You lose some, you gain some

It has been known for 20 years that depletion of the intracellular endoplasmic reticulum (ER) Ca^{2+} stores activates a second Ca^{2+} -entry pathway into cells. This so-called Ca^{2+} -release-activated Ca^{2+} (CRAC) current has been characterized in a number of cell types, but the mechanism by which the ER signals Ca^{2+} depletion to the plasma membrane has remained elusive. A flurry of new studies have shed light on our understanding of this process.

Recently, several of the key players have been discovered. An ER transmembrane protein, stromal interaction molecule-1 (STIM1), is thought to 'sense' the amount of Ca^{2+} that is present in the ER. A second protein of unknown function, ORAI1 (also known as CRACM1), has also been identified. Researchers now show that ORAI1 forms a channel in the plasma membrane, the activity of which is controlled by STIM1.

Three groups generated mutant ORAI1 channels and then used electrophysiological approaches to show this could alter channel's properties. Yeromin *et al.* and Prakriya *et al.* showed that a mutation in either the

first or third transmembrane domain of ORAI1 could abolish store-dependent Ca^{2+} currents or alter the selectivity of the channel for Ca^{2+} over other cations. These results indicate that the transmembrane domains 1 and 3 of ORAI1 line the pore.

The third group, Vig *et al.*, identified an extracellular-loop region that is crucial for the ion selectivity of the channel. This aspartate-rich region probably helps to coordinate Ca^{2+} into the channel and discriminates against other cations. Also, the authors found that ORAI1 formed multimers, supporting the idea that multiple ORAI1 subunits come together to compose a functional channel, as is common for many other ion channels.

But a key question remains: how might STIM1, which is distributed diffusely throughout the ER, communicate with ORAI1 channels at the plasma membrane? Wu *et al.* and Luik *et al.* addressed this question using microscopy-based techniques to show that STIM1 relocates into punctate clusters upon store emptying. STIM1 clusters formed within just 25 nm of the plasma membrane and occurred immediately before the detectable

activation of CRAC currents.

Surprisingly, they found that ORAI1 also moves following store depletion to sites directly opposed to STIM1 clusters. So, the coordinated redistribution of both STIM1 and ORAI1 seems to be a necessary first step in the generation of CRAC currents.

The second step involves a direct interaction between STIM1 and ORAI1, leading to an activation of the channel. Yeromin *et al.* showed a physical interaction between STIM1 and ORAI1 that was enhanced following store depletion. The C terminus of STIM1, which rests in the cytoplasm, is important for this interaction, as Huang *et al.* found that mutations in this region abolished the capability of STIM1 to activate CRAC currents. Further, in cells in which endogenous STIM1 had been knocked down by small interfering RNA, addition of the cytosolic C-terminal region of STIM1 could activate CRAC currents. Interestingly, the authors showed that STIM1 regulates another channel — TRPC1 — in the same manner. TRPC1 had, before the identification of ORAI1, been considered a prime candidate for the elusive CRAC channel.

The implications of the findings by Huang *et al.* raise further questions. Is TRPC1 a second store-dependent channel that is regulated by STIM1? Given the recent rate of progress in this field, we shouldn't have to wait long for an answer.

James Pickett

“...the coordinated redistribution of both STIM1 and ORAI1 seems to be a necessary first step in the generation of CRAC currents.”

Upon store depletion, STIM1 is redistributed close to the plasma membrane and activates CRAC channels. Adapted from figure 9 of Luik *et al.*

ORIGINAL RESEARCH PAPERS Yeromin, A. *et al.* Molecular identification of the CRAC channel by altered ion selectivity in a mutant of Orai. *Nature* **443**, 226–229 (2006) | Prakriya, M. *et al.* Orai1 is an essential pore subunit of the CRAC channel. *Nature* **443**, 230–233 (2006) | Vig, M. *et al.* CRACM1 multimers form the ion-selective pore of the CRAC channel. *Curr. Biol.* **13** Sep 2006 (doi:10.1016/j.cub.2006.08.085) | Wu, M. M. *et al.* Ca^{2+} store depletion causes STIM1 to accumulate in ER regions closely associated with the plasma membrane. *J. Cell Biol.* **174**, 803–814 (2006) | Luik, R. M. *et al.* The elementary unit of store-operated Ca^{2+} entry: local activation of CRAC channels by STIM1 at ER–plasma membrane junctions. *J. Cell Biol.* **174**, 815–825 (2006) | Huang, N. G. *et al.* STIM1 carboxyl-terminus activates native SOC, I_{crac} and TRPC1 channels. *Nature Cell Biol.* **8**, 1002–1010 (2006)