

## On Ca<sup>2+</sup> signalling research

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As a highly versatile intracellular signal, calcium (Ca<sup>2+</sup>) regulates many different cellular processes in both animal and plant systems. Disruption of Ca<sup>2+</sup> homeostasis contributes to several human diseases. Owing to the importance of Ca<sup>2+</sup> signalling, its research is now an active field in life science. There are numerous Ca<sup>2+</sup> signalling systems, consisting of a diverse array of signalling units that deliver Ca<sup>2+</sup> signals with different spatial and temporal properties [1,2], playing roles in ubiquitous biological processes including gene regulation, fuel generation, substance transport, hormone and neurotransmitter secretion, cell motility and muscle contraction [3]. Consequently, exquisite homeostasis of Ca<sup>2+</sup> cycling is the key for health of humans, the disruption of which is related to many human diseases such as heart failure, neuron-degeneration, and diabetes [4–6].

Many remarkable achievements have greatly enhanced our understanding of Ca<sup>2+</sup> signaling, including those from Chinese scientists [7–10]. The 17th International Symposium on Ca<sup>2+</sup>-binding Proteins and Ca<sup>2+</sup> Function in Health and Disease was held in Beijing, China, on July 16–20, 2011 [11], accompany which, a special issue of *Science China Life Sciences* was published for transducing Ca<sup>2+</sup> signals to effectors.

The first part focused on the mechanisms in maintaining a low cytosolic level of Ca<sup>2+</sup>, with two articles reviewing the properties of the plasma membrane calcium ATPases (PMCA) in ejecting Ca<sup>2+</sup> into the extracellular space. First, Carafoli [12] reviewed the role of the plasma membrane calcium pump, PMCA2, in the hearing process. As an im-

portant plasma membrane Ca<sup>2+</sup> ATPases, PMCA2 plays an important role in maintaining intracellular Ca<sup>2+</sup> homeostasis in the inner ear. It is involved in the maintenance of intracellular free calcium levels and the dysfunction of which leads to deafness. Recent studies show that another important isoform of PMCA, PMCA4, has a number of roles for heart functioning [13,14]. Cartwright *et al.* [15] then reviewed the roles of plasma membrane calcium pumps related to cardiovascular disease, focusing on PMCA4, including its function in heart and vasculature, linking PMCA4 to contractile function, cardiac hypertrophy, cardiac rhythm, blood pressure control and hypertension. Undoubtedly, further understanding of the roles of PMCA4 will facilitate the development of new treatment strategies for related diseases.

As a versatile intracellular messenger, Ca<sup>2+</sup> performs roles in many different ways to regulate cellular processes [16]. The second part of this special issue focuses on mechanisms for spatiotemporally-specific increases in cytosolic Ca<sup>2+</sup>. First, Lee [17] reviewed studies on the fraternal twin messengers for calcium signaling, cyclic ADP-ribose (cADPR) and nicotinic acid adenine dinucleotide phosphate (NAADP). Since the initial finding by Lee and his colleagues that cADPR and NAADP could liberate stored Ca<sup>2+</sup>, they have been shown to be active in mobilizing Ca<sup>2+</sup> in a wide range of cells spanning three biological kingdoms. He summarized the cADPR/NAADP/CD38-signalling pathway and also described the structure and function of its components. Kimlicka and van Petegem [18] then reviewed the structural biology aspect of ryanodine receptors (RyRs) which are high-conductance ion channels

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located in the endoplasmic/sarcoplasmic reticulum (ER/SR). They summarized studies using electron microscopy, NMR, and X-ray crystallography. Being permeable to  $\text{Ca}^{2+}$ , RyRs plays important roles in various physiological processes [19], especially in the contraction of cardiac and skeletal muscle. RyRs are the largest known ion channels, presenting great challenges for the structural biology research.

The identification of target proteins is very important for understanding the physiological roles of  $\text{Ca}^{2+}$  mobilizing messengers. Recent studies indicate that NAADP acts upon a novel family of endo-lysosomal channels in animal cells termed two-pore channels (TPCs) [20,21]. Galione *et al.* [22] then summarized the physiological roles of NAADP-mediated  $\text{Ca}^{2+}$  signalling. They provided a historical perspective on the research of TPCs, studies on which unveiled the physiological role of NAADP as an intracellular  $\text{Ca}^{2+}$  mobilizing messenger. The roles of calcium and actin for fertilization, as mediated by a novel NAADP-gated channel in the plasma membrane of starfish oocytes, were then reviewed by Santella and Chun [23].

Alzheimer's disease (AD), an irreversible and progressive neurodegenerative disorder, currently affects approximately 27 million people worldwide. There is still no effective way to treat such diseases and our understanding of it is still limited. Maintenance of intracellular  $\text{Ca}^{2+}$  homeostasis is essential for the functioning and survival of neurons and is a fundamental component of synaptic transmission for both pre- and postsynaptic mechanisms [1,24]. Recent studies suggest that disrupted neuronal  $\text{Ca}^{2+}$  signalling may contribute to AD pathogenesis. The  $\text{Ca}^{2+}$  theory of AD is now becoming increasingly popular. The next two reviews focused on the  $\text{Ca}^{2+}$  theory of AD. First, Supnet and Bezprozvanny [25] discussed Alzheimer's disease pathogenesis related to presenilins as endoplasmic reticulum calcium leak channels. Chakroborty and Stutzmann [26] then discussed the early calcium dysregulation in Alzheimer's disease, overviewing the roles of AD-linked  $\text{Ca}^{2+}$  signalling alterations in neurons and how this may be linked to synaptic dysfunctions at both early and late stages of the disease. The last review of this part focused on the distinctive characteristics and functions of multiple mitochondrial  $\text{Ca}^{2+}$  influx mechanisms [27]. As is well known, mitochondria is not just a  $\text{Ca}^{2+}$  buffering system, but also an important  $\text{Ca}^{2+}$  storage site [28,29]. This review summarized the current progress of mitochondrial  $\text{Ca}^{2+}$  influx pathways and their differences in kinetics,  $\text{Ca}^{2+}$  dependence, and pharmacological characteristics, and their potential physiological and pathological implications.

Another active field in  $\text{Ca}^{2+}$  signaling focuses on the function of various  $\text{Ca}^{2+}$ -related proteins such as Caldesmon [30,31], Osteopontin [32], Cornulin [33], ERp44 [34] and others. The third part of this issue consists of three reviews, all focusing on the proteins that play important roles in cascades transducing  $\text{Ca}^{2+}$  signals to effectors. First, Maki *et al.* [35] summarized the structure and function of ALG-2,

which is a penta-EF-hand  $\text{Ca}^{2+}$ -binding protein, interacting with various proteins in a  $\text{Ca}^{2+}$ -dependent fashion. Zhang and Trebak [36] then summarized the recent studies on the endoplasmic reticulum  $\text{Ca}^{2+}$  sensor STIM1 and the plasma membrane  $\text{Ca}^{2+}$  channel Orai1, pointing out that the contribution of STIM1 and Orai1 to cardiovascular diseases, and discussing the prospects for targeting them in the therapy of vascular diseases. Last but not least, Rivas *et al.* [37] summarized the recent advances in the construction of an interactome of DREAM, a calcium binding protein of the neuronal calcium sensor superfamily that plays an important role in cell physiology through the interaction with specific proteins. DREAM also can interact with downstream regulatory element (DRE) sites in the DNA to regulate transcription.

Although enormous progress and insights have been made on  $\text{Ca}^{2+}$  signalling, there is still many important questions remaining to be answered in the future. It is thus hoped that more studies on  $\text{Ca}^{2+}$  signalling will be carried out to provide better understanding of the cellular and molecular mechanisms of  $\text{Ca}^{2+}$  signalling, contributing to the development of therapeutics for various human diseases related to disruption of  $\text{Ca}^{2+}$  homeostasis. We hope that this special issue of *Science China Life Sciences* will be helpful for this, and stimulate researchers' interest in  $\text{Ca}^{2+}$  signaling studies.

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