EDITORIAL

# Store-operated channels: mechanisms and function

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For many years, how $Ca^{2+}$ entered non-excitable cells remained enigmatic. There was a suspicion that $Ca^{2+}$ channels were involved, but what these were and how they were gated was unclear. By contrast, not only were the $Ca^{2+}$ channels expressed in excitable cells well defined electrophysiologically but their subunit composition and even structure–function profile had been teased apart. This imbalance began to change in 1986, when a landmark paper by James Putney let to a paradigmatic shift in our understanding of $Ca^{2+}$ entry in non-excitable cells (Putney, 1986). In that classic review, Putney proposed the concept of capacitative (now called store-operated) $Ca^{2+}$ influx. In its most fundamental form, emptying of agonist-sensitive intracellular $Ca^{2+}$ stores led to the opening of plasma membrane $Ca^{2+}$ channels.

Although this model was largely overlooked in its early days, two subsequent discoveries established its importance in cell physiology. First was the finding that thapsigargin, a sequiterpene lactone occurring naturally in plants, blocked $Ca^{2+}$ pumps on the stores and therefore depleted them of $Ca^{2+}$. Crucially, after store depletion to thapsigargin, $Ca^{2+}$ influx occurred (Takemura *et al.* 1989). This supported the key tenet of the store-operated model. Second and more crucially perhaps, an elegant series of patch clamp experiments by Hoth & Penner (1992) revealed the presence of a $Ca^{2+}$-selective current that was activated on emptying intracellular stores. The underlying channels, which they called $Ca^{2+}$ release-activated $Ca^{2+}$ (CRAC) channels, could be activated regardless of how stores were emptied and provided a key electrophysiological signature for store-operated $Ca^{2+}$ entry. CRAC channels have several intriguing features for ion channels including a tiny single channel conductance and exquisite selectivity for $Ca^{2+}$ (reviewed in Parekh & Putney, 2005), but for many years the vexing question that engaged most researchers was the molecular basis of store-operated entry. How is $Ca^{2+}$ sensed within the endoplasmic reticular $Ca^{2+}$ store? How is information sent from the store to the plasma membrane? What is the molecular identity of the CRAC channel?

Our understanding of store-operated $Ca^{2+}$ has increased over the past three years with the identification, using primarily siRNA technology, of two key components: STIM1 and Orai1–3 (reviewed in Lewis, 2007). The pace has been breathtaking, and a picture has emerged based on solid experimental evidence from several laboratories. STIM1 is the $Ca^{2+}$ sensor and Orai1 is all or part of the CRAC channel pore. Upon store depletion, STIM1 molecules migrate to form discrete puncta just below the plasma membrane where they recruit and activate Orai1.

At a recent meeting of the Biophysical Society in Long Beach, California, *The Journal of Physiology* held a symposium entitled 'Store-operated channels: mechanism and function'. This provided an opportunity to reflect on the recent rapid progress in the field and identify new avenues for research. Victoria Bolotina (Boston) described her recent work suggesting that a small diffusible messenger called $Ca^{2+}$ influx factor (CIF) linked STIM1 to Orai1 channel activation and that STIM1 might function as an enzyme that produces CIF (Bolotina, 2008). Richard Lewis (Stanford) described how STIM1 movement to specialized ER–PM junctions occurred and that STIM1 oligomerization was sufficient to activate CRAC channels. Anant Parekh (Oxford) showed data documenting that local $Ca^{2+}$ rises near CRAC channels could drive the synthesis of intra- and intercellular signalling molecules and reported the underlying signalling cascades (Parekh, 2008). Reinhold Penner (Hawaii) compared the properties of Orai1, 2 and 3 and found striking differences in how the pharmacological tool 2-APB interacted with the channels, revealing differences in channel gating (Peinelt *et al.* 2008). Finally, James Putney (NIEHS, Research Triangle Park) provided convincing evidence that $Ca^{2+}$ influx through CRAC channels supported intracellular $Ca^{2+}$ oscillations in response to low concentrations of agonist and presented data showing oscillatory movement of STIM1 up to the plasma membrane in parallel with the $Ca^{2+}$ spikes (Putney & Bird, 2008).

The talks presented at the symposium have been included as a series of Symposium Reviews and related research papers in this issue. In short, the symposium showed how far the store-operated channel field has advanced in a relatively short time. No doubt, with the approaches and techniques now available, new findings and unexpected twists will be revealed in the future.

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