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Open Sesame: treasure in store-operated calcium entry pathway for cancer therapy

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Abstract

Store-operated Ca^{2+} entry (SOCE) controls intracellular Ca^{2+} homeostasis and regulates a wide range of cellular events including proliferation, migration and invasion. The discovery of STIM proteins as Ca^{2+} sensors and Orai proteins as Ca^{2+} channel pore forming units provided molecular tools to understand the physiological function of SOCE. Many studies have revealed the pathophysiological roles of Orai and STIM in tumor cells. This review focuses on recent advances in SOCE and its contribution to tumorigenesis. Altered Orai and/or STIM functions may serve as biomarkers for cancer prognosis, and targeting the SOCE pathway may provide a novel means for cancer treatment.

Keywords

Orai1; STIM1; Ca^{2+} oscillations; proliferation; metastasis; oncogenic

The discovery of STIM1 and Orai1 genes reminds us the old folk tale *Ali Baba and Forty Thieves* in *One Thousand and One Nights*. In that story, when Ali Baba spits out the magical phrase “Open Sesame”, it unlocks the gate of a cave where the thieves hide their treasures. Would Orai/STIM-mediated SOCE lead us to the treasure for new diagnostic and prognostic tools, or even novel means for cancer treatment?

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1 Ca²⁺ signaling and store-operated Ca²⁺ entry machinery

Ca²⁺, the mighty signaler, regulates a wide range of downstream cellular processes, including gene transcription, cell proliferation, migration and death [1–6]. It has long been recognized that dysregulation of Ca²⁺ homeostasis is associated with a plethora of pathological conditions including immune deficiency, neurodegeneration, muscular and cardiovascular disorders as well as cancer progression. The altered Ca²⁺ signaling may contribute to tumor angiogenesis, progression, and metastasis. Searching for specific genes that contribute to altered Ca²⁺ signaling in tumor cells has emerged as an exciting area in cancer research [7–15].

Intracellular Ca²⁺ signaling is a complex and fine-tuning network. The spatially-temporally confined Ca²⁺ signaling is tightly regulated in the form of waves, spikes or oscillations (Figure 1). Intracellular Ca²⁺ oscillation is a remarkable process, since its frequency, amplitude and duration can act as “calcium code” to activate transcription factors for gene transcription, cell proliferation and migration [16–18]. Ca²⁺ signaling is orchestrated with the release of Ca²⁺ through IP₃ receptor from internal Ca²⁺ stores such as endoplasmic reticulum (ER), the uptake of Ca²⁺ into the ER, and Ca²⁺ influx across plasma membrane (PM) from extracellular Ca²⁺ reservoir. The latter is mainly mediated by a process named store-operated Ca²⁺ entry (SOCE) [19–24]. SOCE was first described by Jim Putney about three decades ago who coined the term capacitative Ca²⁺ entry (CCE) [20]. In this pathway, activation of the G-protein coupled receptor leads to stimulation of PLC to generate IP₃; IP₃ in turn causes intracellular Ca²⁺ release that is followed by reduction of Ca²⁺ concentration inside the ER lumen. The reduced ER Ca²⁺ store sends a signal to the PM to activate CCE, allowing refill of the empty ER Ca²⁺ stores (Figure 1). Using the whole-cell patch clamp technique, Hoth et al. [25] characterized the electrophysiological property of Ca²⁺ release-activated Ca²⁺ current (CRAC), which mediates SOCE in mast cells. The molecular players mediating SOCE were discovered rather recently. Using RNA interference (RNAi)-based screening, two independent groups identified stromal interaction molecule 1 (STIM1) as the ER Ca²⁺ sensor [26–28]. Shortly after, a genome-wide screening using the severe combined immune deficiency (SCID) disease model that is caused by defective Ca²⁺ entry in T cells led to a groundbreaking discovery of a membrane protein as the SOCE channel [29–32]. This protein is named Orai, a mythological character that served as gate keeper to safeguard the path toward heaven. STIM1 is an ER-resident membrane protein, containing a luminal EF-hand allowing it to detect changes in the ER Ca²⁺ content. Orai1 is an integral membrane protein with four trans-membrane domains that constitutes the pore forming unit of the SOCE channel. Upon ER Ca²⁺ store depletion or reduction in some cases, STIM1 molecules cluster at the ER/PM junctional region [21,26,28,29,33–39], where they send retrograde signals to Orai1 for opening of the Ca²⁺ channels [33,40,41]. In addition to STIM1 and Orai1, mammalian genomes also encode an additional STIM homologue, STIM2; and two Orai1 homologues, Orai2 and Orai3. Extensive studies from CRAC channels in immune system support that Orai1 and STIM1 are necessary and sufficient for the assembly and activation of the “classical” SOCE complex.

2 Emerging role of SOCE in cancer biology

Long before the discovery of *Orai* and *Stim* genes, pharmacological studies have revealed the important role of SOCE in cancer cells. Carboxyamidotriazole is an anti-cancer drug [42] that inhibits angiogenesis due to its ability to target SOCE in many carcinoma cell lines [43–47]. Other SOCE blockers, such as 2-aminoethyl diphenylborate (2-APB) and SKF-96365, were reported to have similar effects on cancer cells. For example, 2-APB inhibits proliferation in human hepatoma HepG2 and Huh-7 cells, lung cancer A549 cells and colon cancer T84 cells [47–50]. Using these pharmacological tools, several studies showed that altered function of SOCE might be a general phenomenon associated with cancer progression [51–54]. Our earlier studies showed a functional interaction between pro-apoptotic protein Bax and SOCE in apoptosis of prostate cancer, suggesting that the androgen-independent prostate epithelial tumor cells could gain their apoptotic resistance by down-regulation of SOCE [55,56]. SOCE may also cross-talk to signaling cascades initiated by tumorigenic and angiogenic growth factors. For example, epidermal growth factor (EGF) is known to stimulate intracellular Ca^{2+} release through PLC/IP₃ pathway leading to activation of SOCE (as illustrated in Figure 1). It was proposed that non-steroidal anti-inflammatory drugs inhibit colorectal carcinogenesis by attenuation of EGF-induced cellular proliferation through a process independent of their inhibitory effect on prostaglandin synthesis but rather by blocking EGF-induced SOCE [57].

3 Different functions of STIM and Orai proteins in different cancers

The discovery of STIM1 and Orai1 as the molecular components of SOCE has greatly advanced our understanding of the pathophysiological roles of SOCE in cancer. While genetic mutations in Orai1 or STIM1 were linked to immune disorders, skeletal muscle myopathy and heart hypertrophy [7,58–63], the functions of these genes in various types of cancer have fascinated many investigators. Combination of pharmacologic and siRNA-mediated gene knockdown approaches has pinpointed the involvement of Orai1 and STIM1 in five key events of tumorigenesis: elevated proliferation, enhanced migration/invasion, increased resistance to apoptosis, angiogenic switch and reduction in antitumor immunity. Orai1 and STIM1 were reported to promote cell proliferation, migration, invasion and apoptotic resistance in breast cancer [15], glioblastoma [64], prostate cancer [65–67], hepatocellular carcinoma [14], esophageal squamous cell carcinoma (ESCC) [68] and clear cell renal cell carcinoma (ccRCC) [69]. They are also required for the anti-tumor activity of cytotoxic T cells, i.e., secretion of cytokines, such as TNF α , IL-2 and IFN γ , which induce apoptosis of cancer cells [70,71].

We recently undertook a study to investigate the clinical significance of Orai1 and STIM1 in esophageal cancer. That study showed that expression of Orai1 in tumors obtained from patients with ESCC was significantly elevated compared with that in neighboring non-tumorous esophageal tissues [68]. High Orai1 expression was associated with the recurrence rate for this disease independent of other variables. This study provided the first evidence in support of an association between Orai1 expression and the clinical outcome of cancer patients. At about the same time as the publication of our study, a Korean group reported a similar observation that Orai1 is overexpressed in tumor tissues from patients with ccRCC

[69]. Thus, these results raise the possibility that Orai1 expression could be a potential prognostic biomarker for ESCC or ccRCC. It should be mentioned that STIM1 was reported to be overexpressed in tumor tissues from subjects with early-stage cervical cancer [9]. However, the study from our group and the Korean group showed that the expression of STIM1 in tumor tissues remained unchanged or was even reduced as compared to that in neighboring normal tissues based on real-time RT-PCR, Western blot and immunohistochemistry assays. These findings suggest that variations of SOCE components and regulatory mechanisms may be different in different types of cancers. Feng et al. [11] identified a signaling pathway in which formation of an Orai1-SPCA2 complex elicits a constitutive store-independent Ca^{2+} entry pathway that regulates tumor-igenesis in breast cancer. Such Ca^{2+} entry pathway appears to be mediated by Orai3 in estrogen receptor-positive breast cancer and non-small cell lung carcinoma cells, whereas the “classical” STIM1/Orai1 pathway predominates in estrogen receptor-negative breast cancer cells [72,73]. In addition, Chantome et al. [74] showed that knockdown of STIM1 had no effect on, whereas knockdown of Orai1 inhibited, migration of breast cancer cells, indicating STIM1 might not be involved in the metastatic process. Our observation of significantly higher expression of STIM2 in ESCC cells implies that STIM2 may play a role in regulation of Orai channel activity and overall intracellular Ca^{2+} signaling in this malignancy [68].

Functional ion channels often form from subunits assembled into homo- or hetero-multimers. Different stoichiometry of Orai1 and STIM1 may result in different channel property and regulatory mechanism. The crystal structure of Orai protein revealed a hexameric structure for the functional channel through coupling with STIM1 [75], and provided evidence to support the model that the optimal Orai1/STIM1 for maximal SOCE activation is 2:1 [76]. Variations in the ratios of Orai1 to STIM1 were reported in different cell types [77]. Dubois et al. [67] showed that varying Orai1/Orai3 ratios modulate the function of SOCE and basal cytosolic Ca^{2+} level, and Orai3 overexpression stimulates cell proliferation and promotes apoptosis resistance in prostate cancer cells. They proposed that remodeling of Orai1/Orai3 may constitute as an oncogenic switch in prostate cancer. Wang et al. [78] identified distinct Orai1- coupling domains in STIM1 and STIM2, which determines the efficacy of interaction between Orai1 and STIM as well as its store-dependent activation properties. In our study, we found an increased expression of Orai1 and STIM2 but not STIM1 in ESCC tumor tissues [68]. Thus, it is possible that STIM2 may replace STIM1 to couple with Orai1 in ESCC cells. Clearly, further studies are required to define the mechanisms underlying the role of specific STIMs and OraIs in regulating the overall function of SOCE. Targeting these specific properties may be used for prevention and/or treatment of cancers.

4 Targeting SOCE-mediated Ca^{2+} signaling in cancer therapy

SOCE machinery as a signaling complex contains several components, e.g., Orai1, Orai3, STIM1 and STIM2. Altered expression of these signaling components may underlie the altered function of SOCE, which in turn activates the downstream cellular events for carcinogenesis and tumor progression (Figure 1). Compared to quiescent non-tumor cells, we identified a striking hyperactivity in Ca^{2+} oscillations in ESCC cells, which is dependent on Orai1-mediated SOCE since these oscillations could be suppressed by reduction of Orai1

function using either pharmacologic or molecular approaches [68]. In the same study, we also showed that inhibition of Orai1-mediated SOCE by pharmacologic antagonists of the channel or reduction of Orai1 expression by Orai1 knockdown impeded the proliferation and migration/invasion of ESCC cells *in vitro*, suppressed the tumor growth *in vivo*. Similar molecular and pharmacologic approaches employed have been utilized by other investigators to evaluate the importance of STIM1, Orai1 or Orai3 to the migration and metastasis of breast, cervical, prostate and renal carcinoma [9,15,67,69,72,73]. All these studies compiled proof of principle for targeting SOCE channel in cancer treatments. For example, injection of SKF-96365 into xenografted breast, cervical and esophageal cancer mice models suppressed tumor growth, angiogenesis and metastasis *in vivo* [9,15,68]. Clearly, a better understanding of the regulatory mechanism underlying Orai-mediated SOCE in different cancers, and the development of specific/potent SOCE channel modulators will greatly advance this field.

5 Summary

Over the past few years we have gained significantly the basic molecular insight of Orai/STIM-mediated SOCE. However, many questions regarding the contribution of STIM and Orai proteins to carcinogenesis and tumor progression remain. Understanding of the mechanisms by which STIM and Orai proteins exert their different patho-physiological roles in different cancers will be a major challenge over the coming years. Orai channels constitute potential therapeutic targets for treatment of human diseases. For millions of cancer patients, we have high expectation that Orai-mediated SOCE pathway may represent the magical code to unlock the gate toward new diagnostic and prognostic means or treatment strategies for combating cancers.

References

1. Berridge MJ, Bootman MD, Roderick HL. Calcium signalling: dynamics, homeostasis and remodelling. *Nat Rev Mol Cell Biol.* 2003; 4:517–529. [PubMed: 12838335]
2. Berridge MJ, Lipp P, Bootman MD. The versatility and universality of calcium signalling. *Nat Rev Mol Cell Biol.* 2000; 1:11–21. [PubMed: 11413485]
3. Hajnoczky G, Davies E, Madesh M. Calcium signaling and apoptosis. *Biochem Biophys Res Commun.* 2003; 304:445–454. [PubMed: 12729578]
4. Lipskaia L, Lompre AM. Alteration in temporal kinetics of Ca²⁺ signaling and control of growth and proliferation. *Biol Cell.* 2004; 96:55–68. [PubMed: 15093128]
5. Rizzuto R, Pinton P, Ferrari D, Chami M, Szabadkai G, Magalhaes PJ, Di Virgilio F, Pozzan T. Calcium and apoptosis: facts and hypotheses. *Oncogene.* 2003; 22:8619–8627. [PubMed: 14634623]
6. Bell N, Hann V, Redfern CP, Cheek TR. Store-operated Ca(2+) entry in proliferating and retinoic acid-differentiated N- and S-type neuroblastoma cells. *Biochim Biophys Acta.* 2013; 1833:643–651. [PubMed: 23220046]
7. Bergmeier W, Weidinger C, Zee I, Feske S. Emerging roles of store-operated Ca(2+) entry through stim and orai proteins in immunity, hemostasis and cancer. *Channels (Austin).* 2013; 7:379–391. [PubMed: 23511024]
8. Barr VA, Bernot KM, Srikanth S, Gwack Y, Balagopalan L, Regan CK, Helman DJ, Sommers CL, Oh-Hora M, Rao A, Samelson LE. Dynamic movement of the calcium sensor STIM1 and the calcium channel Orai1 in activated T-cells: puncta and distal caps. *Mol Biol Cell.* 2008; 19:2802–2817. [PubMed: 18448669]

9. Chen YF, Chiu WT, Chen YT, Lin PY, Huang HJ, Chou CY, Chang HC, Tang MJ, Shen MR. Calcium store sensor stromal-interaction molecule 1-dependent signaling plays an important role in cervical cancer growth, migration, and angiogenesis. *Proc Natl Acad Sci USA*. 2011; 108:15225–15230. [PubMed: 21876174]
10. Chen YT, Chen YF, Chiu WT, Liu KY, Liu YL, Chang JY, Chang HC, Shen MR. Microtubule-associated histone deacetylase 6 supports the calcium store sensor STIM1 in mediating malignant cell behaviors. *Cancer Res*. 2013; 73:4500–4509. [PubMed: 23698468]
11. Feng M, Grice DM, Faddy HM, Nguyen N, Leitch S, Wang Y, Muend S, Kenny PA, Sukumar S, Roberts-Thomson SJ, Monteith GR, Rao R. Store-independent activation of Orai1 by SPCA2 in mammary tumors. *Cell*. 2010; 143:84–98. [PubMed: 20887894]
12. Motiani RK, Hyzinski-Garcia MC, Zhang X, Henkel MM, Abdullaev IF, Kuo YH, Matrougui K, Mongin AA, Trebak M. STIM1 and Orai1 mediate CRAC channel activity and are essential for human glioblastoma invasion. *Pflugers Arch*. 2013; 465:1249–1260. [PubMed: 23515871]
13. Srikanth S, Gwack Y. Orai1-NFAT signalling pathway triggered by T cell receptor stimulation. *Mol Cells*. 2013; 35:182–194. [PubMed: 23483280]
14. Yang N, Tang Y, Wang F, Zhang H, Xu D, Shen Y, Sun S, Yang G. Blockade of store-operated Ca(2+) entry inhibits hepatocarcinoma cell migration and invasion by regulating focal adhesion turnover. *Cancer Lett*. 2013; 330:163–169. [PubMed: 23211538]
15. Yang S, Zhang JJ, Huang XY. Orai1 and STIM1 are critical for breast tumor cell migration and metastasis. *Cancer Cell*. 2009; 15:124–134. [PubMed: 19185847]
16. Lewis RS. Calcium oscillations in T-cells: mechanisms and consequences for gene expression. *Biochem Soc Trans*. 2003; 31:925–929. [PubMed: 14505450]
17. Giannone G, Ronde P, Gaire M, Haiech J, Takeda K. Calcium oscillations trigger focal adhesion disassembly in human U87 astrocytoma cells. *J Biol Chem*. 2002; 277:26364–26371. [PubMed: 12011063]
18. Ronde P, Giannone G, Gerasymova I, Stoeckel H, Takeda K, Haiech J. Mechanism of calcium oscillations in migrating human astrocytoma cells. *Biochim Biophys Acta*. 2000; 1498:273–280. [PubMed: 11108969]
19. Parekh AB, Putney JW Jr. Store-operated calcium channels. *Rev*. 2005; 85:757–810.
20. Putney JW Jr. A model for receptor-regulated calcium entry. *Cell Calcium*. 1986; 7:1–12. [PubMed: 2420465]
21. Mercer JC, Dehaven WI, Smyth JT, Wedel B, Boyles RR, Bird GS, Putney JW Jr. Large store-operated calcium selective currents due to co-expression of Orai1 or Orai2 with the intracellular calcium sensor, STIM1. *J Biol Chem*. 2006; 281:24979–24990. [PubMed: 16807233]
22. Moreau B, Straube S, Fisher RJ, Putney JW Jr, Parekh AB. Ca²⁺-calmodulin-dependent facilitation and Ca²⁺ inactivation of Ca²⁺ release-activated Ca²⁺ channels. *J Biol Chem*. 2005; 280:8776–8783. [PubMed: 15611075]
23. Putney JWJ, Broad LM, Braun FJ, Lievremon JP, Bird GS. Mechanisms of capacitative calcium entry. *J Cell Sci*. 2001; 114:2223–2229. [PubMed: 11493662]
24. Wedel B, Boyles RR, Putney JW, Bird GS. Role of the store-operated calcium entry proteins, STIM1 and Orai1, in muscarinic-cholinergic receptor stimulated calcium oscillations in human embryonic kidney cells. *J Physiol*. 2007; 579:679–689. [PubMed: 17218358]
25. Hoth M, Penner R. Depletion of intracellular calcium stores activates a calcium current in mast cells. *Nature*. 1992; 355:353–356. [PubMed: 1309940]
26. Zhang SL, Yu Y, Roos J, Kozak JA, Deerinck TJ, Ellisman MH, Stauderman KA, Cahalan MD. STIM1 is a Ca²⁺ sensor that activates crac channels and migrates from the Ca²⁺ store to the plasma membrane. *Nature*. 2005; 437:902–905. [PubMed: 16208375]
27. Liou J, Kim ML, Heo WD, Jones JT, Myers JW, Ferrell JE Jr, Meyer T. STIM is a Ca²⁺ sensor essential for Ca²⁺-store-depletion-triggered Ca²⁺ influx. *Curr Biol*. 2005; 15:1235–1241. [PubMed: 16005298]
28. Roos J, DiGregorio PJ, Yeromin AV, Ohlsen K, Lioudyno M, Zhang S, Safrina O, Kozak JA, Wagner SL, Cahalan MD, Velicelebi G, Stauderman KA. STIM1, an essential and conserved component of store-operated Ca²⁺ channel function. *J Cell Biol*. 2005; 169:435–445. [PubMed: 15866891]

29. Yeromin AV, Zhang SL, Jiang W, Yu Y, Safrina O, Cahalan MD. Molecular identification of the CRAC channel by altered ion selectivity in a mutant of Orai. *Nature*. 2006; 443:226–229. [PubMed: 16921385]
30. Prakriya M, Feske S, Gwack Y, Srikanth S, Rao A, Hogan PG. Orai1 is an essential pore subunit of the CRAC channel. *Nature*. 2006; 443:230–233. [PubMed: 16921383]
31. Vig M, Peinelt C, Beck A, Koomoa DL, Rabah D, Koblan-Huberson M, Kraft S, Turner H, Fleig A, Penner R, Kinet JP. CRACM1 is a plasma membrane protein essential for store-operated Ca²⁺ entry. *Science*. 2006; 312:1220–1223. [PubMed: 16645049]
32. Feske S, Gwack Y, Prakriya M, Srikanth S, Puppel SH, Tanasa B, Hogan PG, Lewis RS, Daly M, Rao A. A mutation in Orai1 causes immune deficiency by abrogating CRAC channel function. *Nature*. 2006; 441:179–185. [PubMed: 16582901]
33. Luik RM, Wu MM, Buchanan J, Lewis RS. The elementary unit of store-operated Ca²⁺ entry: local activation of CRAC channels by STIM1 at ER-plasma membrane junctions. *J Cell Biol*. 2006; 174:815–825. [PubMed: 16966423]
34. Wu MM, Buchanan J, Luik RM, Lewis RS. Ca²⁺ store depletion causes STIM1 to accumulate in ER regions closely associated with the plasma membrane. *J Cell Biol*. 2006; 174:803–813. [PubMed: 16966422]
35. Ong HL, Cheng KT, Liu X, Bandyopadhyay BC, Paria BC, Soboloff J, Pani B, Gwack Y, Srikanth S, Singh BB, Gill D, Ambudkar IS. Dynamic assembly of TRPC1/STIM1/Orai1 ternary complex is involved in store operated calcium influx: evidence for similarities in SOC and CRAC channel components. *J Biol Chem*. 2007; 282:9105–9116. [PubMed: 17224452]
36. Vig M, Beck A, Billingsley JM, Lis A, Parvez S, Peinelt C, Koomoa DL, Soboloff J, Gill DL, Fleig A, Kinet JP, Penner R. CRACM1 multimers form the ion-selective pore of the CRAC channel. *Curr Biol*. 2006; 16:2073–2079. [PubMed: 16978865]
37. Soboloff J, Spassova MA, Hewavitharana T, He LP, Xu W, Johnstone LS, Dziadek MA, Gill DL. STIM2 is an inhibitor of STIM1-mediated store-operated Ca²⁺ entry. *Curr Biol*. 2006; 16:1465–1470. [PubMed: 16860747]
38. Soboloff J, Spassova MA, Tang XD, Hewavitharana T, Xu W, Gill DL. Orai1 and STIM1 reconstitute store-operated calcium channel function. *J Biol Chem*. 2006; 281:20661–20665. [PubMed: 16766533]
39. Spassova MA, Soboloff J, He LP, Xu W, Dziadek MA, Gill DL. STIM1 has a plasma membrane role in the activation of store-operated Ca(2+) channels. *Proc Natl Acad Sci USA*. 2006; 103:4040–4045. [PubMed: 16537481]
40. Huang GN, Zeng W, Kim JY, Yuan JP, Han L, Muallem S, Worley PF. STIM1 carboxyl-terminus activates native SOC, I(crac) and TRPC1 channels. *Nat Cell Biol*. 2006; 8:1003–1010. [PubMed: 16906149]
41. Ma J, Pan Z. Retrograde activation of store-operated calcium channel. *Cell Calcium*. 2003; 33:375–384. [PubMed: 12765683]
42. Patton AM, Kassis J, Doong H, Kohn EC. Calcium as a molecular target in angiogenesis. *Curr Pharm Des*. 2003; 9:543–551. [PubMed: 12570802]
43. Guo L, Li ZS, Wang HL, Ye CY, Zhang DC. Carboxyamido-triazole inhibits proliferation of human breast cancer cells via G(2)/M cell cycle arrest and apoptosis. *Eur J Pharmacol*. 2006; 538:15–22. [PubMed: 16696967]
44. Perabo FG, Demant AW, Wirger A, Schmidt DH, Sitia M, Wardelmann E, Muller SC, Kohn EC. Carboxyamido-triazole (CAI) reverses the balance between proliferation and apoptosis in a rat bladder cancer model. *Anticancer Res*. 2005; 25:725–729. [PubMed: 15868902]
45. Ge S, Rempel SA, Divine G, Mikkelsen T. Carboxyamido-triazole induces apoptosis in bovine aortic endothelial and human glioma cells. *Clin Cancer Res*. 2000; 6:1248–1254. [PubMed: 10778947]
46. Mignen O, Brink C, Enfissi A, Nadkarni A, Shuttleworth TJ, Giovannucci DR, Capiod T. Carboxyamidotriazole-induced inhibition of mitochondrial calcium import blocks capacitative calcium entry and cell proliferation in HEK-293 cells. *J Cell Sci*. 2005; 118:5615–5623. [PubMed: 16306224]

47. Enfissi A, Prigent S, Colosetti P, Capiod T. The blocking of capacitative calcium entry by 2-aminoethyl diphenylborate (2-APB) and carboxyamidotriazole (CAI) inhibits proliferation in Hep G2 and Huh-7 human hepatoma cells. *Cell calcium*. 2004; 36:459–467. [PubMed: 15488595]
48. Padar S, Bose DD, Livesey JC, Thomas DW. 2-aminoethoxydiphenyl borate perturbs hormone-sensitive calcium stores and blocks store-operated calcium influx pathways independent of cytoskeletal disruption in human A549 lung cancer cells. *Biochem Pharmacol*. 2005; 69:1177–1186. [PubMed: 15794938]
49. Kazerounian S, Pitari GM, Shah FJ, Frick GS, Madesh M, Ruiz-Stewart I, Schulz S, Hajnoczky G, Waldman SA. Proliferative signaling by store-operated calcium channels opposes colon cancer cell cytostasis induced by bacterial enterotoxins. *J Pharmacol Exp Ther*. 2005; 314:1013–1022. [PubMed: 15937149]
50. Koslowski M, Sahin U, Dhaene K, Huber C, Tureci O. MS4A12 is a colon-selective store-operated calcium channel promoting malignant cell processes. *Cancer Res*. 2008; 68:3458–3466. [PubMed: 18451174]
51. Vanden Abeele F, Roudbaraki M, Shuba Y, Skryma R, Prevarskaya N. Store-operated Ca^{2+} current in prostate cancer epithelial cells. Role of endogenous Ca^{2+} transporter type 1. *J Biol Chem*. 2003; 278:15381–15389. [PubMed: 12584203]
52. Vanden Abeele F, Shuba Y, Roudbaraki M, Lemonnier L, Vanoverberghe K, Mariot P, Skryma R, Prevarskaya N. Store-operated Ca^{2+} channels in prostate cancer epithelial cells: function, regulation, and role in carcinogenesis. *Cell Calcium*. 2003; 33:357–373. [PubMed: 12765682]
53. Skryma R, Mariot P, Bourhis XL, Coppénolle FV, Shuba Y, Vanden Abeele F, Legrand G, Humez S, Boilly B, Prevarskaya N. Store depletion and store-operated Ca^{2+} current in human prostate cancer Lncap cells: involvement in apoptosis. *J Physiol*. 2000; 527(Pt 1):71–83. [PubMed: 10944171]
54. Pigozzi D, Ducret T, Tajeddine N, Gala JL, Tombal B, Gailly P. Calcium store contents control the expression of TRPC1, TRPC3 and TRPV6 proteins in Lncap prostate cancer cell line. *Cell Calcium*. 2006; 39:401–415. [PubMed: 16529812]
55. Pan Z, Bhat MB, Nieminen AL, Ma J. Synergistic movements of Ca^{2+} and Bax in cells undergoing apoptosis. *J Biol Chem*. 2001; 276:32257–32263. [PubMed: 11413128]
56. Lin PH, Pan Z, Zheng L, Li N, Danielpour D, Ma JJ. Overexpression of Bax sensitizes prostate cancer cells to TGF-beta induced apoptosis. *Cell Res*. 2005; 15:160–166. [PubMed: 15780177]
57. Kokoska ER, Smith GS, Miller TA. Nonsteroidal anti-inflammatory drugs attenuate proliferation of colonic carcinoma cells by blocking epidermal growth factor-induced Ca^{++} mobilization. *J Gastrointest Surg*. 2000; 4:150–161. [PubMed: 10675238]
58. Berna-Erro A, Woodard GE, Rosado JA. Orais and STIMs: physiological mechanisms and disease. *J Cell Mol Med*. 2012; 16:407–424. [PubMed: 21790973]
59. Feske S. Immunodeficiency due to defects in store-operated calcium entry. *Ann New York Acad Sci*. 2011; 1238:74–90. [PubMed: 22129055]
60. Fuchs S, Rensing-Ehl A, Speckmann C, Bengsch B, Schmitt-Graeff A, Bondzio I, Maul-Pavicic A, Bass T, Vraetz T, Strahm B, Ankermann T, Benson M, Caliebe A, Folster-Holst R, Kaiser P, Thimme R, Schamel WW, Schwarz K, Feske S, Ehl S. Antiviral and regulatory T cell immunity in a patient with stromal interaction molecule 1 deficiency. *J Immunol*. 2012; 188:1523–1533. [PubMed: 22190180]
61. Le Deist F, Capiod T. Immunodeficiencies and pathologies associated with mutations in STIM/Orai, a membrane complex in the heart of calcium signalling. *Med Sci*. 2011; 27:737–745.
62. Shaw PJ, Feske S. Physiological and pathophysiological functions of SOCE in the immune system. *Front Biosci (Elite Ed)*. 2012; 4:2253–2268. [PubMed: 22202035]
63. Verbsky JW, Chatila TA. T-regulatory cells in primary immune deficiencies. *Curr Opin Allergy Clin Immunol*. 2011; 11:539–544. [PubMed: 21986549]
64. Motiani RK, Hyzinski-Garcia MC, Zhang X, Henkel MM, Abdullaev IF, Kuo YH, Matrougui K, Mongin AA, Trebak M. STIM1 and Orai1 mediate CRAC channel activity and are essential for human glioblastoma invasion. *Pflugers Arch*. 2013; 465:1249–1260. [PubMed: 23515871]

65. Kondratska K, Kondratskyi A, Yassine M, Lemonnier L, Lepage G, Morabito A, Skryma R, Prevarskaya N. Orai1 and STIM1 mediate SOCE and contribute to apoptotic resistance of pancreatic adenocarcinoma. *Biochim Biophys Acta*. 2014; 1843:2263–2269. [PubMed: 24583265]
66. Flourakis M, Lehen'kyi V, Beck B, Raphael M, Vandenberghe M, Abeele FV, Roudbaraki M, Lepage G, Mauroy B, Romanin C, Shuba Y, Skryma R, Prevarskaya N. Orai1 contributes to the establishment of an apoptosis-resistant phenotype in prostate cancer cells. *Cell Death Dis*. 2010; 1:e75. [PubMed: 21364678]
67. Dubois C, Vanden Abeele F, Lehen'kyi V, Gkika D, Guarmit B, Lepage G, Slomianny C, Borowiec AS, Bidaux G, Benahmed M, Shuba Y, Prevarskaya N. Remodeling of channel-forming Orai proteins determines an oncogenic switch in prostate cancer. *Cancer cell*. 2014; 26:19–32. [PubMed: 24954132]
68. Zhu H, Zhang H, Jin F, Fang M, Huang M, Yang CS, Chen T, Fu L, Pan Z. Elevated Orai1 expression mediates tumor-promoting intracellular Ca^{2+} oscillations in human esophageal squamous cell carcinoma. *Oncotarget*. 2014; 5:3455–3471. [PubMed: 24797725]
69. Kim JH, Lkhagvadorj S, Lee MR, Hwang KH, Chung HC, Jung JH, Cha SK, Eom M. Orai1 and STIM1 are critical for cell migration and proliferation of clear cell renal cell carcinoma. *Biochem Biophys Res Commun*. 2014; 448:76–82. [PubMed: 24755083]
70. Weidinger C, Shaw PJ, Feske S. STIM1 and STIM2-mediated Ca^{2+} influx regulates antitumour immunity by CD8(+) T cells. *EMBO Mol Med*. 2013; 5:1311–1321. [PubMed: 23922331]
71. Oh-Hora M, Yamashita M, Hogan PG, Sharma S, Lamperti E, Chung W, Prakriya M, Feske S, Rao A. Dual functions for the endoplasmic reticulum calcium sensors STIM1 and STIM2 in T cell activation and tolerance. *Nat Immunol*. 2008; 9:432–443. [PubMed: 18327260]
72. Motiani RK, Zhang X, Harmon KE, Keller RS, Matrougui K, Bennett JA, Trebak M. Orai3 is an estrogen receptor α -regulated Ca^{2+} channel that promotes tumorigenesis. *FASEB J*. 2013; 27:63–75. [PubMed: 22993197]
73. Ay AS, Benzerdjeb N, Sevestre H, Ahidouch A, Ouadid-Ahidouch H. Orai3 constitutes a native store-operated calcium entry that regulates non small cell lung adenocarcinoma cell proliferation. *PLoS One*. 2013; 8:e72889. [PubMed: 24058448]
74. Chantome A, Potier-Cartreau M, Clarysse L, Fromont G, Marionneau-Lambot S, Gueguinou M, Pages JC, Collin C, Oullier T, Girault A, Arbion F, Haelters JP, Jaffres PA, Pinault M, Besson P, Joulin V, Bougnoux P, Vandier C. Pivotal role of the lipid Raft SK3-Orai1 complex in human cancer cell migration and bone metastases. *Cancer Res*. 2013; 73:4852–4861. [PubMed: 23774210]
75. Hou X, Pedi L, Diver MM, Long SB. Crystal structure of the calcium release-activated calcium channel Orai. *Science*. 2012; 338:1308–1313. [PubMed: 23180775]
76. Li Z, Liu L, Deng Y, Ji W, Du W, Xu P, Chen L, Xu T. Graded activation of CRAC channel by binding of different numbers of STIM1 to Orai1 subunits. *Cell Res*. 2011; 21:305–315. [PubMed: 20838418]
77. Hoover PJ, Lewis RS. Stoichiometric requirements for trapping and gating of Ca^{2+} release-activated Ca^{2+} (CRAC) channels by stromal interaction molecule 1 (STIM1). *Proc Natl Acad Sci USA*. 2011; 108:13299–13304. [PubMed: 21788510]
78. Wang X, Wang Y, Zhou Y, Hendron E, Mancarella S, Andrade MD, Rothberg BS, Soboloff J, Gill DL. Distinct Orai-coupling domains in STIM1 and STIM2 define the Orai-activating site. *Nat Commun*. 2014; 5:3183. [PubMed: 24492416]

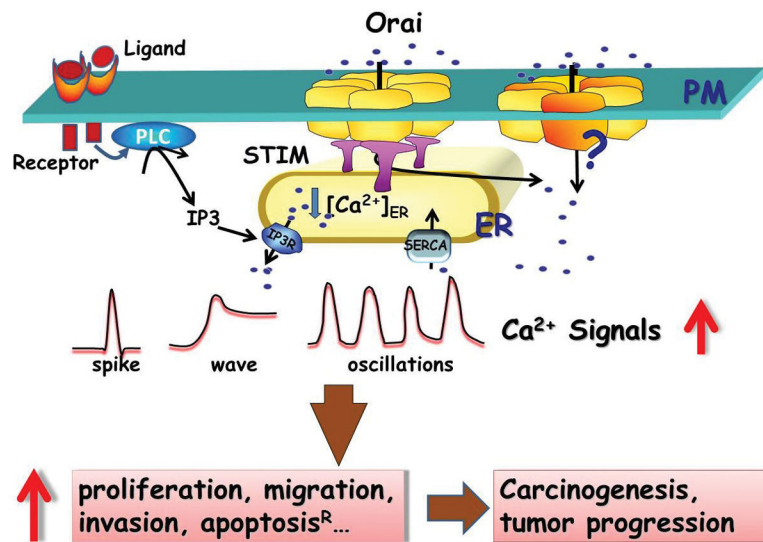


Figure 1. Oncogenic function of Orai1 and STIM1. Intracellular Ca^{2+} signals are in the forms of spike, wave or oscillation, which require G-protein coupled receptor-PLC-IP₃R pathway and Orai1/STIM1-mediated SOCE. Orai1 complex is composed of six subunits, coupling with STIM1 with 2:1 ratio for optimal channel regulation and activation. In cancer cells, elevated expression of Orai1 (Orai3) is not always accompanied by upregulation of STIM1, which raises the question whether Orai1 (Orai3) channel is activated without coupling with STIM1. Nevertheless, the overall increased SOCE result in hyperactivity of intracellular Ca^{2+} signals, which in turn stimulate cell proliferation, migration/invasion and develop apoptotic resistance in cancer cells.