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Editorial overview: Calcium signaling

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Calcium, the element, was discovered (i.e. isolated in its pure form) by Sir Humphry Davy in 1808. Davy was a prolific chemist and inventor. He was also an enthusiastic devotee of recreational nitrous oxide inhalation, and prone to daring experimentation on himself. Of course, in his time Davy could not have known that the utility of calcium ions had already been ‘discovered’ more than a billion years earlier by the primitive organisms populating our planet. The unique chemistry of calcium lent itself not only to the formation of structural features (bones and exoskeletons) but also permitted the evolution of sophisticated intracellular (and intercellular) communication systems.

Used by single celled organisms (e.g. bacteria) and complex multicellular beings (e.g. vertebrates and plants), the divalent cation form of calcium is undoubtedly the most versatile signaling molecule found in nature. This collection of articles from leading investigators throughout the world captures the beautiful diversity of the calcium signaling pathway in animal cells and highlights some of the most important recent developments in the field.

One of the overriding themes of this issue is that of ‘intimate connections’, such as those between Ca^{2+} and downstream signaling pathways, between intracellular organelles, and between cellular Ca^{2+} -dependent regulatory proteins.

The success of Ca^{2+} as a local signaling molecule is in large part due to its relatively slow diffusion rate in the cytosol, despite its low molecular weight. In addition to capitalizing on its inherently slow movement in the cytosol, cells have also strategically localized all the players in the calcium handling game to further promote the specificity of signaling events. Together these determine the spatiotemporal characteristics as well as the amplitude of the Ca^{2+} signal. Both localized increases in $[\text{Ca}^{2+}]$ as well as more global changes that occur across the cytosol are generated, which are distinctly decoded by cells and utilized for regulating specific cell functions.

This theme is elaborated in several of the chapters in this issue which discuss calcium signaling and inter-organelle connections that take place at ‘membrane contact sites’, that is, regions of close (~30 nm) apposition between two membranes. Over 25 years ago Sarino Rizzuto, Tullio Pozzan *et al.* provided compelling evidence that close contacts between calcium release channels in the endoplasmic reticulum (ER) and mitochondria were critical for efficient transfer of Ca^{2+} to the mitochondrial matrix. This arrangement had major implications towards promoting the efficiency of mitochondrial metabolism. Recently there has been an explosion of information on this topic owing to the molecular identification of

the key proteins that participate in these close interactions such as the mitochondrial calcium uniporter (MCU).

In this issue, [Anna Raffaello](#), [Madesh Muniswamy et al.](#) provide us with comprehensive updates on the protein complexes present in ‘MAMs’ or mitochondrial associated membranes. [Geert Bultynck](#) and his coauthors provide further details on how Ca^{2+} fluxes through inositol 1,4,5-trisphosphate receptors (InsP3Rs) in the ER fuel mitochondrial Ca^{2+} signals while [Ivan Bogeski](#) has focused on redox regulation of mitochondria by H_2S and H_2O_2 . Articles by [Riccardo Filadi and Paola Pizzo](#), and Raj Motiani *et al.* highlight how defects in mitochondrial calcium signaling relates to pathological conditions, in particular neurodegenerative disorders such as Alzheimer’s Disease, but also cancer and metabolic disorders.

Mitochondria are not the only cellular structures to exploit close contacts with the ER. Another ‘intimate connection’ of major importance to all cells involves the membrane contact site that forms between ER and plasma membrane upon depletion of ER luminal Ca^{2+} to activate a process known as Store-Operated Calcium Entry (SOCE). The formation of this dynamic junction is driven by the clustering of the transmembrane protein STIM1 in the ER, and the Ca^{2+} conducting Orai channels in the plasma membrane.

Detailed accounts of the most recent structural information about STIM, Orai and their interactions are presented in articles by [Cristoph Romanin](#), [Mohamed Trebak](#), [James Baraniak](#), [Irene Frischauf](#), and their respective coauthors. [Barbara Niemeyer et al.](#) discuss some ‘alternative’ cellular functions of STIM proteins, for example interactions that serve to remodel the actin and microtubule cytoskeleton, and in the control of the cAMP and AMPK signaling pathways.

The conditions whereby activation of Orai channels give rise to localized Ca^{2+} signaling microdomains is nicely presented by [Bjorn-Phillipp Diercks](#) and Andreas Guse. In their review on ER calcium ‘tunneling’, [Courjaret and Machaca](#) describe a twist on this theme. They concisely present the evidence for a mechanism whereby calcium ions entering through SOCE channels are avidly taken up into the ER at membrane contact sites. These ions effectively diffuse through the ER network and are released at remote locations within cells via InsP3 receptors.

Another major class of calcium-conducting channels in the plasma membrane are represented by the interesting and diverse TRP family of cation channels. [Mike Zhu et al.](#) review how one such TRP channel, the canonical TRPC4, becomes activated physiologically by specific heterotrimeric G-protein subunits. [Klaus Groschner](#) and his coauthors present an overview of all seven canonical TRPC isoforms and how they are regulated. They provide us with the latest information on their Ca^{2+} permeation properties, and the importance of TRPC’s interactions with membrane lipids. The control of channel gating by membrane lipids is a recurring theme that is further explored by [Tamás Balla et al.](#) in their article on the ‘marriage’ between membrane inositol phospholipids and Ca^{2+} signaling at ER-plasma membrane contact sites.

Although the ER Ca^{2+} release channels (InsP3 receptors) were identified many years ago, several articles in this collection show that there is still much to learn about these complex proteins. [M. Fátima Leite et al.](#) describe current knowledge on the differential functions of the three InsP3R isoforms in epithelial cells of the gastrointestinal tract in health and disease. [Gaiti Hasan](#) and [Anamika Sharma](#) share their insights on role of InsP3 receptors in neuronal pathophysiology in both mammalian and *Drosophila* neurons, highlighting some of the interesting differences between these two cell models.

The recurring theme of ‘intimate connections’ is again recalled by [Colin Taylor et al.](#), who review how a subset of strategically positioned InsP3 receptors permit communication at membrane contact sites with plasma membrane, mitochondria, and lysosomes. The topic of lysosomal Ca^{2+} signaling is further addressed by [Sandip Patel](#) and co-workers in their article on the lysosomal two-pore channels (TPCs). These interesting Ca^{2+} /cation conducting channels populate acidic compartments of the endocytic pathway and are able to regulate trafficking and lysosomal function. As described in their article, modulation of TPCs may be exploited to alter the entry and trafficking of viruses that include Ebola virus and the SARS-CoV virus responsible for the 2003 SARS pandemic.

Organelles frequently maintain Ca^{2+} signaling properties that differ from the cytoplasmic compartment. An extremely interesting example of this is manifested by the non-motile primary cilium, a very small organelle that projects from the surface of most vertebrate cells. The independent nature of the ciliary signaling compartment is surprising because the ciliary membrane is contiguous with the plasma membrane and moreover, small molecules are freely diffusible between cilioplasm and cytoplasm (analogous to the free transfer through nuclear pore complexes). Here [Zhaoxia Sun](#) provides us with a comprehensive look at the fascinating and sometimes contentious findings that have emerged on this topic.

Although calcium is most well-known for signaling inside the cell, the possibility that fluctuations in extracellular calcium outside of the cell could mediate signaling events is also gaining some traction. [Maiellaro, Colella et al.](#) provide an update on the extracellular calcium-sensing receptor (CaSR), a G-protein coupled receptor that is found in a variety of tissues. Meanwhile, [Jenny Yang](#) and her team provide us with a detailed snapshot of the structure-function relationship of the CaSR that was enabled by recent X-ray crystallography and NMR studies of the large extracellular domain of the receptor.

Another common theme of this collection reflects the remarkable progress in our understanding of the relationship between aberrant calcium signaling and human disease. It has long been appreciated that calcium signals are essential for the normal function of T cells, and [Stefan Feske et al.](#) tackle emerging questions on ‘immunometabolism’, specifically the ways in which calcium modifies immune function through various effects on metabolic programs. [Johanna Lanner](#) and co-authors describe how alterations in the function of STIM, Orai, the ryanodine receptor and the InsP3R lead to miscommunication underlying many diseases, with emphasis on muscle pathologies. [Alexei Tepikin](#) provides an excellent discussion on calcium signaling and pathophysiology of the exocrine pancreas in the context of acute pancreatitis, while [Silviya Radoslavova](#) and co-authors focus on calcium-dependent activation of pancreatic stellate cells and its relationship to fibrosis and

pancreatic cancer. The endocrine pancreas also gets its due in a review by [Tom Fischer](#) and Barbara Ehrlich, who provide us with the latest evidence on alterations in cellular calcium handling in Wolfram syndrome. Wolfram syndrome is a rare monogenic disorder resulting from mutations in the gene encoding the protein wolframin (Wfs1). One of the hallmarks of the disease is childhood onset insulin-dependent diabetes, although there are many other devastating manifestations Wolfram syndrome that develop over time (e.g. optic nerve atrophy, hearing loss, neurodegeneration), all of which are potentially linked to inappropriate calcium signaling.

Creative approaches for measuring and manipulating calcium have been at the cornerstone of the calcium signaling field since its inception. [Yubin Zhou et al.](#) provide a hint of the tools and tricks of the future in their article describing approaches for manipulating calcium remotely using optogenetic techniques. As the field moves progressively towards the study of calcium signaling in physiological contexts, for example, in living animal models, innovations such as these will undoubtedly provide many new opportunities for discovery.

Finally, perhaps the reader is a newcomer to the calcium signaling field and is overwhelmed by the complexity of the calcium signal in all its varied forms. We then direct you to reviews by [Brij Singh](#) and [Anant Parekh](#) and their respective co-authors who provide us with beautiful overviews of how signals are integrated in the cell. Parekh *et al.* also cover the most recent thinking on the topic of Ca^{2+} oscillations, including the various mechanisms by which repetitive spikes are generated, how signals are integrated by organelles, and insights into the ways in which these signals are decoded by the cell.

We truly hope you enjoy this special edition and thank all of the authors for their illuminating contributions!

Biographies

Dr. Indu Ambudkar received her M.Sc. degree from Lucknow University and Ph.D. degree from Madurai Kamaraj University in India. She joined University of Maryland, School of Medicine, as a post-doctoral researcher in 1980 and then moved to the National Institute of Dental and Craniofacial Research in 1985, where she is now Chief of the Secretory Physiology Section. Research in her laboratory is focused on the molecular mechanisms mediating and regulating Ca^{2+} entry in salivary gland cells, with special focus on TRP and Orai channels and the ER-proteins STIM1 and STIM2 which play key roles in regulation of Ca^{2+} entry and Ca^{2+} signaling. Her research also seeks to identify Ca^{2+} signaling mechanisms and components that contribute to disease and dysfunction. Her studies have

identified critical Ca^{2+} signaling defects that underlie loss of salivary gland fluid secretion caused by radiation treatment and the autoimmune disease Sjogren's Syndrome.

Aldebaran M Hofer received her Ph.D. in Physiology in the lab of Terry Machen at the University of California, Berkeley (USA). She did further post-doctoral studies on the topic of calcium signaling in Homburg/Saar (Germany) under Irene Schulz, and later in Padova (Italy) with Tullio Pozzan. She is currently an Associate Professor of Surgery at Harvard Medical School. Dr. Hofer formerly served as Deputy Associate Chief of Staff for Research at the VA Boston Healthcare System (Boston, MA). Her research interests include second messenger signaling in and around organelles, and calcium/cyclic AMP signaling interactions.