the plasma membrane in all cells\(^\text{23,25} \).

Dr. Peter McNaughton from King’s College London presented the identification of TRPM2, a TRP channel, as a novel thermal detector which is responsible for detection of non-painful warmth\(^\text{26} \). They used calcium imaging to monitor the responses of isolated somatosensory neurons to warm and hot stimuli by eliminating neurons responding to agonists for known heat-sensitive TRP channels \( \text{e.g., TRPV2, TRPV1, TRPM3 and ANO1, TRPV3 and TRPV4} \) and focusing on a population of neurons that expressed a novel thermal response. An RNA sequencing strategy was used to identify the thermally-sensitive ion channel expressed in these neurons as TRPM2, a TRP channel not previously reported to be involved in warmth sensation. The TRPM2 knockout mice; however, were unable to distinguish between 33 and 38°C, suggesting that removal of TRPM2 had ablated a “warm” detector.

Dr. Yifan Cheng at UCSF presented lipid nanodisc technology using membrane-scaffolding proteins (MSP) to reconstitute integral membrane proteins into lipid nanoparticles. This highly native-like lipid bilayer system provides a first choice for a general platform for single particle cryo-electron microscopy (cryo-EM) of membrane proteins. By using this approach, they demonstrated the power of combining electron cryo-microscopy to ascertain the structure of rat TRPV1 channel\(^\text{27} \).

6. Summary

A number of talks presented at the 2017-IICC reviewed recent original findings on ion channel structure, function and therapeutics. The conference nicely covered the latest advances in ion channel research. Moreover, channelopathy and related drug discovery was thoroughly presented as well. Many young principal investigators showed their novel advanced technologies. The talks at IICC-2017, as well as the subsequent insightful questions and vivid discussions will undoubtedly further advance the cutting-edge research in the ion channel research field.

References

1. Hille B. \textit{Ion Channels of Excitable Membranes}. 3rd ed. Sunderland, MA: Sinauer; 2001.
2. Yan Z, Zhang W, He Y, Gorczyca D, Xiang Y, Cheng LE, et al. \textit{Drosophila} NOMPC is a mechanotransduction channel subunit for gentle-touch sensation. \textit{Nature} 2013;493:221–5.
3. Zhang W, Yan Z, Jan LY, Jan YN. Sound response mediated by the TRP channels NOMPC, NANCHUNG, and INACTIVE in chordotonal organs of \textit{Drosophila} larvae. \textit{Proc Natl Acad Sci U S A} 2013;110:13612–7.
4. Zhang W, Yan Z, Li B, Jan LY, Jan YN. Identification of motor neurons and a mechanosensitive sensory neuron in the defecation circuitry of \textit{Drosophila} larvae. \textit{Elife} 2014;3:e03293.
5. Jin P, Bulkeley D, Guo Y, Zhang W, Guo Z, Huynh W, et al. Electron cryo-microscopy structure of the mechanotransduction channel NOMPC. \textit{Nature} 2017;547:118–22.
6. Zhang W, Cheng LE, Kittelmann M, Li J, Petkovic M, Cheng T, et al. Ankyrin repeats convey force to gate the NOMPC mechanotransduction channel. *Cell* 2015;162:1391–403.

7. Ge J, Li W, Zhao Q, Li N, Chen M, Zhi P, et al. Architecture of the mammalian mechanosensitive Piezo1 channel. *Nature* 2015;527:64–9.

8. Murphy JG, Sanderson JL, Gorski JA, Scott JD, Catterall WA, Sather WA, et al. AKAP-anchored PKA maintains neuronal L-type calcium channel activity and NFAT transcriptional signaling. *Cell Rep* 2014;7:1577–88.

9. Liu N, Yang Y, Ge L, Liu M, Colecraft HM, Liu X. Cooperative and acute inhibition by multiple C-terminal motifs of L-type Ca\(^{2+}\) channels. *Elife* 2017;6:e21989.

10. Schroeder BC, Cheng T, Jan YN, Jan LY. Expression cloning of TMEM16A as a calcium-activated chloride channel subunit. *Cell* 2008;134:1019–29.

11. Huang F, Rock JR, Harfe BD, Cheng T, Huang X, Jan YN, et al. Studies on expression and function of the TMEM16A calcium-activated chloride channel. *Proc Natl Acad Sci U S A* 2009;106:21413–8.

12. Huang F, Zhang H, Wu M, Yang H, Kudo M, Peters CJ, et al. Calcium-activated chloride channel TMEM16A modulates mucin secretion and airway smooth muscle contraction. *Proc Natl Acad Sci U S A* 2012;109:16354–9.

13. Tien J, Lee HY, Minor Jr DL, Jan YN, Jan LY. Identification of a dimerization domain in the TMEM16A calcium-activated chloride channel (CaCC). *Proc Natl Acad Sci U S A* 2013;110:6352–7.

14. Peters CJ, Yu H, Tien J, Jan YN, Li M, Jan LY. Four basic residues critical for the ion selectivity and pore blocker sensitivity of TMEM16A calcium-activated chloride channels. *Proc Natl Acad Sci U S A* 2015;112:3547–52.

15. Tien J, Peters CJ, Wong XM, Cheng T, Jan YN, Jan LY, et al. A comprehensive search for calcium binding sites critical for TMEM16A calcium-activated chloride channel activity. *Elife* 2014;3:e02772.

16. Sadja R, Alagem N, Reuveny E. Graded contribution of the G\(\beta\gamma\) binding domains to GIRK channel activation. *Proc Natl Acad Sci U S A* 2002;99:10783–8.

17. Mullins C, Fishell G, Tsien RW. Unifying views of autism spectrum disorders: a consideration of autoregulatory feedback loops. *Neuron* 2016;89:1131–56.

18. Ma H, Groth RD, Cohen SM, Emery JF, Li B, Hoedt E, et al. \(\gamma\)CaMKII shuttles Ca\(^{2+}\)/CaM to the nucleus to trigger CREB phosphorylation and gene expression. *Cell* 2014;159:281–94.

19. Li B, Tadross MR, Tsien RW. Sequential ionic and conformational signaling by calcium channels drives neuronal gene expression. *Science* 2016;351:863–7.

20. Ahuja S, Mukund S, Deng L, Khakh K, Chang E, Ho H, et al. Structural basis of Nav1.7 inhibition by an isoform-selective small-molecule antagonist. *Science* 2015;350:aac5464.

21. Yuan Y, Bai X, Luo C, Wang K, Zhang H. The virtual heart as a platform for screening drug cardiotoxicity. *Br J Pharmacol* 2015;172:5531–47.

22. Xu H, Ren D. Lysosomal physiology. *Annu Rev Physiol* 2015;77:57–80.

23. Zhang L, Bellve K, Fogarty K, Kobertz WR. Fluorescent visualization of cellular proton fluxes. *Cell Chem Biol* 2016;23:1449–57.

24. Bandara HM, Hua Z, Zhang M, Pauff SM, Miller SC, Davie EA, et al. Palladium-mediated synthesis of a near-infrared fluorescent K\(^+\) sensor. *J Org Chem* 2017;82:8199–205.

25. Tan CH, McNaughton PA. The TRPM2 ion channel is required for sensitivity to warmth. *Nature* 2016;536:460–3.

26. Gao Y, Cao E, Julius D, Cheng Y. TRPV1 structures in nanodiscs reveal mechanisms of ligand and lipid action. *Nature* 2016;534:547–51.