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• EDITORIAL •

Ca^{2+}: a versatile master key for intracellular signaling cascades

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Ca^{2+} is one of the most ancient and versatile intracellular messengers in both animal and plant systems. Ca^{2+} interacts with a huge array of signaling proteins, and coordinates the integration of non-signaling proteins into cellular communication systems. In doing so, Ca^{2+} plays crucial roles in many biological processes, including gene regulation, fuel generation in the metabolic pathways, substance transport across membranes, hormone and neurotransmitter secretion, cell motility and muscle contraction [1]. Ca^{2+} also controls the life cycle at various stages, from regulating fertilization and cell growth to modulating programmed cell death (apoptosis). Ca^{2+} is unequivocally a master key with the ability to control most cellular processes.

This special issue brings together 12 invited reviews of some of the key functions of Ca^{2+} in cells, most of which were presented at the 17th International Symposium on Ca^{2+}-binding Proteins and Ca^{2+} Function in Health and Disease in Beijing, China, on July 16–20, 2011. As reflected in these reviews, the current era of Ca^{2+} research is characterized by intense interest in the structure and functional regulation of Ca^{2+} transporters and Ca^{2+}-binding proteins, and the roles of Ca^{2+} in health and disease processes.

1 Mechanisms for maintaining low cytosolic Ca^{2+}

In the early stages of biological evolution, systems were developed to maintain a low cytosolic Ca^{2+} concentration to prevent the precipitation of many phosphates and organic molecules [2]. Because phosphate was evolutionarily established as the essential energy 'currency' of cells , the formation of calcium phosphate was a deleterious event that needed minimizing. The intracellular Ca^{2+} concentration must be lowered from the environmental level of 10^{-3}–10^{-2} mol L^{-1} to around 10^{-7} mol L^{-1}. It is believed that Ca^{2+}-transporting proteins evolved rapidly to extrude intracellular Ca^{2+} from the cell. Indeed, DNA sequencing supports the idea that Ca^{2+} pumps arose early in evolution, together with other outwardly directed ion pumps [3].

In eukaryotic cells, Ca^{2+} is either pumped out of the cells by plasma membrane Ca^{2+}-ATPase (PMCA pump) or sequestered into the endoplasmic reticulum (ER) (or sarcoplasmic reticulum (SR) in muscle cells) by the sarco-/endoplasmic reticulum Ca^{2+}-ATPase (SERCA pump). More recently, a Ca^{2+} pump (the SPCA pump) has also been described in the Golgi membranes. Cell membrane systems, including the plasma, inner mitochondrial and lysosomal membranes, also contain antiporters that transport Ca^{2+} at the expense of chemical energy stored in Na^+ or H^+ gradients. The relative contribution of these transport mechanisms varies between cell types. For example, in heart cells, the Na^+/Ca^{2+} exchanger plays a more important role than the PMCA pump in extruding Ca^{2+} during myocardial relaxation [4].

Under physiological conditions, the export of cytosolic Ca^{2+} by these Ca^{2+} transporters balances the Ca^{2+} entry

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('leak') from the extracellular fluid and intracellular organelles. In this special issue, Carafoli [5] and Neyses *et al*. [6] review the roles of different subtypes of the PMCA pumps in maintaining intracellular Ca^{2+} homeostasis in the inner ear and the cardiovascular system, respectively. In keeping with the present interest in the "negative" role of Ca^{2+}, they also summarize recent findings that dysfunction of the PMCA pumps causes disturbance of the balance between Ca^{2+} entry and extrusion, and can lead to deafness and cardiovascular disease.

2 Mechanisms for spatiotemporally-specific increases in cytosolic Ca^{2+}

The large Ca^{2+} gradient that exists across the plasma membrane and the organellar membranes provides a dynamic force for Ca^{2+} to act as an intracellular messenger. As mentioned, the cytosolic Ca^{2+} concentration in most eukaryotic cells is four orders of magnitude lower than that in the extracellular fluid or the lumen of the ER. Therefore, even a small amount of Ca^{2+} entry into the cytosol causes a dramatic and immediate change against the low-Ca^{2+} background. While fast, transient Ca^{2+} signals are usually generated by Ca^{2+}-permeable ion channels residing on the plasma membrane and on the membrane of organelles, slow, tonic Ca^{2+} signals tend to arise from reverse-mode operation of Ca^{2+} exchangers and from slower operation of Ca^{2+} pumps. Different Ca^{2+} channels and/or transporters generate Ca^{2+} signals with different amplitude, duration, location and kinetics. The variability in the spatiotemporal patterning of different Ca^{2+} signals forms the fundamental basis for the unique versatility of Ca^{2+} as a signaling messenger [1].

Since the finding by Berridge *et al*. that ER Ca^{2+} can be mobilized by inositol 1,4,5-trisphosphate (IP_3), the mobilization of stored Ca^{2+} has become a central concept of Ca^{2+} signaling. In the late 1980s, Lee and colleagues (for their review in this issue, see ref. [7]) found that stored Ca^{2+} could also be liberated by two other messengers: cyclic ADP-ribose (cADPR) and nicotinic acid adenine dinucleotide phosphate (NAADP). Further studies have shown that cADPR activates the so-called ryanodine receptors (RyRs) in the ER. RyR, the largest known membrane-expressed protein, is another major Ca^{2+} release channel of ER/SR, and is particularly important in muscle cells and some neurons. In this special issue, Van Petegem and colleague have built upon their important recent research on the RyR to provide a comprehensive overview of the structural aspects of this giant channel protein [8]. Surprisingly, although cADPR and NAADP are synthesized by the same enzyme, NAADP does not target RyR, instead acting upon two-pore channels (TPCs) in lysosomes. In their review [9], Galione and colleagues discuss how studies of TPCs are enhancing our understanding of NAADP-mediated Ca^{2+} signaling. Furthermore, Santella and her colleague also describe a novel NAADP-gated channel in the plasma membrane of starfish oocytes [10].

The alteration of Ca^{2+} signals as a pathological basis of disease is the topic of two papers in this special issue. Bezprozvanny *et al*. [11] and Stutzmann *et al*. [12] discuss presenilin, a putative novel ER Ca^{2+} channel. Mutations of presenilin cause mishandling of ER Ca^{2+}, and play important role in the pathogenesis of Alzheimer's disease. The Ca^{2+} theory of Alzheimer's disease is now becoming increasingly popular.

Mitochondria are also important Ca^{2+} stores transporting Ca^{2+} very efficiently. The discovery of "Ca^{2+} marks" has provided direct evidence that Ca^{2+} signals can also be generated in mitochondria. The mechanisms that mediate Ca^{2+} flux through the mitochondrial inner membrane have long been controversial. In this special issue, Sheu and colleagues [13] discuss the major candidate mechanisms that may be involved in generating mitochondrial Ca^{2+} signals.

3 Mechanisms that transduce Ca^{2+} signals to effector cascades

Intracellular Ca^{2+} signals originating from Ca^{2+} channels act either on local targets within proximal microdomains, or regulate distant cellular events by diffusing through the cytosol. The efficiency and target selectivity of Ca^{2+} signaling are thus determined by the affinity and stoichiometry of the interaction between Ca^{2+} and Ca^{2+}-binding proteins. Therefore, uncovering the mechanisms by which Ca^{2+} activates its targets is important in understanding the profound specificity of Ca^{2+} signals in activating different signaling cascades. In their review, Maki and colleagues [14] describe how the binding of Ca^{2+} induces a conformational change in the penta-EF-hand Ca^{2+}-binding protein, ALG-2, and facilitates the binding of ligand.

The recent finding regarding STIM1-Orai1 interaction during store-operated Ca^{2+} entry (SOCE) is an elegant example of Ca^{2+} signal transduction. The STIM1 protein acts as a Ca^{2+} sensor in the lumen of the ER, and can be activated by depletion of ER Ca^{2+} during Ca^{2+} release. Activated STIM1 in turn stimulates Orai1, a plasma membrane Ca^{2+} channel, which delivers Ca^{2+} to the cytosol to enhance the refilling of ER. Trebak and his colleague [15] summarize the studies on STIM1-Orai1 signaling in the vascular system, and discuss the prospects for drugs targeting STIM1/Orai1 in the treatment of vascular diseases.

To understand the versatile roles of Ca^{2+} signaling, it is important to identify the downstream cascades of Ca^{2+}-binding proteins. The combination of bioinformatics with molecular biological experiments has greatly enhanced our ability to find Ca^{2+} signaling targets. Here, Naranjo [16] reviews recent advances in the construction of an interactome of DREAM/calsenilin/KChIP3, member(s) of the neuronal Ca^{2+} sensor superfamily. Interestingly, DREAM

has an essential role in the nucleus as a Ca^{2+}-dependent gene silencer.

In addition to the activation of signaling cascades, another major role of Ca^{2+} is to regulate mechanical remodeling of the cytoskeleton, a fundamental mechanism of cell motility. The review by Santella *et al*. shows that Ca^{2+} signals, and their interaction with actin, play an important role during egg fertilization [10].

Transporters, channels and signaling targets for Ca^{2+} comprise a coordinated system. Given the versatility of Ca^{2+} signaling, the exquisite homeostasis of Ca^{2+} cycling between the cytosol, organelles and extracellular medium is a prerequisite for the healthy operation of the cell system. As mentioned above, and as shown in a number of reviews in this special issue, disturbance of the homeostasis of Ca^{2+} signaling due to genetic or regulatory factors is deleterious to cells. In particular, Neyses [6], Stutzmann [12] and their colleagues have shown that pathogenesis involves multiple errors in Ca^{2+} handling. It is thus hoped that better understanding of the cellular and molecular mechanisms underlying Ca^{2+} mishandling will yield new targets in the battle against major human diseases.

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