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# The hills and valleys of calcium signaling

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Calcium is important for life. Studies over the last several decades have gradually revealed the critical involvement of calcium, especially its ionic form ($Ca^{2+}$), in every aspect of life forms on earth. Among them, a great deal of work has been done to illustrate how $Ca^{2+}$ levels are regulated in the cytoplasm and how many of the cytosolic enzymes and signaling molecules respond to the rise and fall of intracellular $Ca^{2+}$ concentrations ($[Ca^{2+}]_i$). Thanks to the men and women who worked tirelessly for numerous hours in the laboratory, who made meticulous efforts to invent powerful and innovative tools, and who thought extremely hard to solve the difficult puzzles on signaling pathways, we now know so much about this spectacular cellular functioning process, which we refer to as "$Ca^{2+}$ signaling".

The diverse roles of $Ca^{2+}$ signaling and fascinating stories about how $Ca^{2+}$ signals to regulate cellular functions have been the subjects of many excellent research and review articles. Some of them had appeared in this particular journal over the past decades, especially in the two previous special spotlight issues dedicated to $Ca^{2+}$ Signaling (*Science China Life Sciences*, 2011 54 (8) and 2015 58 (1)). The fundamental knowledge about $Ca^{2+}$ signaling and its importance in the life and death of cells have been nicely summarized in the previous editorials (Wang et al., 2012; Zheng et al., 2015) and therefore will not be repeated here. The highlights in recent years have included molecular identification of a large number of $Ca^{2+}$-permeable channels that exert their functions not only on the plasma membrane but also the membranes of intracellular organelles, such as the endoplasmic reticulum (ER), mitochondria, and endo-lysosomes.

## Some recent advances in $Ca^{2+}$ signaling

The first wave of discoveries that strongly impacted this field began some twenty years ago with the molecular cloning of Transient Receptor Potential (TRP) channels first from fruit flies (Montell and Rubin, 1989) and then mammalian systems (Zhu et al., 1996; Caterina et al., 1997). These later expanded to a superfamily of 28 members just in mammalian species alone, with more diverse subtypes in invertebrates (Montell et al., 2002). Numerous functions have now been assigned to various TRP channels from temperature sensation to stress response to many different environmental challenges (Nilius and Owsianik, 2011; Julius, 2013; Ong et al., 2014).

The second wave was the consecutive identification of STIM (Liou et al., 2005; Zhang et al., 2005) and Orai (Feske et al., 2006; Vig et al., 2006; Zhang et al., 2006), an ER $Ca^{2+}$ sensor and its channel partner on the plasma membrane, respectively, which work together to carry out "store-operated" or capacitative $Ca^{2+}$ entry. The idea that internal $Ca^{2+}$ store depletion signals a plasma membrane

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channel to mediate $Ca^{2+}$ entry for the purpose mainly to replenish the emptied store was originally proposed by James Putney Jr. thirty years ago (Putney, 1986; 1990). Since then, it has been one of the most active areas of $Ca^{2+}$ signaling research. In fact, the concept of store-operated $Ca^{2+}$ entry motivated the initial characterization of $Ca^{2+}$-release activate $Ca^{2+}$ (CRAC) currents in non-excitable cells (Lewis and Cahalan, 1989; Hoth and Penner, 1992) and helped to explain the extracellular $Ca^{2+}$-dependent $[Ca^{2+}]_i$ elevation that follows stimulation of receptors coupling to either some G proteins or tyrosine kinases and/or pharmacologically induced store depletion in many cell types, including both non-excitable and excitable cells (see reviews in Cheng et al., 2013; Pan and Ma, 2015; Prakriya and Lewis, 2015). It was also the major drive behind the molecular cloning of not only STIM and Orai, but also the canonical subfamily of mammalian TRP channels (Hardie and Minke, 1993; Zhu et al., 1996). Over the last ten years, great details about store-operated $Ca^{2+}$ entry, especially that mediated by the CRAC channel, have been unfolded owing to the tremendous efforts devoted to the studies of STIM and Orai. The remarkable progress in this particular pathway has somehow overshadowed other store-operated $Ca^{2+}$ entry mechanisms, which also play unique roles in various systems. The diversity of $Ca^{2+}$ entry pathways in cancer and muscle cells are described in this $Ca^{2+}$ spotlight issue of *Science China Life Sciences* (Evans et al., 2016; Hooper et al., 2016).

The third wave included molecular identification and functional characterization of $Ca^{2+}$-permeable channels associated with intracellular organelles. In the endolysosomal systems, two-pore channels (TPCs), TRPML, and P2X4 have been shown to mediate $Ca^{2+}$ release from these acidic organelles, each under specific conditions (Calcraft et al., 2009; Dong et al., 2010; Cao et al., 2015). The cloning of the major component of mitochondrial uniporter (Baughman et al., 2011; De Stefani et al., 2011) has been revolutionizing studies on mitochondrial $Ca^{2+}$ uptake, although other uptake mechanisms may also exist (Feng et al., 2013). More recently, a novel $Ca^{2+}$ release channel on the ER membrane, TMCO1, which helps relief ER stores from $Ca^{2+}$ overload, has been described (Wang et al., 2016). Thus, new players are emerging for the moment-to-moment regulation of $Ca^{2+}$ contents both in the cytosol and at the luminal side of intracellular organelles. Three articles in this spotlight issue (Evans et al., 2016; Zhou et al., 2016; Xiong and Zhu, 2016) include insights on the roles and regulation the new organellar $Ca^{2+}$ signaling pathways.

The fourth wave that is pushing the field forward consists of many near-atomic resolution structures of $Ca^{2+}$-permeable channels and $Ca^{2+}$ binding proteins recently resolved by either X-ray crystallography or single particle cryo-electron microscopy (Hou et al., 2012; Cao et al., 2013; Wang et al., 2014; Yan et al., 2015; Paulsen et al., 2015; Fan et al., 2015; Ge et al., 2015; Guo et al., 2016; Oxenoid et al., 2016; Saotome et al., 2016). The detailed structural information is empowering both computational and experimental biologists to gain better understanding of the $Ca^{2+}$ signaling molecules and processes. In the current issue, Gilston and his colleagues provide excellent examples on how structures of S100 proteins, a well-known class of $Ca^{2+}$ binding proteins, were utilized to illustrate their binding to transition metals (Gilston et al., 2016).

Finally, innovative research tools and new techniques have always had special roles in advancing the studies on $Ca^{2+}$ signaling. From very early on, the invention of synthetic fluorescence $Ca^{2+}$ probes (Grynkiewicz et al., 1985) had made incredible impacts on much of what we know nowadays about the spatiotemporal dynamics of $[Ca^{2+}]_i$ changes under various resting and stimulated conditions. The later introduction of genetically encoded fluorescence and luminescence probes further boosted our capabilities to monitor these changes in more specialized areas, for longer durations, with broader ranges of lights, or at much faster time scales (Miyawaki et al., 1997; Tian et al., 2009; Zhao et al., 2011; Zhou et al., 2015). These were further aided by advancements in instrumentation as well as new techniques such as whole-lysosome patch clamp recording (Dong et al., 2008) and Förster resonance energy transfer (FRET) and related methods. New genetically encoded probes have also been invented to examine the formation of junctions between ER and plasma membrane (Chang et al., 2013) and to achieve optical control of CRAC channel activation for immunomodulation (He et al., 2015). It is anticipated that investment into the new probes and techniques will continue to bring fruitful results on $Ca^{2+}$ signaling and its contributions to health and disease. Some of the new optical tools are described and discussed in the current issue (Tiapko et al., 2016; Chan et al., 2016). The use of existing probes in the studies of mitochondrial $Ca^{2+}$ signaling is nicely summarized (Zhou et al. 2016).

## Networking opportunities for $Ca^{2+}$ signaling enthusiasts

The current special issue was also made to support the 11th Symposium on $Ca^{2+}$ Signaling in China (SCSC), to be held on July 20–24, 2016, in Zunyi city, Guizhou province, China. The conference is organized by the Biophysical Society of China and hosted by Zunyi Medical College. Specialized symposia focusing on $Ca^{2+}$-related research offer unique opportunities for $Ca^{2+}$ signaling enthusiasts to share results, exchange research ideas, cultivate friendship, and foster collaborations. The very first "international $Ca^{2+}$ meeting" is believed to be the Symposium on Calcium Binding Proteins and Calcium Function in Health and Disease held in Jablonna, Poland, in 1973. This conference series, which has pretty much kept its original name and general themes, has continued at two to three year intervals in different places of the world for the next forty some years. The last

meeting was the 19th symposium hosted by Vanderbilt University in Nashville, Tennessee, USA, in summer 2015. *Science China Life Sciences* was the proud sponsor of the 17th International Symposium on Calcium Binding Proteins and Calcium Function in Health and Disease held in Beijing in summer 2011. Many of the speakers contributed to the first $Ca^{2+}$ spotlight issue published in late 2011.

Now, there are a number of established international $Ca^{2+}$ meeting series, including the FASEB Science Research Conferences on $Ca^{2+}$ and Cell Function started in 1984; the Gordon Research Conference on $Ca^{2+}$ signaling started in 1993, and the European Calcium Society biennial meetings which were inaugurated in 1998. These meetings all have strong international representation, but nevertheless lean towards Europeans and North Americans.

$Ca^{2+}$ signaling is not new to many Chinese scientists. Soon after China opened its door for exchanging scholarly activities with Western countries after Culture Revolution, the fluxes of information on $Ca^{2+}$ signaling and researchers who returned to the country after short periods of studies abroad have instilled the interest in this active field of biomedicine. The first Chinese Symposium on Calcium Signaling (CSCS) was held in the city of Xuzhou, Jiangsu province, in 1987. After that, nine more such conferences were held in different parts of China at initially three- and then two-year intervals. The later symposia all emphasized greater international participations and the format that resembles more closely to that of FASEB and Gordon Research Conferences. Particularly, the 8th symposium in Beijing (2010 New Horizons in Calcium Signaling) was jointly sponsored and organized by the Biophysical Society and the Biophysical Society of China, with the participation of dozens of world-renowned $Ca^{2+}$ signaling experts. *Science China Life Sciences* was also the proud sponsor of the 10th CSCS held in Yichun, Jiangxi province, in summer 2014. Many of the speakers contributed to the second $Ca^{2+}$ spotlight issue published in early 2015.

During this time period, $Ca^{2+}$ signaling research has flourished in China, with increasing number of young scholars, trained either in China or oversea, actively engaged in studying $Ca^{2+}$ transporters, channels, binding proteins and $Ca^{2+}$-regulated functions. A number of examples of their remarkable achievements have already been cited above (Wang et al., 2015, Yan et al., 2015; Ge et al., 2015; Wang et al., 2016). The $Ca^{2+}$ Signaling meetings, therefore, not only provide an important platform for networking and information exchange but also offer the opportunity to celebrate the recent success. Because of the advancement in $Ca^{2+}$ signaling research in China and its increasing visibility to the outside world, stronger ties with the international $Ca^{2+}$ signaling community is a must. To promote its international recognition, during the 10th CSCS (2014), the scientific advisory committee decided to use SCSC as the new acronym for this conference series to emphasize its geological location rather than language or ethnicity. In accordance with such spirit, the 11th symposium in Zunyi has attracted participants from ~ten nations from three continents. The official language of the symposium is unquestionably English. Since this editorial will be published before the symposium, we can only guess how successful it will be from its preliminary scientific program, which already looks very impressive with the large number of high caliber speakers from both within and outside of China. Many of the symposium participants were major contributors of the landmark studies that have been cited above in this editorial. Therefore, we fully expect the 11th SCSC to be a showcase of the current state-of-the- art and extraordinary research done in the field and $Ca^{2+}$ signaling and a unique new platform for the Chinese $Ca^{2+}$ experts and enthusiasts to connect with their international peers.

Located in the northern part of the mountainous Guizhou province in southwestern China, Zunyi has not had much exposure to the $Ca^{2+}$ signaling community either in China or in the world. However, this is about to change. Just like the exploration to the hidden secretes of cell signaling by $Ca^{2+}$, the participants of the 11th SCSC will explore the hills and valleys that make this mystic land so rich in culture and natural beauties. To the locals, Zunyi is a proud place which had turned Chinese history and the home of the famous Maotai liquor. Quite possibly, it will also become a turning point of the "Long March" for $Ca^{2+}$ signaling research, from which stronger ties form between the Chinese $Ca^{2+}$ signaling community and the outside world to further advance this fascinating field.

As correctly pointed out by Evans and his colleagues about nanojunctions around sarco/endoplasmic reticulum for site- and function-specific $Ca^{2+}$ signals (Evans et al., 2016), the creation of nanoscale $Ca^{2+}$ signals is a result of concerted actions of a unique set of channels, pumps, binding proteins and the geometric constrains. The $Ca^{2+}$ signaling cluster has been working very hard to make its presentation in every major area of life science research. The efforts at multiple levels and in many forms, from daily observations in the laboratory, publications in high impact journals, presentations and networking in conferences, all spark lights to science and to society. We anticipate that the 11th SCSC will mark the beginning of active engagement of $Ca^{2+}$ signaling researchers from all over the world to meet regularly in China, making it another stronghold for $Ca^{2+}$ signaling enthusiasts to network, akin to its counterparts in Europe and North America.

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## Biographical Sketch

Dr. Michael Xi Zhu is professor of Department of Integrative Biology and Pharmacology, McGovern Medical School, the University of Texas Health Science Center at Houston. He received his B.S. degree in Biology from Fudan University, China, in 1984, and his M.S. and Ph.D. degrees from University of Houston, USA, in 1988 and 1991, respectively. He had his postdoctoral training in Cellular and Molecular Biology from 1991–1994 at Baylor College of Medicine. He then worked as an Assistant Researcher in the Department of Anesthesiology, UCLA, from 1994 to 1997. In autumn of 1997, he went to the Ohio State University to build his own lab and rose from the rank of Assistant Professor to Full Professor in the Department of Neuroscience there. In 2010, he moved to his current position at the University of Texas-Houston. Dr. Zhu's research interests include several aspects of cell signaling, especially those that involve heterotrimeric G proteins and ion channels that affect $Ca^{2+}$ signaling. He has published more than 130 research papers, reviews, and monographs on these topics and delivered lectures at many international conferences and symposia. Dr. Zhu's main contributions include identification and characterization of multiple Transient Receptor Potential Canonical (TRPC) channels in mammalian species and determination of the molecular identity of endolysosomal $Ca^{2+}$ release channels activated by the $Ca^{2+}$ mobilizing messenger, nicotinic acid adenine dinucleotide phosphate (NAADP). Dr. Zhu serves as a Series Editor of the CRC Methods in Signal Transduction Book Series, an Associate Editor of *Journal of Cellular Physiology* and editorial board members of *Pflügers Archiv European Journal of Physiology*, *Biophysics Reports* and *Molecular Pharmacology*. He was a regular member of the US NIH Molecular and Integrative Signal Transduction study section from 2010–2014. Dr. Zhu is serving as a co-chair for organizing the 2nd Gordon Research Conference on Organellar Channels and Transporters, to be held in Vermont, USA, in summer 2017. He served as the vice chair of the 2nd International Conference on Ion channels in Technology and Drug Discovery held in Harbin, 2009, an oversea chair of the 2010 symposium for Chinese Neuroscientists Worldwide held in Nanchang, a scientific committee chair of the 17th International Symposium on $Ca^{2+}$-Binding Proteins and $Ca^{2+}$ Function in Health and Disease held in Beijing, 2011, the chair of the 3rd International Ion Channel Conference-Ion Channels: Structure, Function & Therapeutics held in Shanghai, 2011, the oversea chair for the 9th Chinese Symposium on Calcium Signaling in Huangshan, 2012.

Dr. Biguang Tuo is professor at Zunyi Medical College, who works in Affiliated Hospital of Zunyi Medical College, where he serves as chief of Department of Gastroenterology and Institute of Digestive Diseases of Guizhou Province. Dr. Tuo is a chief of Guizhou Gastroenterology Association, China, and a member of American Gastroenterology Association. Dr. Tuo earned his bachelor's degree in Medicine from Guiyang Medical College, China, and a master's degree in Medicine from Peking University Healthy Science Center, Beijing, China. He earned his Ph.D. in Gastroenterology from Hannover Medical School, Germany, and finished his postdoctoral training in the University of California, San Diego, USA, where he undertook studies in ion channels and intestinal secretion. Currently, his research focuses on ion channels and development and progress of tumor, especially calcium signaling and development and progress of hepatocellular carcinoma. Dr. Tuo is a co-Chair of the 11th Symposium on Calcium Signaling in China, Zunyi, 2016.

Dr. Jenny Jie Yang is a Distinguished University Professor of Chemistry and Associate Director of the Center for Diagnostics and Therapeutics at Georgia State University. She received her Ph.D. in Biochemistry at the Florida State University in 1992. She was a Research Fellow at Syntex Discovery Research (Roche Biosciences). From 1993 to 1995, she was an Oxford Center for Molecular Sciences (OCMS) Research Fellow at the University of Oxford, UK. She was also a Harford Research Fellow of Molecular Biophysics and Biochemistry at Yale University. In 1997, Dr. Yang joined the faculty at the Chemistry Department of Georgia State University, where she was promoted to full professor in 2006. Dr. Yang received the Outstanding Junior Faculty Award, the Outstanding Faculty Achievement Award, and the Alumni Distinguished Faculty Achievement Award at GSU. Dr. Yang's laboratory applies protein design and engineering approaches to understand molecular basis of diseases, modulate calcium signaling, and create novel reagents and tools for research, diagnostics and disease treatment. Her research on Calciomics enables visualization of the roles of calcium in extracellular, intracellular $Ca^{2+}$ signaling & cell-cell communication under both biological and pathological processes. Key determinants for calcium binding, selectivity and conformational changes have been identified by design and analysis of calcium-binding proteins. Dr. Yang's research group has designed $Ca^{2+}$ and enzyme sensors for monitoring rapid cellular signaling events. Her research team has also developed novel classes of protein reagents including MRI contrast agent (ProCA) to enable non-invasive early and precision detection of various types of cancers and fibrosis and created protein drug candidates with improved therapeutic effects. The research activities in Dr. Yang's laboratory lead to many important inventions including over 120 publications and > 20 patent applications. She has mentored ~110 trainees. Dr. Yang is a co-Chair of the 11th Symposium on Calcium Signaling in China, Zunyi, 2016.