Cytoplasmic Ca\(^{2+}\) is an universal intracellular messenger that activates cellular responses over a broad temporal range, from neurotransmitter release to cell growth and proliferation.\(^1,2\) Inherent to the use of the multifarious Ca\(^{2+}\) signal is the question of specificity: how can some Ca\(^{2+}\)-dependent responses be activated in a cell and not others? A rise in cytoplasmic Ca\(^{2+}\) can evoke a response either by binding directly to the target (as occurs with certain Ca\(^{2+}\)-activated K\(^+\) and Cl\(^-\) channels, for example) or through recruitment of intermediary proteins, such as calmodulin and troponin C. A substantial body of evidence has now established that Ca\(^{2+}\)-binding proteins differ both in their affinities for Ca\(^{2+}\) and in their on- and off-rates for Ca\(^{2+}\) binding/unbinding. Furthermore, different Ca\(^{2+}\)-binding proteins often occupy distinct locations within the cell. Therefore, the size, kinetics and spatial profile of a cytoplasmic Ca\(^{2+}\) signal are all important in determining which Ca\(^{2+}\)-dependent response will be activated, when and for how long.\(^3\)

**Store-Operated CRAC Channels**

In general, cells can increase cytoplasmic Ca\(^{2+}\) in one of two ways. Ca\(^{2+}\) can be released from intracellular Ca\(^{2+}\) stores by second messengers including inositol trisphosphate,\(^2\) cyclic ADP-ribose and nicotinic acid adenine dinucleotide phosphate (NAADP).\(^4\) Alternatively, Ca\(^{2+}\) can enter cells by permeating through Ca\(^{2+}\) channels in the plasma membrane. Four major classes of Ca\(^{2+}\) entry channel have been described, differing both in their pattern of expression and mechanisms of gating. Voltage-gated Ca\(^{2+}\) channels increase their open probability when the membrane potential is depolarized and are found mainly in excitable cells.\(^5\) Ligand-gated channels, which include N-methyl D-aspartate (NMDA) ionotropic receptors activated by neurotransmitters, are non-selective cation channels with varying permeabilities to Ca\(^{2+}\).\(^6\) Channels gated by physical stimuli (such as temperature, stretch) are often members of the transient receptor potential (TRP) family and also tend to be non-selective channels.\(^7\) Finally, store-operated Ca\(^{2+}\) channels are widely distributed and are activated following the loss of Ca\(^{2+}\) from within the endoplasmic reticulum.\(^8\) Store-operated Ca\(^{2+}\) channels likely encompass a family of channels in which the Ca\(^{2+}\) release-activated Ca\(^{2+}\) (CRAC) channel is the dominant member, being expressed in a disparate array of cell types. CRAC channels are activated following stimulation of receptors coupled to phospholipase C.\(^9\) These receptors include those for growth factors and immunoreceptors (antigen and Fc receptors, which activate phospholipase C\(\gamma\) via tyrosine kinase activation) and G protein-coupled receptors that recruit phospholipase C\(\beta\). In both cases, activated phospholipase C hydrolyses phosphatidylinositol-4,5-bisphosphate to produce the second messengers InsP\(_3\) and diacylglycerol. InsP\(_3\) releases Ca\(^{2+}\) through activation of InsP\(_3\) receptors on the ER membrane. The subsequent loss of Ca\(^{2+}\) from the store leads to the opening of CRAC channels in the plasma membrane.\(^8\) The molecular basis of store-operated Ca\(^{2+}\) entry has now been identified and is discussed in detail elsewhere in this volume by Christoph Romanin and Murali Prakriya. In brief, STIM1 is a single pass ER-resident protein that detects the Ca\(^{2+}\) content of the stores through an EF-hand domain that is exposed to the lumen.\(^10,11\) Loss of Ca\(^{2+}\) from the store leads to Ca\(^{2+}\) dissociation from STIM1, resulting in the formation of STIM1 multimers. These oligomeric complexes then migrate toward the plasma membrane and cluster at regions of ER closely apposed to the plasma membrane (ER-PM junctions). At these sites, located within 20 nm of the plasma membrane,\(^12\) STIM1 binds to the N- and C-termini of the plasma membrane protein Orai1, which forms the CRAC channel, and this interaction leads to channel opening.\(^13,14\)

CRAC channels exhibit a high selectivity for Ca\(^{2+}\) over monovalent cations and also discriminate, at least to some extent, between different divalent cations.\(^15\) The permeability ratio of Ca\(^{2+}\) to Na\(^+\) is estimated to be > 1000, placing CRAC channels as among the most selective of all known Ca\(^{2+}\) channels. This high selectivity pairs up with a very low unitary conductance of ~10 fS, estimated from noise analysis studies in Jurkat T lymphocytes\(^16\) and rat basophilic leukemia (RBL-1) mast cells.\(^17\) Despite the tiny conductance, calculations place upwards of 8,000 functional channels in various immune cells. Site-directed mutagenesis and cysteine scanning have identified a major role for a highly conserved glutamate residue at position 106 in contributing to Ca\(^{2+}\) selectivity.\(^18-21\) The crystal structure of Drosophila Orai, the only isoform present in the fruit fly and which is conserved with human Orai1, has been obtained at 3.35Å resolution and reveals a hexameric arrangement of Orai subunits, with a ring of glutamate residues at the extracellular side forming the selectivity filter.\(^22\) A basic region near the intracellular side might bind anions and stabilize the channel closed state.
CRAC Channels and Cell Function

Ca\(^{2+}\) entry through CRAC channels activates a spectrum of kinetically distinct responses.\(^{23}\) Many of these responses are triggered by spatially restricted Ca\(^{2+}\) microdomains near open CRAC channels. Ca\(^{2+}\) influx can rapidly activate Ca\(^{2+}\)-dependent Cl\(^{-}\) channels, which are located close to the Ca\(^{2+}\) entry sites.\(^{44}\) Ca\(^{2+}\) influx can also trigger fusion of TRPC channel-containing vesicles.\(^{25}\) Plasma membrane adenyl cyclase isofrom 8 is physically coupled to Orai1, providing a mechanism for coordinating Ca\(^{2+}\) and cAMP signals.\(^{26}\) Ca\(^{2+}\) microdomains near open CRAC channels also stimulate the cytoplasmic enzymes cPLA\(_2\) and 5-lipoxygenase to generate arachidonic acid and the pro-inflammatory signaling molecule leukotriene C\(_4\) (LTC\(_4\)).\(^{27,28}\) LTC\(_4\) in turn activates phospholipase C-coupled cysteinyI leukotriene type I receptors, leading to LTC\(_4\) secretion and the generation of a positive feedback cycle that spreads through the mast cell population.\(^{29}\) Local Ca\(^{2+}\) entry through CRAC channels also has a longer lasting impact on cell physiology through regulation of gene expression (see below). In vivo studies with STIM1- and Orai1-deficient mice have revealed reduced innate immunity as well as impaired musculoskeletal development.\(^{30,31}\) Orai1\(^{-/-}\) mice also suffer from ectodermal dysplasia, sporadic hair loss and irritation of the eyelids.\(^{32}\)

CRAC Channels and Gene Expression

In T lymphocytes and mast cells, CRAC channel activation leads to the expression of genes that help shape the subsequent immune response. In mast cells, Ca\(^{2+}\) entry following opening of CRAC channels leads to increased transcription and subsequent translation of the transcription factor c-fos, an integral component of the AP-1 complex that in turn regulates the expression of various chemokines such as tumor necrosis factor-\(\alpha\) that help orchestrate the inflammatory response.

c-fos

Several lines of evidence suggest that Ca\(^{2+}\) microdomains near open CRAC channels and not a rise in bulk cytoplasmic Ca\(^{2+}\) are important in activating c-fos gene expression.\(^{33,34}\) First, loading the cytosol with the slow Ca\(^{2+}\) chelator EGTA, which is too slow to buffer Ca\(^{2+}\) within ~100 nm of an open Ca\(^{2+}\) channel,\(^{35,36}\) suppressed the bulk Ca\(^{2+}\) rise following CRAC channel activation but c-fos expression was unimpaired.\(^{32,36}\) By contrast, cytosolic loading with the Ca\(^{2+}\) chelator BAPTA, which can restrict local Ca\(^{2+}\) to within ~7 nm of the source,\(^{34,35}\) reduced gene expression. Second, despite increasing bulk Ca\(^{2+}\) to broadly similar extents, activation of CRAC channels in 2 mM external Ca\(^{2+}\) was considerably more effective in activating c-fos expression than in 0.5 mM external Ca\(^{2+}\), consistent with a major role for local Ca\(^{2+}\) entry.\(^{32}\) Finally, repetitive cytoplasmic Ca\(^{2+}\) oscillations activated in response to cysteinyI leukotriene type I receptor stimulation in the absence of external Ca\(^{2+}\) failed to induce c-fos expression whereas Ca\(^{2+}\) oscillations of identical amplitude and frequency evoked robust gene expression when Ca\(^{2+}\) entry through CRAC channels occurred.\(^{16}\) In response to a physiological trigger, local Ca\(^{2+}\) entry thus couples much more effectively to c-fos induction than bulk oscillatory Ca\(^{2+}\) changes. How is this local Ca\(^{2+}\) sensed and how is the signal transduced into increased c-fos expression? Pharmacological block of the non-receptor tyrosine kinase Syk or siRNA-directed gene knockdown both impaired coupling between local Ca\(^{2+}\) entry and c-fos expression,\(^{32}\) suggesting a pivotal role for this protein kinase. Syk was located at the plasma membrane, positioning it within close proximity of the CRAC channels,\(^{32}\) although it is not clear whether it co-localizes with the channels. Following local Ca\(^{2+}\) entry, Syk remained at the cell periphery and did not migrate toward the nucleus. Hence an intermediary signal is required to link the spatially restricted Ca\(^{2+}\) microdomains at the plasma membrane to nuclear c-fos expression. This is likely STAT5,\(^{32}\) a member of the STAT family of transcription factors. STATS are directly phosphorylated by tyrosine kinases leading to their dimerization\(^{37}\) and store depletion leads to increased STAT5 phosphorylation via Syk.\(^{32}\) This greatly increases retention within the nucleus by stabilization of DNA binding.

NFAT

The best understood example of activation of a transcription factor by Ca\(^{2+}\) entry through CRAC channels is the nuclear factor of activated T cells (NFAT).\(^{38}\) Four members of the NFAT family (NFAT1–4) are stimulated by a rise in cytoplasmic Ca\(^{2+}\) and activated NFAT regulates expression of genes that are involved in fundamental processes including synaptic plasticity, axonal growth, neuronal survival and cardiac hypertrophy in excitable cells as well as T-cell development, the generation of effective immune responses and epithelial cell remodelling in non-excitable cells. NFAT-driven gene expression often occurs in tandem with the AP-1 complex and it is interesting to recall that CRAC channel activation also increases c-fos expression.\(^{32,39}\)

The mechanism whereby cytoplasmic Ca\(^{2+}\) activates NFAT is well established.\(^{38,40}\) Elevated Ca\(^{2+}\) increases occupancy of the EF hands on the N- and C-lobes of calmodulin. The Ca\(^{2+}\)-calmodulin complex stimulates calcineurin, a cytoplasmic protein phosphatase which dephosphorylates cytosolic NFAT. Upon dephosphorylation, NFAT exposes a nuclear localization sequence that enables it to bind to the importin protein cmr1 and be transported into the nucleus. Pioneering work in T cells established a tight functional link between CRAC channels and NFAT activation. First, pulsatile fluxes of Ca\(^{2+}\) through CRAC channels, activated by the SERCA pump blocker thapsigargin, led to stimulation of NFAT and subsequent NFAT-driven gene expression.\(^{41}\) Second, Jurkat T cell mutants lacking functional CRAC channels showed impaired NFAT activity following stimulation.\(^{42}\) Finally, stimulation of T cells and fibroblasts taken from patients with an immunodeficiency caused by a single point mutation in Orai1 that renders the channel inactive failed to activate NFAT.\(^{43,44}\) In the mast cell line RBL-1, Ca\(^{2+}\) influx following stimulation with either thapsigargin or two different physiological agonists (LTC\(_4\) acting on cysLT1 receptors and IgE on FceRI receptors) activated NFAT migration into the nucleus and subsequent expression of an NFAT-driven reporter gene.\(^{45}\) These responses were abolished by block of CRAC channels with the inhibitor Synta66\(^{46}\) or after knockdown of Orai1.\(^{46}\)

As is the case with c-fos, local Ca\(^{2+}\) entry through CRAC channels more effectively activates NFAT than a bulk Ca\(^{2+}\)
rise following physiological levels of stimulation in mast cells. Stimulation of cysteinyi leukotriene receptors with a low concentration of LTC₄ evokes a series of repetitive Ca²⁺ oscillations and this leads to NFAT movement into the nucleus and subsequent gene expression. By contrast, only a few Ca²⁺ oscillations occur when cells are stimulated in the absence of external Ca²⁺ or after block of CRAC channels and these spikes fail to trigger NFAT activation. Moreover, stimulation with LTC₄ in Ca²⁺-free solution under conditions where Ca²⁺ efflux is inhibited results in the generation of Ca²⁺ oscillations that are identical in amplitude and frequency to those seen in the presence of external Ca²⁺. However, despite such regular Ca²⁺ signals, NFAT fails to migrate into the nucleus. Additional support for a role for local Ca²⁺ entry include the findings that first, loading the cytoplasm with EGTA abolished the Ca²⁺ rise following CRAC channel activation but NFAT activation was unimpaired (Fig. 1). Second, NFAT activation correlated better with the predicted unitary channel flux than the bulk Ca²⁺ rise. As with c-fos expression, CRAC channel activation in the presence of 2 mM or 0.5 mM external Ca²⁺ elicited similar bulk Ca²⁺ increases but NFAT activation was stronger in 2 mM Ca²⁺. However, it is important to note that bulk Ca²⁺ does activate NFAT under certain conditions. Stimulation with thapsigargin in Ca²⁺-free solution under conditions where plasma membrane Ca²⁺ removal is suppressed raised cytoplasmic Ca²⁺ to high levels and this resulted in strong NFAT activation. Under these conditions, Ca²⁺ entry through CRAC channels could not take place (absence of external Ca²⁺) yet NFAT activated. Hence NFAT can be activated by both local and bulk Ca²⁺, depending on the intensity of the stimulus. Modest, physiological levels of activation recruit NFAT primarily through the local Ca²⁺ route in mast cells whereas stronger stimulation recruits the transcription factor through a bulk Ca²⁺ rise. Another contributing factor is likely to be the accessible cytoplasmic volume, which depends on cell size. The cytoplasmic volume of a typical spherical Jurkat T lymphocyte (diameter of ~7 μm) would be ~20-fold less than that of a spherical RBL-1 cell (diameter of ~20 μm). Because Jurkat T and RBL-1 cells have similar cytoplasmic Ca²⁺ binding ratios [125 and 170 (Bakowski and Parekh, unpublished)] as well as CRAC current amplitudes (~−20 pA and −30 pA at −80 mV in high intracellular EGTA and saturating external Ca²⁺), the bulk Ca²⁺ rise would be considerably larger in Jurkat cells following similar levels of CRAC channel activation. In T cells, NFAT activation is probably tightly linked to bulk Ca²⁺ levels, except at very weak levels of stimulation where local Ca²⁺ would be favored. By contrast, in larger cells such as RBL-1 mast cells or certain types of neuron, local Ca²⁺ signals may determine NFAT activation except at high stimulus intensities.

### Agonists Activate Orai1-Dependent Gene Expression through Selection of Different STIM Proteins

Although Ca²⁺ entry through Orai1 drives gene expression, different agonists that couple to phospholipase C activate the channels through recruitment of distinct complements of STIM proteins. Mammalian cells can co-express two different STIM proteins, STIM1 and STIM2, products of different genes. Despite significant homology, there are some important differences between these proteins. First, STIM2 activates Ca²⁺ influx through Orai1 less well than STIM1, for similar levels of Orai1 expression. This is thought to reflect structural differences within the N-terminal domain of the STIM proteins as well as selective inhibition of STIM2-Orai1 coupling by cytoplasmic calmodulin. Second, STIM2 has an approximately 2-fold lower affinity for luminal Ca²⁺ than STIM1 and therefore requires less ER Ca²⁺ store emptying for activation. STIM2 is thought to be better suited both for ensuring that the stores are replete with calcium in the absence
of stimulation and for activation of Ca\(^{2+}\) entry through Orai1 after weak stimulation. By contrast, STIM1 requires a more substantial fall in stored Ca\(^{2+}\) for activation and is thought to gate CRAC channels after strong stimulation.

Following stimulation of G protein-coupled cysteiny1 leukotriene type I receptors with LTC\(_4\), in RBL-1 cells, large cytoplasmatic Ca\(^{2+}\) oscillations were generated and the accompanying local Ca\(^{2+}\) entry near open CRAC channels activated NFAT-dependent gene expression. Knockdown of STIM1 but not STIM2 resulted in loss of agonist-evoked Ca\(^{2+}\) entry, rundown of the Ca\(^{2+}\) oscillations (measured over 10 min stimulation) and a significant reduction in gene expression. At least over this time frame of LTC\(_4\) exposure, STIM1 and not STIM2 supports Ca\(^{2+}\) signals and gene expression following receptor activation. A similar dependence of all-or-none Ca\(^{2+}\) oscillations on STIM1 but not STIM2 has been seen in HEK293 cells in response to muscarinic receptor stimulation. On the other hand, stimulation of RBL-1 cells with IgE elicited smaller Ca\(^{2+}\) oscillations on an elevated Ca\(^{2+}\) baseline and the Ca\(^{2+}\) signal and NFAT-driven gene expression depended on both STIM1 and STIM2 as well as Orai1. Hence different agonists activate different patterns of Ca\(^{2+}\) signal and downstream responses through recruitment of different combinations of STIM proteins. Differences in the kinetics of InsP\(_3\) production and hence the extent of store depletion might explain the differential involvement of STIM1 and STIM2, depending on the stimulus. Activation of G protein-coupled receptors such as the cysteiny1 leukotriene type I receptor rapidly increases InsP\(_3\) levels and generally triggers large cytoplasmatic Ca\(^{2+}\) oscillations, which reflect significant mobilization of ER Ca\(^{2+}\). The drop in ER Ca\(^{2+}\) is sufficiently large, albeit transient, to exceed the threshold required for STIM1 activation. IgE on the other hand increases InsP\(_3\) levels slowly, reflecting tyrosine kinase-dependent activation of phospholipase C\(\gamma\). A smaller rise in InsP\(_3\) occurs, reflecting a balance between InsP\(_3\) production and breakdown.

This more modest rise in InsP\(_3\) will lead to moderate store depletion, and thereby recruit STIM2 along with some STIM1 molecules, in agreement with studies from STIM-deficient T cells.

In addition to regulating gene expression through activation of Ca\(^{2+}\) entry through Orai1, STIM1 has been found to bind to nuclear carrier proteins including importin-\(\beta1\) and exportin-1. Interactions with these transport proteins were mediated by POST (partner of stromal interaction molecule 1), a ten transmembrane domain spanning protein in the ER and plasma membrane and which binds to STIM1 after store depletion with thapsigargin in the absence of external Ca\(^{2+}\). It will be interesting to see if STIM-regulated karyopherin movement in and out of the nucleus impacts on gene expression independent of Ca\(^{2+}\) entry.

**Concluding Remarks**

Ca\(^{2+}\) entry through store-operated CRAC channels leads to gene expression in various types of immune cell, through activation of cytoplasmatic transcription factors including c-fos and NFAT. Although a large rise in bulk Ca\(^{2+}\) can activate NFAT, more physiological levels of stimulation recruit the transcription factor through the generation of spatially restricted Ca\(^{2+}\) signals near open CRAC channels. Orai1 is essential for agonist-evoked Ca\(^{2+}\)-dependent gene expression but different stimuli utilize different components of STIM protein to activate the Ca\(^{2+}\) channel. Identifying how local Ca\(^{2+}\) signals are sensed, how high local Ca\(^{2+}\) rises and whether different Orai proteins are equally effective in signaling to the nucleus are interesting questions for the future.

**Disclosure of Potential Conflicts of Interest**

No potential conflicts of interest were disclosed.

**Acknowledgments**

Research in our laboratory is supported by the MRC.
20. Yeromin AV, Zhang SL, Jiang W, Yu Y, Safinya O, Cahalan MD. Molecular identification of the CRAC channel by altered ion selectivity in a mutant of Orai. Nature 2006; 443:226-9; PMID:16921385; http://dx.doi.org/10.1038/nature05108
21. McNally BA, Yamashita M, Engh A, Prakriya M. Structural determinants of ion permeation in CRAC channels. Proc Natl Acad Sci U S A 2009; 106:22516-21; PMID:20081736; http://dx.doi.org/10.1073/pnas.0909574106
22. Hou X, Pedli L, Driver MM, Long SB. Crystal structure of the calcium-release-activated calcium channel Orai. Science 2012; 338:1308-13; PMID:23180775; http://dx.doi.org/10.1126/science.1228775
23. Parekh AB. Store-operated CRAC channels: function in health and disease. Nat Rev Drug Discov 2010; 9:399-410; PMID:20395953; http://dx.doi.org/10.1038/nrd3136
24. Lemonnier L, Prevarskaya N, Shuba Y, Vanden Abeele Kurosaki T. Essential function for the calcium sensor in the 
family of store-operated calcium release-activated calcium channel Orai. Nature 2008; 9:81-8; PMID:18059272; http://dx.doi.org/10.1038/nature0731
25. Parekh AB. Ca2+ microdomains near plasma membrane store-operated Ca2+ channels: impact on cell function. J Physiol 2008; 586:9043-54; PMID:18467565; http://dx.doi.org/10.1113/jphysiol.2008.153460
26. Di Capite J, Ng SW, Parekh AB. Decoding of cytoplastic Ca2+ oscillations through the spatial signature drives gene expression. Curr Biol 2009; 19:853-8; PMID:19375314; http://dx.doi.org/10.1016/j.cub.2009.03.063
27. Reich NC, Liu L. Tracking STAT nuclear traffic. Nat Rev Immunol 2006; 6:602-12; PMID:16868551; http://dx.doi.org/10.1038/nri1885
28. Hogan PG, Chen L, Nardone J, Rao A. Transcriptional regulation by calcium, calmodulin, and NFAT. Genes Dev 2003; 17:2205-32; PMID:12975316; http://dx.doi.org/10.1101/gad.1102703
29. Ng SW, Bakowski D, Nelson C, Mehta R, Almeyda R, Bates G, et al. Cysteinyl leukotriene type 1 receptor desensitization sustains Ca2+-dependent gene expression. Nature 2012; 482:111-5; PMID:22230957; http://dx.doi.org/10.1038/nature10731
30. Neher E. Vesicle pools and Ca2+ microdomains: new tools for understanding their roles in neurotransmitter release. Neon 1998; 20:389-99; PMID:9539117; http://dx.doi.org/10.1016/S0086-6273(00)80983-6
31. Parekh AB. Ca2+ microdomains near plasma membrane CRAC channels: impact on cell function. J Physiol 2008; 586:9043-54; PMID:18467565; http://dx.doi.org/10.1113/jphysiol.2008.153460
32. Ng SW, Bakowski D, Nelson C, Mehta R, Almeyda R, Bates G, et al. Cysteinyl leukotriene type 1 receptor desensitization sustains Ca2+-dependent gene expression. Nature 2012; 482:111-5; PMID:22230957; http://dx.doi.org/10.1038/nature10731
33. Gallo EM, Castron-Barrett K, Craibree GR. Lymphocyte calcium signaling from membrane to nucleus. Nat Immunol 2006; 7:25-32; PMID:16357855; http://dx.doi.org/10.1038/ni1071
34. Dolmetsch RE, Xu K, Lewis RS. Calcium oscillations increase the efficiency and specificity of gene expression. Nature 1998; 392:933-6; PMID:9582075; http://dx.doi.org/10.1038/31960
35. Fanger CM, Hoth M, Lewis RS. Characterization of T cell mutants with defects in capacitative calcium entry: genetic evidence for the physiologic roles of CRAC channels. J Cell Biol 1999; 151:655-7; PMID:9793187; http://dx.doi.org/10.1083/jcb.1999.003618
36. Feske S, Gwack Y, Prakriya M, Srikanth S, Puppel SH, Whipp ER, et al. Mutations in Orai1 cause the apparent absence of the store-operated calcium channel Orai. Nature 2006; 443:226-9; PMID:16921385; http://dx.doi.org/10.1038/nature05108
37. Kar P, Paliyovski D, Di Capite J, Nelson C, Parekh AB. Different agonists recruit different stromal interaction molecule proteins to support cytoplasmic Ca2+ oscillations and gene expression. Proc Natl Acad Sci U S A 2012; 109:6969-74; PMID:22509043; http://dx.doi.org/10.1073/pnas.1201294109
38. Bausista DM, Hoth M, Lewis RS. Enhancement of calcium signalling dynamics and stability by delayed modulation of the plasma-membrane calcium-ATPase in human T cells. J Physiology 2002; 541;977-9; PMID:12068359; http://dx.doi.org/10.1113/jphysiol.2001.016154
39. Cahalan MD. STIMulating store-operated Ca2+ entry. Nat Cell Biol 2009; 11:669-77; PMID:19488056; http://dx.doi.org/10.1038/ncll0609-669
40. Bird GS, Hwang SY, Smyth JT, Fukushima M, Boyles RR, Purney JW Jr. STIM1 is a calcium sensor specialized for digital signaling. Curr Biol 2009; 19:1724-9; PMID:19765994; http://dx.doi.org/10.1016/j.cub.2009.08.022
41. Zhou Y, Mancarella S, Wang Y, Yue C, Ritchie M, Gill DL, et al. The short N-terminal domains of STIM1 and STIM2 control the activation kinetics of Orai channels. J Biol Chem 2009; 284:19164-8; PMID:19487696; http://dx.doi.org/10.1074/jbc.fci.09010900
42. Parvez S, Beck A, Peinelt C, Soboloff J, Lis A, Monreil-Zoller M, et al. STIM2 protein mediates distinct store-dependent and store-independent modes of CRAC channel activation. FASEB J 2008; 22:752-61; PMID:17905723; http://dx.doi.org/10.1096/fj.07-9445com
43. Brandman O, Liu J, Park WS, Meyer T. STIM2 is a feedback regulator that stabilizes basal cytosolic and endoplasmic reticulum Ca2+ levels. Cell 2007; 131:1327-39; PMID:18160041; http://dx.doi.org/10.1016/j.cell.2007.11.039
44. Ol-Hora M, Yamashita M, Hogan PG, Sharma S, Lamperti E, Chung W, et al. Dual functions for the endoplasmic reticulum calcium sensors STIM1 and STIM2 in T cell activation and tolerance. Nat Immunol 2008; 9:432-43; PMID:18327260; http://dx.doi.org/10.1038/ni.1574
45. Krapivinsky G, Krapivinsky L, Stotz SC, Manasian Y, Neher E. Vesicle pools and Ca2+ microdomains: new tools for understanding their roles in neurotransmitter signaling. J Physiol 2002; 541;894-9; PMID:12068359; http://dx.doi.org/10.1113/jphysiol.2001.016154
46. Saitoh N, Oritani K, Saito K, Yokota T, Ichii M, Sudo T, et al. Identification of functional domains and novel binding partners of STIM proteins to support cytoplasmic Ca2+ oscillations and gene expression. Proc Natl Acad Sci U S A 2010; 109:1982-7; PMID:20353660; http://dx.doi.org/10.1073/pnas.100229910

©2013 Landes Bioscience. Do not distribute.