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Review

Store operated calcium entry: From concept to structural mechanisms

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ABSTRACT

In 1986, J.W. Putney presented a model for capacitative calcium (Ca^{2+}) entry conveying that depletion of endoplasmic reticulum stored Ca^{2+} levels leads to activation of plasma membrane Ca^{2+} channels which mediate influx of Ca^{2+} from the extracellular space into cells. Presently, the biomolecules regulating this process, more widely known as store operated Ca^{2+} entry (SOCE) which is vital to myriad signaling pathways in health and disease, are known and the focus of intense structural biology research aiming to illuminate the atomic mechanisms of function. This brief review highlights the known structures with respect to the mechanisms of SOCE regulation and possible future directions in this field developed out of Putney's conceptualization of this process.

Forty years ago, the J.W. Putney group demonstrated that potassium (K^+) permeability in response to acetylcholine exposure of parotid gland occurred through sequential transient and sustained phases [1], and remarkably, the transient response was dependent on intracellularly stored calcium (Ca^{2+}) [2]. Soon after, they showed that the presence of internally stored Ca^{2+} was dependent on the existence of external Ca^{2+}, revealing the first association between intracellular stored ion release and influx into cells [2]. Consistent with these initial observations, Putney's group discovered that ^{86}rubidium (Rb^+) efflux, used as a surrogate for K^+, through Ca^{2+} activated K^+ channels was only transient in lacrimal acinar cells when the external medium lacked Ca^{2+}, and a second transient response was only observed when Ca^{2+} was restored to the extracellular medium [3]. Although inconspicuous at the time, these studies laid the foundation for the capacitive Ca^{2+} entry model articulated a decade later by Putney that first described the process of store operated Ca^{2+} entry (SOCE): depletion of endoplasmic reticulum (ER) Ca^{2+} stores signals the opening of plasma membrane (PM) Ca^{2+} channels [4,5].

Just as inconspicuous were the molecular players and mechanisms involved in directly mediating SOCE. Introduction of the SOCE model was followed by a 'dark ages' period whereby candidate proteins and mechanisms including transient receptor potential (TRP) channels [6], diffusible messengers [7,8], vesicle fusion/exocytosis [9,10] and direct coupling between ER inositol 1,4,5-trisphosphate receptor channels and PM Ca^{2+} channels [11–14] were put forth, but the real molecular players were still unknown during that time interval. It was not until 2005 using a large scale small inhibiting RNA screen against 2304 signaling proteins [15] and an RNA interference gene knockdown approach directed against *Drosophila* genes in S2 cells [16] that stromal interaction molecules (*i.e.* Stim in *Drosophila*, STIM1 and STIM2 in humans) were identified as the key proteins directly regulating SOCE. Importantly, the ability of STIMs to detect changes in ER luminal Ca^{2+} levels and activate SOCE was demonstrated by mutation in a primary sequence predicted single EF-hand motif where disruption of Ca^{2+} binding led to activation of SOCE [15,17]. One year later, the Orai1 subunits making up the PM channel pore were identified through similar interfering RNA, pedigree analyses of a family with inherited immunodeficiency disease and Ca^{2+} release activated Ca^{2+} (CRAC) current measurements after rationalized mutagenesis [18–23]. With the identification of these molecular players, Putney and others showed that ectopic co-expression of STIM1 and Orai1 produced enormous synergistic levels of SOCE [24–26].

The discovery of STIM1/-2 and Orai1 led to the proliferation of functional studies aimed at teasing out the cellular mechanisms of SOCE. These cellular studies were highlighted by discoveries revealing that upon luminal Ca^{2+} depletion, STIM proteins homo-oligomerize [27] and translocate to ER-PM junctions where they

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assemble into larger aggregates described as puncta [17,27–31]. The PM-resident Orai1 channel proteins are recruited to the same puncta via direct interactions with STIM1 [28,32–34] where they are gated and form functional channels (see below).

STIM proteins are modular with a single pass transmembrane (TM) segment separating the ER luminal from the cytosolic domains. The first atomic resolution structure of any domain involved in mediating SOCE was the luminal Ca^{2+} sensing region of human STIM1 corresponding to the evolutionarily conserved EF-hand together with the sterile α-motif (SAM) domains (EFSAM) [35]. It was already known that Ca^{2+} depletion from this ER luminal STIM1 region causes a profound destabilization-coupled with oligomerization [36]; however, this structure provided atomic-level mechanistic insights into the basis for this oligomerization and thus, the initiation of SOCE via STIM1. The work revealed that the luminal domain of STIMs indeed contain a sequence-unidentifiable EF-hand which pairs with the canonical Ca^{2+} binding EF-hand in the formation of an extensive hydrophobic cleft; moreover, in the Ca^{2+}-bound state, the C-terminal helix of the SAM domain is anchored in EF-hand cleft, keeping EFSAM in a compact, monomeric conformation and maintaining STIM1 in a quiescent state (Fig. 1A) [35]. Upon Ca^{2+}-depletion, EFSAM undergoes a destabilization-coupled oligomerization linked to increased hydrophobic residue exposure [35,36]. The luminal domain oligomerization initiates conformational changes in the STIM1 cytosolic domains, the translocation process and activation of PM Orai1 channels.

Remarkably, the human STIM1 homologue, STIM2, has a distinctive luminal Ca^{2+} sensitivity and plays a prominent role in basal ER luminal and cytosolic Ca^{2+} homoeostasis [37]. STIM2 functions as a feedback regulator of basal Ca^{2+} levels by becoming active after smaller decreases in ER Ca^{2+} concentrations [37], owing to a lower EF-hand Ca^{2+} binding affinity compared to STIM1 EFSAM [38]. Mechanistically, this lower affinity was initially somewhat puzzling since STIM2 EFSAM is more stable than STIM1 [38]. However, structural studies revealed a more extensive hydrophobic cleft and SAM domain core as well as ionic interactions between the EF-hand:SAM domains enhance STIM2 stability by promoting the compact conformation (Fig. 1B) [39], despite the lower Ca^{2+} binding affinity mediated by the canonical EF-hand motif. Collectively, these structural studies revealed that STIM1 EFSAM is a robust ON/OFF regulator of Orai1 channels using a balance of higher Ca^{2+} binding affinity (*i.e.* responsive to large magnitude ER luminal Ca^{2+} depletion) with lower stability (*i.e.* increasing oligomerization propensity and rates), while STIM2 EFSAM is an ideal regulator of basal Ca^{2+} homeostasis with a lower Ca^{2+} binding affinity (*i.e.* responsive to small magnitude ER luminal Ca^{2+} depletion) and higher stability (*i.e.* mediating lower oligomerization propensity) [39,40].

While EFSAM is responsible for Ca^{2+} sensing and initiation of STIM1 oligomerization, the cytosolic domains including the coiled-coil (CC) regions play roles in oligomerization, translocation, Orai1 coupling as well as gating [20,22,27,31,41,42]. In fact, STIM1 cytosolic fragments encompassing only the CC domains are sufficient for eliciting constitutively active SOCE when co-expressed with Orai1 [33,41,43–46]. There are three conserved CC domains in the cytosolic region of STIMs (*i.e.* CC1, CC2 and CC3); CC2 together with CC3 (*i.e.* residues ~342–448) constitute the minimal region required for coupling to and activation of Orai1 channels in cells [43,45,46]. A L374M/V419A/C436T triple mutant crystal structure of this minimum region revealed a V-shaped dimer structure where CC3 runs antiparallel to CC2, and the CC2-CC3 linker region is positioned at the apex of each monomer [47] (Fig. 2A). Moreover, a M244L/L321M double mutant crystal structure of CC1 (*i.e.* residues 237–340) revealed a helical conformation that extends ~13 nm, confirming the ability of ER-inserted STIM1 to bridge the distance to the PM during Orai1 channel activation [48] (Fig. 2B). CC1 also plays important roles in keeping the CC2-CC3 regions in a quiescent state through direct CC1:CC2-CC3 interactions [49]. In fact, mutations in CC1 are capable of inducing a conformational extension which culminates in CC2-CC3 constitutively activating Orai1 channels [50].

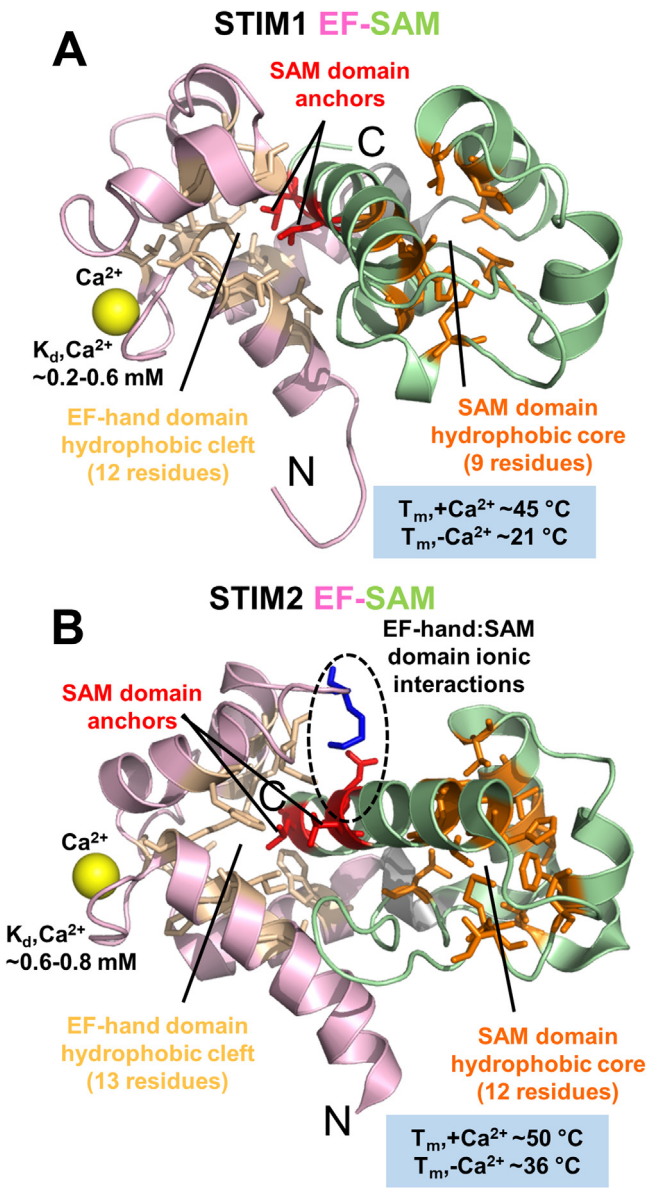

Fig. 1. Atomic resolution structures of the STIM1 and STIM2 Ca^{2+} sensing luminal domains. *A*. Solution NMR structure of Ca^{2+}-loaded STIM1 EFSAM. The STIM1 EF-hand (pink) hydrophobic cleft is made up of 12 residues (beige sticks: V68, I71, H72, L74, M75, V83, L92, L96, K104, F108, I115, L120). The SAM domain (green) hydrophobic core is made up of 9 residues (orange sticks: V137, L141, V145, L159, L167, M174, H186, L190, A194). The anchor residues (red sticks: L195, L199) that keep the SAM domain closely apposed to the hydrophobic cleft are shown. *B*. Solution NMR structure of Ca^{2+}-loaded STIM2 EFSAM. The STIM2 EF-hand (pink) hydrophobic cleft is made up of 13 residues (beige sticks: L72, I75, H76, M79, I87, F95, M100, K103, K108, L112, L119, L124, W128). The SAM domain (green) hydrophobic core is made up of 9 residues (orange sticks: L142, L145, V149, F158, V163, L168, M179, I180, L183, H190, K193, L194). The anchor residues (red sticks: L199, L203) and the ionic interaction (D200 and K203; red and blue sticks, respectively) that keep the SAM domain closely apposed to the hydrophobic cleft are indicated. In *A* and *B*, the estimated equilibrium dissociation constants (K_d) of Ca^{2+} binding and midpoints of temperature denaturation (T_m) are from [35,36] and [38,39] for STIM1 and STIM2, respectively. Ca^{2+} is represented by a yellow sphere and the images were rendered using 2K60 and 2L5Y in PyMOL.

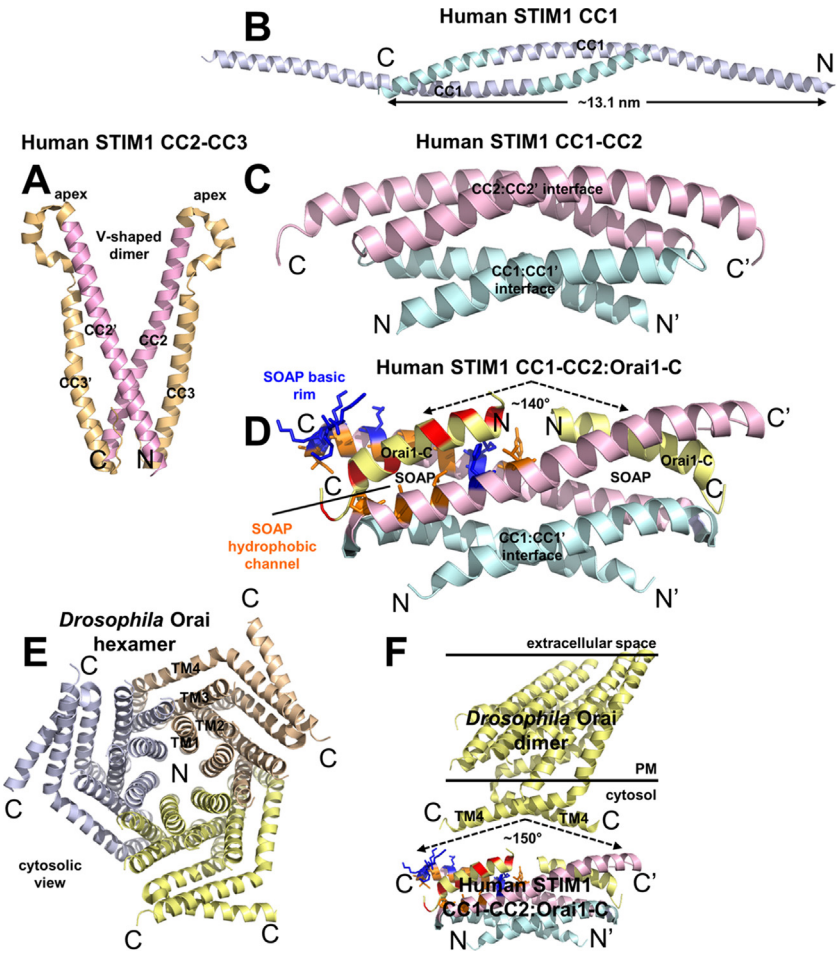

Fig. 2. Atomic resolution structures of the STIM1 CC domains and *Drosophila* Orai. *A.* Crystal structure of the STIM1 CC2-CC3 (*i.e.* SOAR/CAD/ccb9) region. *B.* Crystal structure of the STIM1 CC1 domain. The ~13.1 nm distance spanned by this extended conformation that likely bridges the ER-PM distance during Orai1 channel activation [48] is indicated. *C.* Solution NMR structure of the STIM1 CC1-CC2 fragment. The CC1:CC1′ (cyan) and CC2:CC2′ (pink) interfaces which interact via supercoiling are indicated. *D.* Solution NMR structure of the STIM1 CC1-CC2 fragment in complex with two Orai1 C-terminal domain peptides. The CC1:CC1′ (cyan) interface is indicated. The SOAP made up of hydrophobic (orange sticks: P344, L347, L351, H355, V359, Y362′, K366′, A369′, L373′, A376′, A380′, I383′) and basic residues (blue sticks: H355, K365′, K366′, K377′, K382′, K384′, K385′, K386′, R387′) exclusively from the CC2 helices (pink) are indicated. The complementary acidic residues (red cartoon: E272, E275, E278, D284, D287, D291) from the Orai1 C-termini (yellow) are also shown. *E. Drosophila melanogaster* hexameric Orai crystal structure. Each dimer building block is coloured distinctly (*i.e.* blue, brown, and yellow). *F.* Zoomed view of the Orai dimer exhibiting a high degree of C-terminal domain structural compatibility with the human STIM1 CC1-CC2:Orai1 C-terminal conformation and hypothetical binding mode in the cytosol. The similar interhelical angles in *E* and *F* are indicated. The overlapping CC1 regions in *B*, *C* and *D* are coloured cyan. The overlapping CC2 regions in *A*, *C* and *D* are coloured pink. The images in *A*–*F*, were rendered using 3TEQ, 4O9B, 2MAJ, 2MAK and 4HKR, respectively, in PyMOL. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

While static crystal structure snapshots have provided a wealth of information on the mechanisms of STIM1 cytosolic domain function, a series of elegant live cell fluorescence resonance energy transfer experiments indicate the CCs undergo large structural changes concomitant with activation [33,44,49,50]. In the inactive state, the CC1 region interacts with CC2-CC3 (*i.e.* CAD/SOAR/ccb9) [49,51], maintaining a compact cytosolic conformation. While, studies are in agreement about the domains which interact and lock STIM1 in a quiescent state (*i.e.* CC1:CC3), the precise CC1 residues involved may include L251 [49] or L258/L261 [52]. Dimerization of the ER STIM1 luminal domains brings the STIM1 CC1 regions into close apposition, triggering the cytosolic extension required for coupling and gating of PM Orai1 channels [51]. The single TM domain of STIM1 plays a role in the ER luminal to cytosolic domain signal transmission, as a change in the interhelical TM angle between adjacent STIM1 monomers (*i.e.* that would be induced by EFSAM dimerization/oligomerization) is sufficient to bring CC1 regions together and unlock SOAR/CAD/ccb9 region for Orai1 activation [52].

STIM1 cytosolic CC domain conformational changes are also evident from the solution NMR structures of a STIM1 CC1-CC2 fragment (*i.e.* residues 312–387). CC1-CC2 forms a dimer structure made up of two U-shaped monomers with CC1:CC1′ and CC2:CC2′ interfaces formed in an antiparallel manner (Fig. 2C) [53]. In complex with the Orai1 C-terminal domain (*i.e.* residues 272–292) linked with recruitment and gating on the PM [54], CC1-CC2 undergoes a dilation between the CC2:CC2′ interface, a registry shift in the CC1:CC1′ interface and new supercoiling interactions between Orai1-C:CC2′ (Fig. 2D) [53]. To accommodate two Orai1-C terminal domains, the CC2 forms a symmetrical STIM-Orai association pocket (SOAP) that has a hydrophobic interior and is surrounded by a positively charged rim. These features are complementary to the negatively charged Orai1 C-terminal domain containing distinct hydrophobic residues that insert into the SOAP [53].

The CC2 region of the CC1-CC2 protein in complex with the Orai1 C-terminal domain assembles differently than CC2 in the CC2-CC3 crystal structure (Fig. 2B and D), reinforcing the capability for extensive conformational changes in the CC regions of

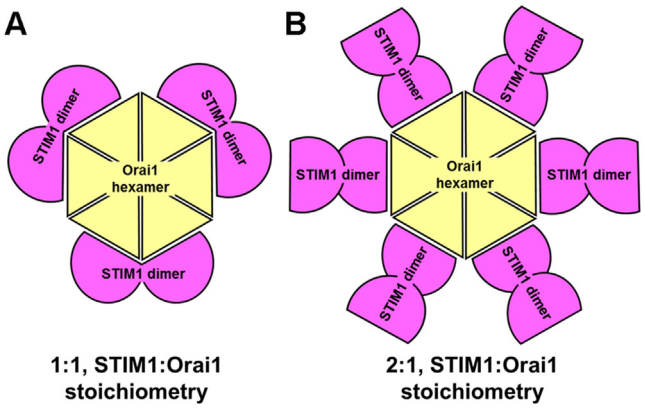

Fig. 3. STIM1:Orai1 stoichiometric coupling models. *A.* STIM1 dimers coupling to Orai1 dimers in a hexameric channel assembly derived from the solution NMR structure of STIM1 CC1-CC2 in a symmetric complex with two Orai1 C-terminal domains [53]. *B.* STIM1 dimers coupling to Orai1 monomers in a hexameric channel assembly derived from STIM1 CC2-CC3 dimer concatemers with an inactivating mutation in one subunit fully activating SOCE [61].

STIM1. More remarkable than these differences, however, is the high degree of structural similarity between the orientation of the Orai1-C terminal helices observed in the CC1-CC2:Orai1-C NMR structure and the conformation of the Orai C-terminal helices (*i.e.* residues 318–334) observed in the C224S/C283T/P276R/P277R quadruple mutant *Drosophila melanogaster* Orai crystal structure (Fig. 2E) [55]. Considering Levinthal's protein folding paradox [56], it is unlikely that the two structures (*i.e.* fly Orai crystal and human solution STIM1:Orai1-C complex) are structurally similar by chance, implying a compelling coupling and stoichiometric assembly mechanism for the STIM1:Orai1 interaction. This structural congruency suggests that the coupling of two STIM1 molecules to two Orai1 C-terminal helices (*i.e.* 1:1 stoichiometry) plays a role in the assembly and activation of Orai1 channels (Fig. 3A). This docking arrangement is supported by studies which show that mutational alteration of the bend architecture of the Orai1 C-terminal helices attenuates binding to STIM1 CC2-CC3, locking the Orai1 C-terminal bend through Cys crosslinking still permits binding to STIM1 CC2-CC3 and the crosslinking efficiency of residues central in the Orai1 C-termini crossover position exhibited in the NMR complex structure is greater than peripheral residues in this region [57].

Absent from the NMR-derived STIM1:Orai1 coupling scheme due to construct design is the F394 residue located on CC3 which may be important for Orai1 channel gating [58] via interactions with the N-terminal Orai1 extensions [33,45,54,58–60]. Furthermore, concatenated STIM1 CC2-CC3 dimers carrying an activity-diminishing F394H mutation in one monomer are still able to elicit maximal channel activation, leading to a recent contrasting model which proposes STIM1 dimers couple to Orai1 monomers (2:1 stoichiometry) through only one STIM1 subunit [61] (Fig. 3B).

With universal and crucial cell signaling roles in health and disease, a tremendous amount of research has been invested in understanding the cellular, molecular and atomic mechanisms of SOCE regulation since Putney's initial conceptualization several decades ago. However, growing scientific knowledge will continue to spawn new inquiries, and at the structural level, several prominent questions remain: *What is the structure of human wild-type Orai1 in the open channel configuration? What is the structure of the full cytosolic STIM1 domain in the compact and extended conformations? How does full-length STIM1 couple to full-length Orai1 and in what stoichiometry? What role does membrane insertion play in the mechanisms of STIM1 activation? How do post-translational modifications contribute to these structural mechanisms? How do the different isoforms of STIM and Orai differentially regulate Ca^{2+} signaling?* Clearly, the mechanisms of SOCE activation will be the focus of intense research for many decades in the future, all borne out of J.W. Putney's conceptualization of SOCE.

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References

[1] J.W. Putney Jr., Biphasic modulation of potassium release in rat parotid gland by carbachol and phenylephrine, J. Pharmacol. Exp. Ther. 198 (1976) 375–384.
[2] J.W. Putney, Jr., Muscarinic, alpha-adrenergic and peptide receptors regulate the same calcium influx sites in the parotid gland, J. Physiol. 268 (1977) 139–149.
[3] R.J. Parod, J.W. Putney Jr., The role of calcium in the receptor mediated control of potassium permeability in the rat lacrimal gland, J. Physiol. 281 (1978) 371–381.
[4] J.W. Putney Jr., A model for receptor-regulated calcium entry, Cell Calcium 7 (1986) 1–12.
[5] J.W. Putney, Origins of the concept of store-operated calcium entry, Front. Biosci. (Schol Ed) 3 (2011) 980–984.
[6] L. Birnbaumer, X. Zhu, M. Jiang, G. Boulay, M. Peyton, B. Vannier, D. Brown, D. Platano, H. Sadeghi, E. Stefani, M. Birnbaumer, On the molecular basis and regulation of cellular capacitative calcium entry: roles for Trp proteins, Proc. Natl. Acad. Sci. U. S. A. 93 (1996) 15195–15202.
[7] J.W. Putney Jr., Capacitative calcium entry revisited, Cell Calcium 11 (1990) 611–624.
[8] C. Randriamampita, R.Y. Tsien, Emptying of intracellular Ca2+ stores releases a novel small messenger that stimulates Ca2+ influx, Nature 364 (1993) 809–814.
[9] C. Fasolato, M. Hoth, R. Penner, A GTP-dependent step in the activation mechanism of capacitative calcium influx, J. Biol. Chem. 268 (1993) 20737–20740.
[10] Y. Yao, A.V. Ferrer-Montiel, M. Montal, R.Y. Tsien, Activation of store-operated Ca2+ current in Xenopus oocytes requires SNAP-25 but not a diffusible messenger, Cell 98 (1999) 475–485.
[11] R.F. Irvine, 'Quantal' Ca2+ release and the control of Ca2+ entry by inositol phosphates–a possible mechanism, FEBS Lett. 263 (1990) 5–9.
[12] R. Penner, A. Fleig, Store-operated calcium entry: a tough nut to CRAC, Sci. STKE 2004 (2004) e38.
[13] J.W. Putney Jr., L.M. Broad, F.J. Braun, J.P. Lievremont, G.S. Bird, Mechanisms of capacitative calcium entry, J. Cell Sci. 114 (2001) 2223–2229.
[14] L. Vaca, D.L. Kunze, Depletion of intracellular Ca2+ stores activates a Ca(2+)-selective channel in vascular endothelium, Am. J. Physiol. 267 (1994) C920–925.
[15] J. Liou, M.L. Kim, W.D. Heo, J.T. Jones, J.W. Myers, J.E. Ferrell Jr., T. Meyer, STIM is a Ca2+ sensor essential for Ca2+-store-depletion-triggered Ca2+ influx, Curr. Biol. 15 (2005) 1235–1241.
[16] J. Roos, P.J. DiGregorio, A.V. Yeromin, K. Ohlsen, M. Lioudyno, S. Zhang, O. Safrina, J.A. Kozak, S.L. Wagner, M.D. Cahalan, G. Velicelebi, K.A. Stauderman, STIM1, an essential and conserved component of store-operated Ca2+ channel function, J. Cell Biol. 169 (2005) 435–445.
[17] S.L. Zhang, Y. Yu, J. Roos, J.A. Kozak, T.J. Deerinck, M.H. Ellisman, K.A. Stauderman, M.D. Cahalan, STIM1 is a Ca2+ sensor that activates CRAC channels and migrates from the Ca2+ store to the plasma membrane, Nature 437 (2005) 902–905.
[18] S. Feske, Y. Gwack, M. Prakriya, S. Srikanth, S.H. Puppel, B. Tanasa, P.G. Hogan, R.S. Lewis, M. Daly, A. Rao, A mutation in Orai1 causes immune deficiency by abrogating CRAC channel function, Nature 441 (2006) 179–185.
[19] M. Prakriya, S. Feske, Y. Gwack, S. Srikanth, A. Rao, P.G. Hogan, Orai1 is an essential pore subunit of the CRAC channel, Nature 443 (2006) 230–233.
[20] M. Vig, A. Beck, J.M. Billingsley, A. Lis, S. Parvez, C. Peinelt, D.L. Koomoa, J. Soboloff, D.L. Gill, A. Fleig, J.P. Kinet, R. Penner, CRACM1 multimers form the ion-selective pore of the CRAC channel, Curr. Biol. 16 (2006) 2073–2079.
[21] M. Vig, C. Peinelt, A. Beck, D.L. Koomoa, D. Rabah, M. Koblan-Huberson, S. Kraft, H. Turner, A. Fleig, R. Penner, J.P. Kinet, CRACM1 is a plasma membrane protein essential for store-operated Ca2+ entry, Science 312 (2006) 1220–1223.
[22] A.V. Yeromin, S.L. Zhang, W. Jiang, Y. Yu, O. Safrina, M.D. Cahalan, Molecular identification of the CRAC channel by altered ion selectivity in a mutant of Orai, Nature 443 (2006) 226–229.
[23] S.L. Zhang, A.V. Yeromin, X.H. Zhang, Y. Yu, O. Safrina, A. Penna, J. Roos, K.A. Stauderman, M.D. Cahalan, Genome-wide RNAi screen of Ca(2+) influx identifies genes that regulate Ca(2+) release-activated Ca(2+) channel activity, Proc. Natl. Acad. Sci. U. S. A. 103 (2006) 9357–9362.
[24] J.C. Mercer, W.I. Dehaven, J.T. Smyth, B. Wedel, R.R. Boyles, G.S. Bird, J.W. Putney Jr., Large store-operated calcium selective currents due to

co-expression of Orai1 or Orai2 with the intracellular calcium sensor, Stim1, J. Biol. Chem. 281 (2006) 24979–24990.
[25] C. Peinelt, M. Vig, D.L. Koomoa, A. Beck, M.J. Nadler, M. Koblan-Huberson, A. Lis, A. Fleig, R. Penner, J.P. Kinet, Amplification of CRAC current by STIM1 and CRACM1 (Orai1), Nat. Cell Biol. 8 (2006) 771–773.
[26] J. Soboloff, M.A. Spassova, X.D. Tang, T. Hewavitharana, W. Xu, D.L. Gill, Orai1 and STIM reconstitute store-operated calcium channel function, J. Biol. Chem. 281 (2006) 20661–20665.
[27] J. Liou, M. Fivaz, T. Inoue, T. Meyer, Live-cell imaging reveals sequential oligomerization and local plasma membrane targeting of stromal interaction molecule 1 after Ca2+ store depletion, Proc. Natl. Acad. Sci. U. S. A. 104 (2007) 9301–9306.
[28] R.M. Luik, M.M. Wu, J. Buchanan, R.S. Lewis, The elementary unit of store-operated Ca2+ entry: local activation of CRAC channels by STIM1 at ER-plasma membrane junctions, J. Cell Biol. 174 (2006) 815–825.
[29] M.M. Wu, J. Buchanan, R.M. Luik, R.S. Lewis, Ca2+ store depletion causes STIM1 to accumulate in ER regions closely associated with the plasma membrane, J. Cell Biol. 174 (2006) 803–813.
[30] P. Xu, J. Lu, Z. Li, X. Yu, L. Chen, T. Xu, Aggregation of STIM1 underneath the plasma membrane induces clustering of Orai1, Biochem. Biophys. Res. Commun. 350 (2006) 969–976.
[31] Y. Baba, K. Hayashi, Y. Fujii, A. Mizushima, H. Watarai, M. Wakamori, T. Numaga, Y. Mori, M. Iino, M. Hikida, T. Kurosaki, Coupling of STIM1 to store-operated Ca2+ entry through its constitutive and inducible movement in the endoplasmic reticulum, Proc. Natl. Acad. Sci. U. S. A. 103 (2006) 16704–16709.
[32] V.A. Barr, K.M. Bernot, S. Srikanth, Y. Gwack, L. Balagopalan, C.K. Regan, D.J. Helman, C.L. Sommers, M. Oh-Hora, A. Rao, L.E. Samelson, Dynamic movement of the calcium sensor STIM1 and the calcium channel Orai1 in activated T-cells: puncta and distal caps, Mol. Biol. Cell 19 (2008) 2802–2817.
[33] M. Muik, I. Frischauf, I. Derler, M. Fahrner, J. Bergsmann, P. Eder, R. Schindl, C. Hesch, B. Polzinger, R. Fritsch, H. Kahr, J. Madl, H. Gruber, K. Groschner, C. Romanin, Dynamic coupling of the putative coiled-coil domain of ORAI1 with STIM1 mediates ORAI1 channel activation, J. Biol. Chem. 283 (2008) 8014–8022.
[34] L. Navarro-Borelly, A. Somasundaram, M. Yamashita, D. Ren, R.J. Miller, M. Prakriya, STIM1-Orai1 interactions and Orai1 conformational changes revealed by live-cell FRET microscopy, J. Physiol. 586 (2008) 5383–5401.
[35] P.B. Stathopulos, L. Zheng, G.Y. Li, M.J. Plevin, M. Ikura, Structural and mechanistic insights into STIM1-mediated initiation of store-operated calcium entry, Cell 135 (2008) 110–122.
[36] P.B. Stathopulos, G.Y. Li, M.J. Plevin, J.B. Ames, M. Ikura, Stored Ca2+ depletion-induced oligomerization of stromal interaction molecule 1 (STIM1) via the EF-SAM region: an initiation mechanism for capacitive Ca2+ entry, J. Biol. Chem. 281 (2006) 35855–35862.
[37] O. Brandman, J. Liou, W.S. Park, T. Meyer, STIM2 is a feedback regulator that stabilizes basal cytosolic and endoplasmic reticulum Ca2+ levels, Cell 131 (2007) 1327–1339.
[38] L. Zheng, P.B. Stathopulos, G.Y. Li, M. Ikura, Biophysical characterization of the EF-hand and SAM domain containing Ca2+ sensory region of STIM1 and STIM2, Biochem. Biophys. Res. Commun. 369 (2008) 240–246.
[39] L. Zheng, P.B. Stathopulos, R. Schindl, G.Y. Li, C. Romanin, M. Ikura, Auto-inhibitory role of the EF-SAM domain of STIM proteins in store-operated calcium entry, Proc. Natl. Acad. Sci. U. S. A. 108 (2011) 1337–1342.
[40] P.B. Stathopulos, L. Zheng, M. Ikura, Stromal interaction molecule (STIM) 1 and STIM2 calcium sensing regions exhibit distinct unfolding and oligomerization kinetics, J. Biol. Chem. 284 (2009) 728–732.
[41] G.N. Huang, W. Zeng, J.Y. Kim, J.P. Yuan, L. Han, S. Muallem, P.F. Worley, STIM1 carboxyl-terminus activates native SOC, I(crac) and TRPC1 channels, Nat. Cell Biol. 8 (2006) 1003–1010.
[42] H.L. Ong, K.T. Cheng, X. Liu, B.C. Bandyopadhyay, B.C. Paria, J. Soboloff, B. Pani, Y. Gwack, S. Srikanth, B.B. Singh, D.L. Gill, I.S. Ambudkar, Dynamic assembly of TRPC1-STIM1-Orai1 ternary complex is involved in store-operated calcium influx. Evidence for similarities in store-operated and calcium release-activated calcium channel components, J. Biol. Chem. 282 (2007) 9105–9116.
[43] T. Kawasaki, I. Lange, S. Feske, A minimal regulatory domain in the C terminus of STIM1 binds to and activates ORAI1 CRAC channels, Biochem. Biophys. Res. Commun. 385 (2009) 49–54.
[44] M. Muik, M. Fahrner, I. Derler, R. Schindl, J. Bergsmann, I. Frischauf, K. Groschner, C. Romanin, A cytosolic homomerization and a modulatory domain within STIM1C terminus determine coupling to ORAI1 channels, J. Biol. Chem. 284 (2009) 8421–8426.
[45] C.Y. Park, P.J. Hoover, F.M. Mullins, P. Bachhawat, E.D. Covington, S. Raunser, T. Walz, K.C. Garcia, R.E. Dolmetsch, R.S. Lewis, STIM1 clusters and activates CRAC channels via direct binding of a cytosolic domain to Orai1, Cell 136 (2009) 876–890.
[46] J.P. Yuan, W. Zeng, M.R. Dorwart, Y.J. Choi, P.F. Worley, S. Muallem, SOAR and the polybasic STIM1 domains gate and regulate Orai channels, Nat. Cell Biol. 11 (2009) 337–343.
[47] X. Yang, H. Jin, X. Cai, S. Li, Y. Shen, Structural and mechanistic insights into the activation of Stromal interaction molecule 1 (STIM1), Proc. Natl. Acad. Sci. U. S. A. 109 (2012) 5657–5662.
[48] B. Cui, X. Yang, S. Li, Z. Lin, Z. Wang, C. Dong, Y. Shen, The inhibitory helix controls the intramolecular conformational switching of the C-terminus of STIM1, PLoS One 8 (2013) e74735.
[49] M. Fahrner, M. Muik, R. Schindl, C. Butorac, P. Stathopulos, L. Zheng, I. Jardin, M. Ikura, C. Romanin, A coiled-coil clamp controls both conformation and clustering of stromal interaction molecule 1 (STIM1), J. Biol. Chem. 289 (2014) 33231–33244.
[50] M. Muik, M. Fahrner, R. Schindl, P. Stathopulos, I. Frischauf, I. Derler, P. Plenk, B. Lackner, K. Groschner, M. Ikura, C. Romanin, STIM1 couples to ORAI1 via an intramolecular transition into an extended conformation, EMBO J. 30 (2011) 1678–1689.
[51] Y. Zhou, P. Srinivasan, S. Razavi, S. Seymour, P. Meraner, A. Gudlur, P.B. Stathopulos, M. Ikura, A. Rao, P.G. Hogan, Initial activation of STIM1, the regulator of store-operated calcium entry, Nat. Struct. Mol. Biol. 20 (2013) 973–981.
[52] G. Ma, M. Wei, L. He, C. Liu, B. Wu, S.L. Zhang, J. Jing, X. Liang, A. Senes, P. Tan, S. Li, A. Sun, Y. Bi, L. Zhong, H. Si, Y. Shen, M. Li, M.S. Lee, W. Zhou, J. Wang, Y. Wang, Y. Zhou, Inside-out Ca(2+) signalling prompted by STIM1 conformational switch, Nat. Commun. 6 (2015) 7826.
[53] P.B. Stathopulos, R. Schindl, M. Fahrner, L. Zheng, G.M. Gasmi-Seabrook, M. Muik, C. Romanin, M. Ikura, STIM1/Orai1 coiled-coil interplay in the regulation of store-operated calcium entry, Nat. Commun. 4 (2013) 2963.
[54] B.A. McNally, A. Somasundaram, A. Jairaman, M. Yamashita, M. Prakriya, The C- and N-terminal STIM1 binding sites on Orai1 are required for both trapping and gating CRAC channels, J. Physiol. 591 (2013) 2833–2850.
[55] X. Hou, L. Pedi, M.M. Diver, S.B. Long, Crystal structure of the calcium release-activated calcium channel Orai, Science 338 (2012) 1308–1313.
[56] C. Levinthal, Are there pathways for protein folding? J. Chim. Phys. 65 (1968) 44–45.
[57] L. Tirado-Lee, M. Yamashita, M. Prakriya, Conformational changes in the orai1 C-terminus evoked by STIM1 binding, PLoS One 10 (2015) e0128622.
[58] X. Wang, Y. Wang, Y. Zhou, E. Hendron, S. Mancarella, M.D. Andrake, B.S. Rothberg, J. Soboloff, D.L. Gill, Distinct Orai-coupling domains in STIM1 and STIM2 define the Orai-activating site, Nat. Commun. 5 (2014) 3183.
[59] Z. Li, J. Lu, P. Xu, X. Xie, L. Chen, T. Xu, Mapping the interacting domains of STIM1 and Orai1 in Ca2+ release-activated Ca2+ channel activation, J. Biol. Chem. 282 (2007) 29448–29456.
[60] Y. Zhou, P. Meraner, H.T. Kwon, D. Machnes, M. Oh-hora, J. Zimmer, Y. Huang, A. Stura, A. Rao, P.G. Hogan, STIM1 gates the store-operated calcium channel ORAI1 in vitro, Nat. Struct. Mol. Biol. 17 (2010) 112–116.
[61] Y. Zhou, X. Wang, X. Wang, N.A. Loktionova, X. Cai, R.M. Nwokonko, E. Vrana, Y. Wang, B.S. Rothberg, D.L. Gill, STIM1 dimers undergo unimolecular coupling to activate Orai1 channels, Nat. Commun. 6 (2015) 8395.