Chapter 5
Role of TRPC Channels in Store-Operated Calcium Entry

Hwei Ling Ong, Lorena Brito de Souza, and Indu S. Ambudkar

Abstract Store-operated calcium entry (SOCE) is a ubiquitous Ca^{2+} entry pathway that is activated in response to depletion of Ca^{2+} stores within the endoplasmic reticulum (ER) and contributes to the control of various physiological functions in a wide variety of cell types. The transient receptor potential canonical (TRPC) channels (TRPCs 1–7), that are activated by stimuli leading to PIP_2 hydrolysis, were first identified as molecular components of SOCE channels. TRPC channels show a miscellany of tissue expression, physiological functions and channel properties. However, none of the TRPC members display currents that resemble I_{CRAC}. Intensive search for the CRAC channel component led to identification of Orai1 and STIM1, now established as being the primary constituents of the CRAC channel. There is now considerable evidence that STIM1 activates both Orai1 and TRPC1 via distinct domains in its C-terminus. Intriguingly, TRPC1 function is not only dependent on STIM1 but also requires Orai1. The critical functional interaction between TRPC1 and Orai1, which determines the activation of TRPC1, has also been identified. In this review, we will discuss current concepts regarding the role of TRPC channels in SOCE, the physiological functions regulated by TRPC-mediated SOCE, and the complex mechanisms underlying the regulation of TRPCs, including the functional interactions with Orai1 and STIM1.

Keywords TRPC channels • SOCE • Trafficking • Function

H.L. Ong (✉) • L.B. de Souza • I.S. Ambudkar (✉)
Secretory Physiology Section, Molecular Physiology and Therapeutics Branch, National Institute of Dental and Craniofacial Research, National Institutes of Health, Building 10, Room 1N-113, NIH, Bethesda, MD 20892, USA
e-mail: ongh@mail.nih.gov; indu.ambudkar@nih.gov

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5.1 Introduction

Elevation of cytosolic calcium levels ($[Ca^{2+}]_i$) in response to neurotransmitter stimulation of cells acts as a trigger for activation of many physiological processes, including cell proliferation and differentiation, cell migration, lymphocyte activation, endothelial cell function, as well as protein and fluid secretion from exocrine gland cells. Plasma membrane Ca^{2+} entry channels contribute to $[Ca^{2+}]_i$ elevation and provide critical Ca^{2+} signals that are utilized for regulation of different cell functions. Store-operated calcium entry (SOCE) is a major ubiquitous Ca^{2+} entry pathway that contributes to the control of various physiological functions in a wide variety of cell types. SOCE is a unique mechanism in that it is activated in response to depletion of Ca^{2+} stores within the endoplasmic reticulum (ER). Physiologically, this occurs following stimulation of plasma membrane receptors that lead to phosphatidylinositol 4,5-bisphosphate (PIP_2) hydrolysis and generation of inositol 1,4,5-triphosphate (IP_3). IP_3 binds to its receptor (IP_3R) in the ER membrane and induces Ca^{2+} release from the ER, resulting in a decrease in ER-$[Ca^{2+}]$ and activation of SOCE. This Ca^{2+} entry can also be activated by treating cells with sarco-endoplasmic reticulum (SERCA) pump blockers like thapsigargin or cyclopiazonic acid that inhibit Ca^{2+} uptake into ER, unmasking a passive Ca^{2+} leak pathway that has not yet been clearly elucidated. Importantly, this leads to loss of ER-Ca^{2+} and triggers activation of SOCE in the absence of receptor-stimulated signaling. SOCE is inactivated by refilling the Ca^{2+} stores within the ER, providing further evidence that the activity of channels mediating SOCE are governed by the status of $[Ca^{2+}]$ in the ER [1–3]. The first channel current associated with SOCE, Ca^{2+}-release activated calcium current (I_{CRAC}), was measured in mast cells and T lymphocytes. This highly Ca^{2+}-selective current has a characteristic inward rectification with reversal potential >+40 mV [4–7]. Under the same experimental conditions, currents with varying characteristics and ionic selectivities, ranging from relatively Ca^{2+}-selective to non-selective, have been described in different cell types. These currents have been generally referred to as store-operated calcium current (I_{SOC}) to distinguish them from I_{CRAC} [2, 8].

Search for the molecular components of SOCE, led to the identification of the transient receptor potential canonical (TRPC) channels, part of the superfamily of TRP channels. Mammalian TRPC channels were cloned based on the *Drosophila* TRP channel, which functions as a light-sensitive Ca^{2+}-permeable channel involved in phototransduction. The *Drosophila* phototransduction process, a phospholipase C-mediated pathway [9–11], provided further impetus to the search for mammalian TRP channels. The TRPC subfamily consists of seven members (TRPCs 1–7) that are divided into four subsets based on their amino acid (aa) homology: TRPC1, TRPC2, TRPC3/TRPC6/TRPC7 and TRPC4/TRPC5. All TRPC channels display activation in response to receptor-stimulated PIP_2 hydrolysis and have six transmembrane domains with a pore-forming domain localized between the fifth and sixth domains. The channels contain N-terminal ankyrin repeats, a highly conserved TRP domain in the C-terminus, several calmodulin (CaM)-binding domains and a

putative IP_3R binding site [9–11]. TRPC channels show diverse tissue expression, physiological functions and channel properties. Recent reviews have presented a general overview of the molecular components and mechanisms regulating SOCE [1, 12] as well as overviews of the individual TRPC channels: TRPC1 [13], TRPC2 [14], TRPC3 [15], TRPC4 [16], TRPC5 [17], TRPC6 [18], and TRPC7 [19]. We will not be discussing TRPC2, which is a pseudogene in humans [20, 21], in this review. While the discovery of TRPC channels spurred a large number of studies, none of the TRPC family of Ca^{2+}-permeable cation channels generated currents that resembled I_{CRAC}. Thus, identity of the components for this channel, as well as the regulatory proteins in SOCE continued to be a major focus in the field. Intensive search for these finally led to the identification of the CRAC channel component, Orai1, a four-transmembrane domain protein which is assembled as a hexamer to form the pore of the CRAC channel. Two other Orai proteins, Orai2 and Orai3, were also identified and reported to have some similarity with Orai1 and display store-dependent activation. However, since they also contribute to other non-SOCE mechanisms, such as the arachidonic acid-activated channels, further studies are required to fully understand their physiological function. Importantly, the main components involved in sensing ER-$[Ca^{2+}]$ and activating SOCE were also identified. The STIM family of proteins includes two members, STIM1 and STIM2, both of which are Ca^{2+}-sensing proteins that are localized in the ER membrane and sense $[Ca^{2+}]$ within the ER lumen to regulate SOCE. Of the two, STIM1 has been more extensively studied and is now well established as the critical and indispensable regulatory component of SOCE [22]. Furthermore, there is now considerable evidence that STIM1 can activate both Orai1 and TRPC1. The domains of STIM1 involved in gating of these channels are also known. Intriguingly, TRPC1 function is not only dependent on STIM1 but also requires Orai1. The critical functional interaction between TRPC1 and Orai1, which determines the activation of TRPC1, has also been resolved. In the following sections of this review, we will discuss current concepts regarding the role of TRPC channels in SOCE, the physiological functions regulated by TRPC-mediated SOCE, and the complex mechanisms underlying the regulation of TRPCs, including the functional interactions with Orai1 and STIM1.

5.2 Contribution of TRPC Channels to SOCE

All seven TRPC channels have been implicated as components of SOCE. Furthermore, a variety of physiological functions have been associated with TRPC-mediated SOCE. Recent studies also demonstrate that some human diseases are linked to either loss or gain of function of TRPC channels [23–25]. However, not all the TRPC channels consistently display the hallmarks of SOCE, namely (i) activation by store depletion in response to stimulation with an agonist or treatment with SERCA pump blockers, and (ii) inhibition by Gd^{3+} (1 μM) and 2-aminophenyl borate (2-APB; ≤10 μM). A large number of the studies assessing the role of TRPCs

have used heterologous expression systems where the channels are relatively overexpressed. This does not always result in generation of a functional channel in cells. Some studies have also demonstrated that the mode of regulation of the channels appears to differ depending on the level of their expression. This led to the suggestion that channel overexpression likely results in an unbalanced stoichiometry between TRPCs and the endogenous accessory proteins that regulate and/or modulate their activities. In contrast, more consistent and conclusive data have been provided by studies which assess the function of endogenous TRPCs in SOCE by modulating their expression and/or function in cell lines, primary cell preparations, as well as animal models. So far, the strongest evidence for the contribution of TRPC channels to SOCE has been provided for TRPC1 and TRPC4, whereas the contribution of TRPC3 to SOCE appears to be dependent on cell type and level of expression. TRPCs 5, 6 and 7 have been generally described to be store-independent, with a few exceptions. Note that unlike with Orai1 or STIM1, TRPC channel contribution to SOCE is not seen in all cell types.

TRPC1 was the first mammalian TRPC channel to be cloned and reported to have a role in SOCE [20, 21, 26, 27]. Among the many studies reported, exogenous expression of TRPC1 did not consistently increase SOCE while knockdown of endogenous TRPC1 significantly decreased SOCE (e.g. in HSG, smooth muscle and endothelial cells, as well as platelets) [26–32]. Further conclusive evidence was provided by studies with mice lacking TRPC1 ($TRPC1^{-/-}$), which despite having normal viability, development, and behavior [33], showed reduced SOCE in cell preparations from several tissues. Among these, salivary gland and pancreatic acinar cells and aortic endothelial cells from $TRPC1^{-/-}$ mice displayed significant reductions in SOCE as well as attenuation in Ca^{2+}-dependent physiological functions [34–36]. SOCE is fundamentally important for fluid secretion in salivary glands and for protein secretion in the exocrine pancreas. $TRPC1^{-/-}$ mice displayed reduction in salivary gland fluid secretion which was associated with a decrease in SOCE and K_{Ca} activity in acinar cells from the mice [36, 37]. Similarly defects in Ca^{2+}-activated Cl^- channel activity and protein secretion, as a consequence of reduced SOCE, were reported in pancreatic acinar cells [34]. Notably while there is no change in Orai1 in salivary gland and pancreatic acinar cells from $TRPC1^{-/-}$ mice, the channel does not appear to compensate for the lack of TRPC1 or support cell function on its own. Hence, decreased secretory function in these exocrine glands is primarily due to the loss of TRPC1-mediated SOCE. In endothelial cells, TRPC1 forms a heteromeric channel with TRP vanilloid 4 (TRPV4) to mediate SOCE. This Ca^{2+} entry was significantly reduced in cells from $TRPC1^{-/-}$ mice which adversely impacted vasorelaxation [35].

The caveolae-residing protein, caveolin-1 (Cav-1), is an important modulator of TRPC1 activity and functions as a plasma membrane scaffold for the channel. In the absence of Cav-1, TRPC1 is mislocalized and is unable to interact with STIM1, which is a requirement for TRPC1 activation [38]. Consistent with this, localization of TRPC1, its interaction with STIM1, as well as SOCE were disrupted in salivary gland acinar cells from $Cav\text{-}1^{-/-}$ mice [39]. Together, these findings further establish a role for TRPC1 in mediating SOCE in salivary gland cells. Other physiological

functions that are dependent on TRPC1-mediated SOCE are the contractile function of glomerular mesangial cells [40, 41] and osteoclast formation and function [42]. Loss of TRPC1 has also been implicated in aberrant vasorelaxation [43], muscle fatigue and slower regeneration after muscle injury [44, 45], whereas elevated TRPC1 expression has been linked to myopathies such as those observed in patients with Duchenne's Muscular Dystrophy and *mdx* mice lacking dystrophin [46–48]. However, it remains to be established whether these effects are due to changes in TRPC1-SOCE.

TRPC3 is reported to contribute to both the store-operated and receptor-activated calcium entry pathways. Loss of endogenous TRPC3 in cell lines and tissue preparations (pancreatic acinar and submandibular gland cells) from $TRPC3^{-/-}$ mice led to significant reductions in SOCE [49, 50]. In contrast, overexpression of TRPC3 increased SOCE in COS, HEK293 and HEK293T cells, as well as DT40 chicken B-lymphocytes. However, when the channel was expressed to very high levels, the regulatory mode was switched from store-operated to receptor-activated. Cells with relatively lower levels of TRPC3 expression displayed Gd^{3+} (1 μM)-sensitive Ca^{2+} entry, while those with higher levels of channel expression required higher [Gd^{3+}]. Hence, the mechanism by which TRPC3 is regulated appears to be determined by the level of channel expression in the cells [51–54]. TRPC3-mediated Ca^{2+} entry can also contribute to pathology and tissue damage. Pancreatic acini from $TRPC3^{-/-}$ mice showed significant protection from acute pancreatitis induced by hyperactivation of SOCE. Similar effects were seen by blocking channel function in $TRPC3^{+/+}$ mice by treatment with pyrazole 3, a TRPC3 inhibitor [55, 56]. Unlike TRPC3, TRPC6 and TRPC7 channels are largely believed be receptor-activated as both channels are consistently activated by the second messenger, diacylglycerol and its analogs [11, 18, 19, 57].

Both TRPC4 and TRPC5 have been suggested to contribute to SOCE, although there are very few studies reported for either channel. Moreover, TRPC5 can also be directly activated by Ca^{2+}, which makes it difficult to establish conclusively whether TRPC5 is directly regulated by store depletion [58, 59]. Exogenous expression of TRPC4 in HEK293 cells increased SOCE and generated a relatively Ca^{2+}-selective, inwardly rectifying current [60]. Similar results were obtained by overexpression TRPC4 in CHO, RBL cells [61] and *Xenopus laevis* oocytes [62]. Further evidence for TRPC4-mediated SOCE was provided by studies where TRPC4 expression was suppressed in several cell lines or by knockout of the channel in mice ($TRPC4^{-/-}$ mice). Following siRNA treatment, TRPC4-mediated SOCE was diminished in mouse mesangial cells [63], human adrenal cells [64], both mouse and human endothelial cells [65], human gingival keratinocytes [66], human corneal epithelial cells [67] and human pulmonary artery smooth muscle cells [68]. Additionally, TRPC4 forms a heteromeric channel complex with TRPC1 in human mesangial cells [69] as well as human and mouse endothelial cells [65]. Similar to what has been reported for $TRPC1^{-/-}$, knockout of TRPC4 did not adversely impact mortality and fertility of the mice. Nonetheless, $TRPC4^{-/-}$ mice show significantly reduced TRPC4-mediated SOCE in aortic [70] and lung endothelial cells [65, 71], resulting in defective regulation of vascular tone and endothelial permeability, respectively.

TRPC channels interact with numerous proteins which can underlie the diversity of calcium channel activity, their regulation, and specificity of downstream signaling events in the cells (recently reviewed in [1]). Not only do TRPC channels have the ability to undergo homomeric interactions to form functional channels, they also interact with other TRPCs to generate functional heteromeric channels. Most of the available data in this regard comes from studies with exogenously expressed channels. TRPC1 interacts with TRPC4 and TRPC5, whereas TRPC3 interacts with TRPC6 and TRPC7 [72–74]. It is presently not clear whether the resulting heteromeric channels have distinct properties and functions as compared to those of the individual channels. Very few studies have elucidated the status of endogenous store-dependent heteromeric TRPC channels and their physiological function. The contribution of endogenous heteromeric channel complexes to SOCE have been reported for TRPC1/TRPC3 in a human parotid gland ductal cell line [75] and rat H19-7 hippocampal cell lines [76]; TRPC1/TRPC5 in vascular smooth muscle [77]; TRPC1/TRPC4 in endothelial cells [65], and TRPC1/TRPC3/TRPC7 in HEK293 cells [50]. Given the overlapping expression of more than one TRPC channel in different cells and tissues, some physiological functions may involve multiple channels. For example, SOCE mediated by both TRPC1 and TRPC4 has been proposed to control endothelial cell permeability [65] and myogenesis [78, 79]. Multiple TRPC channels have been implicated in cardiac hypertrophy [80, 81], but it is not clear whether aberrant TRPC-mediated SOCE underlies this phenomena. A few studies have utilized double TRPC knockout mouse models to determine the role of heteromeric TRPC channels. Knockout of both TRPC1 and TRPC4 in mice severely impaired neuronal burst firing and caused neurodegeneration [82], whereas loss of both TRPC3 and TRPC6 impaired sensitivity to mechanical pressure and hearing [83]. The underlying basis for creating these double knockout mice models was the preponderance of co-expressed TRPC1 and TRPC4 in the brain [82] and TRPC3 and TRPC6 in sensory neurons and cochlear hair cells [83]. Whether the pathophysiological effects observed from double knockouts of endogenous TRPC heteromeric channel complexes can be conclusively linked to impaired regulation of SOCE also remains to be shown.

TRPC channels have also been found to associate with other TRP channels, including TRPV6, TRPV4, although in most of these cases it is not clear whether the associating channels form a single channel pore and/or contribute to SOCE. Co-expression of TRPC1 and TRPV4 resulted in formation of a heteromeric channel complex that is activated in response to store depletion in HEK293, vascular smooth muscle and endothelial cells. Moreover, the TRPC1/TRPV4 heteromeric channel exhibited distinct current characteristics when compared to currents mediated by either TRPV4 or TRPC1 alone [35, 84, 85]. TRPC1 was reported to interact with TRPV6 and exert negative regulation of TRPV6 function [86]. A critical heteromeric interaction involving TRPC channels is the TRPC-Orai1 interaction. TRPC1, TRPC3 and TRPC6 functionally interact with Orai1. TRPC1-Orai1 interaction has been confirmed by co-immunoprecipation data as well as TIRFM measurements, where store depletion-dependent clustering of the two channels has been observed in several cell types [87–92]. Further, and more importantly, Orai1 is

required for TRPC function, as knockdown of endogenous Orai1 abolished TRPC1 channel activation [88, 92]. A similar requirement for Orai1 has been reported for activation of TRPC3 and TRPC6 in response to ER-Ca^{2+} store depletion [93–95]. The mechanism underlying the Orai1-dependent regulation of TRPC1 has now been resolved (more details will be presented below). Importantly, TRPC1 and Orai1 have been shown to generate two distinct channels that appear to contribute to specific cellular functions [88, 96]. Interestingly, a recent study reported that a splice variant of TRPC1 interacts with and positively regulates Orai1 channel activity in HEK293 cells. This splice variant, TRPC1ε, was first identified in early pre-osteoclasts and together with I-mfa (an inhibitor of MyoD family), has been proposed to function antagonistically to decrease Orai1 channel activity, fine tuning the Ca^{2+} signaling process that regulates osteoclastogenesis [42]. The multiplicity of interactions between various TRPC channels, as well as between TRPC and other channels or regulatory proteins, lead to the generation of a plethora of signaling complexes that can regulate a wide variety of cellular functions. It is possible that the composition of these heteromeric channels as well as the interacting signaling proteins depends on the type of cell and the particular physiological function to be regulated. There are an increasing number of studies that highlight the importance of spatial and temporal aspects as well as the magnitude of Ca^{2+} signals as major determining factors in the regulation of cellular responses to different physiological stimuli. It is important that these should be taken into account when the physiological functions of TRPC channels are being assessed.

5.3 Role of STIM1 and STIM2 in SOCE and TRPC Channel Regulation

STIM1 and STIM2 were discovered in studies using siRNA screening to identify proteins required for SOCE. Both proteins reside within the ER and during resting (unstimulated) conditions, have Ca^{2+} bound to the luminal N-terminal EF hand domains. Following store depletion, Ca^{2+} is released from the EF hand which leads to multimerization of the protein and translocation to the peripheral region of the cells where it concentrates in the form of puncta within distinct ER-plasma membrane (ER-PM) junctions. Within this microdomain, the ER membrane and plasma membrane are in close apposition to each other [22, 97, 98]. More importantly, the proximity between the two membranes allows STIM1 in the ER to interact with and gate both TRPC and Orai1 channels. Different aa regions in the cytosolic C-terminus of STIM1 are involved in activating Orai1 and TRPC1. Orai1 activation is mediated by the STIM1 Orai1 Activating Region (SOAR; aa 344–442) [99], whereas TRPC channel gating occurs via the polybasic domain (aa 672–685) [91, 100]. It has been suggested that TRPC1 and TRPC4 are the main TRPC channels that can interact with and be gated by STIM1. However, if other TRPC channels are assembled in a heteromeric channel complex with either TRPC1 or TRPC4, they appear to become store-dependent due to the activation of TRPC1 and TRPC4 by STIM1. For

example, although STIM1 does not interact with TRPC3 and TRPC6, STIM1 can activate TRPC1/TRPC3 or TRPC4/TRPC6 channels [101].

Strong evidence for STIM1 in gating TRPC channels comes from studies showing an effect on channel activity of either knockdown or overexpression of STIM1 or STIM1 with mutations that impair STIM1-TRPC channel interactions. TRPC1 was the first TRPC channel shown to be regulated by STIM1. Knockdown of endogenous STIM1 severely reduced endogenous TRPC1-mediated SOCE and Ca^{2+} currents, whereas co-expression of TRPC1 and STIM1 increased SOCE [87, 88, 91]. Store depletion induced interaction between TRPC1 and STIM1, shown by co-immunoprecipitation experiments as well as FRET and TIRFM measurements. Conversely, store refilling terminated TRPC1 function as well as STIM1-TRPC1 association [91, 100–104]. Thus the TRPC1-STIM1 interaction is dictated by the ER-[Ca^{2+}] status. Conclusive studies by Muallem and co-workers resolved the mechanism by which STIM1 gates TRPC1. Their findings demonstrated that gating of TRPC1 involves electrostatic interactions between the negatively charged aspartate residues in TRPC1 (^{639}DD^{640}) with the positively charged lysines in the STIM1 polybasic domain (^{684}KK^{685}) [100]. Further studies showed that these negatively charged residues are conserved in TRPC3, TRPC4, TRPC5, TRPC6 and TRPC7, suggesting the possibility that STIM1 can also gate these other TRPC channels [100]. Consistent with this study, TRPC4-mediated SOCE in murine and human endothelial cells was suppressed by knockdown of STIM1 or expression of a charge-swap mutant of STIM1 (KK684,685EE). Similarly, disrupting the electrostatic interaction between STIM1 and TRPC4 by mutation of the conserved negatively charged residues on TRPC4 (EE647,648KK) significantly reduced SOCE and STIM1-TRPC4 interactions [65]. Co-immunoprecipitation of STIM1 and TRPC3 was also increased following store depletion in salivary gland duct cells, although this could be due to TRPC1-TRPC3 interaction in these cells [105]. In yet another study, mutations in the conserved negative residues in the C-terminus of TRPC3 (DD697,698KK), TRPC4 (EE648,649KK), TRPC5 (DE651,652KK) and TRPC6 (EE755,756KK) prevented electrostatic interactions with and gating by STIM1. While these mutants did not respond to store depletion induced by cyclopiazonic acid, they could still be activated by muscarinic receptor stimulation in a STIM1-independent manner. However, co-expression of the charge-swap STIM1 mutant (KK684,685EE) restored store responsiveness to these TRPC mutants [106].

Collectively, these data demonstrate that STIM1 has the ability to gate all TRPC channels via similar electrostatic interactions, even though not all channels appear to interact directly with STIM1. Since TRPC channels are widely expressed in tissues and species, it is not yet clear what determines the interaction of any particular TRPC channel with STIM1 and thus their mode of activation. In neuroblastoma cells, STIM1 promoted SOCE mediated via TRPC1 and TRPC6, while inhibiting TRPC6-mediated store-independent Ca^{2+} entry [107]. TRPC5 was also reported to contribute to SOCE in RBL cells. In these cells co-expression of STIM1 with TRPC5 increased, while knockdown of STIM1 abolished, thapsigargin-induced cation entry [108]. Thus, STIM1 might not only be involved in gating some TRPC channels but also determine their recruitment into a store-dependent mode. However,

further studies are required to establish this role of STIM1 on the mode of activation of TRPC channels. Involvement of other factors that might contribute to this switch in the mode of regulation also needs further detailed studies. Since several TRP channels show polymodal regulation of their function, possible activation of TRPC channels by mechanisms other than store depletion appears to be quite feasible.

There is considerable information regarding the exact intramolecular rearrangements and molecular domains involved in activation of STIM1. Further, a large number of structure-function studies have now been reported describing the configuration of STIM1 required for binding and activation of Orai1 (recently reviewed in [109]). However, a similar detailed understanding of STIM1-TRPC channel interaction is currently lacking. An ezrin/radixin/moesin (ERM) domain (aa 251–535) was shown to mediate the binding of STIM1 to TRPC channels [91]. However, since the SOAR domain resides within this ERM region of STIM1 it was suggested that the SOAR domain might also be involved in mediating STIM1 binding to TRPC channels [12, 105]. The coiled-coil (CC) motif within the C-terminus of Orai1 is proposed to interact with STIM1 [110]. TRPC channels also have CC domains in both their N- and C-termini. Further, co-immunoprecipitation studies have revealed strong interactions between exogenously expressed SOAR and endogenous TRPC1, TRPC4 and TRPC5, minimal interactions with endogenous TRPC3 and TRPC6, and no interactions with TRPC7 [101, 105]. Mutation of residues in the N-terminal CC domains severely weakened SOAR interactions with TRPC1, TRPC4 and TRPC5 but enhanced association of TRPC3 and TRPC6 with SOAR. Based on this data, it was proposed that interaction of TRPC1 with TRPC3 induces a structural change which exposes a domain in TRPC3 that promotes its binding to STIM1 [105]. A recent study investigating the stoichiometry of TRPC, STIM1, and CaM assembly in a signaling complex reported TRPC channel activation using recombinantly purified SOAR [111]. This study demonstrated that only TRPC channel complexes containing TRPC1, TRPC4 and TRPC5 could be activated by SOAR. Each TRPC tetrameric complex required two SOAR domains for activation and four CaMs for inactivation. SOAR and CaM appeared to reciprocally regulate TRPC channel activity when co-expressed in HEK293 cells. Following application of tenfold higher amounts of CaM, TRPC1 channel activity was reduced, even though SOAR was still bound to the tetramers at the initial stages of inhibition. SOAR eventually detached from TRPC1, which led to further CaM-dependent decline in channel activity [111]. However, to conclusively establish that SOAR directly affects TRPC channel activity, data need to be provided to exclude SOAR-Orai1 effects in the same cell since SOAR domain will also gate Orai1 and Orai1-mediated Ca^{2+} entry will lead to TRPC channel activation. It is worth noting that some studies suggest that Orai1 binding to STIM1 might limit availability of STIM1 for TRPC channels. However, these studies have yet to be confirmed at the level of endogenous proteins. Further studies are required to establish whether STIM1 is indeed a limiting factor for channels contributing to SOCE and whether different physiological conditions favor binding of STIM1 to one type of channel vs the other.

STIM1 shares significant homology with another family member, STIM2. While functional domains such as the EF hand, CC domains, SOAR and polybasic domain are conserved between STIM1 and STIM2 there are several key differences which determine their diverse physiological function and role in SOCE. For example, STIM2 can interact with Orai1 but is a poor activator of the channel compared to STIM1. The difference in the gating efficiency of STIM1 and STIM2 was shown to be due to a single aa difference in their respective SOAR domains; F394 in SOAR1 vs L485 in SOAR2 [112]. The EF hand of STIM2 has a lower affinity for Ca^{2+} than STIM1. Thus, STIM2 can sense and respond to small changes in ER-[Ca^{2+}]. The triggering threshold level of $[Ca^{2+}]_{ER}$ for STIM2 is >400 μM, while STIM1 responds when ER-[Ca^{2+}] is around 200 μM. Based on this, STIM2 has been suggested to aggregate and translocate to ER-PM junction under conditions when there is minimal depletion ER-Ca^{2+} [113] One reported function for STIM2 is the regulation of Orai1 in resting cells to maintain $[Ca^{2+}]_i$ [114]. Another study suggests that STIM2 gates Orai1 in cells stimulated with low agonist where there is less depletion of ER-Ca^{2+} stores while STIM1 is involved in gating Orai1 at high agonist concentration when there is greater depletion [115]. A recent study provides a novel role for STIM2 showing that STIM2 associates with STIM1 and promotes the clustering of STIM1 in ER-PM junctions in cells stimulated with low [agonist]. STIM2 co-clusters with Orai1 and promotes STIM1-Orai1 interactions at low levels of stimulation while STIM1 aggregates efficiently, in a STIM2-independent manner, and interacts with Orai1 in cells stimulated with high [agonist] [116]. Knockdown of STIM2 in HEK293 cells or targeted knockout of STIM2 in mouse salivary glands attenuated STIM1-mediated activation of Orai1 and decreased the agonist sensitivity of SOCE activation. This was especially prominent at lower levels of agonist. On the other hand, knockdown of STIM1 completely eliminated SOCE at low and high levels of stimulus. Hence, STIM2 appears to tune the agonist-sensitivity of the STIM1-Orai1 interactions and associated Ca^{2+} signals [116]. Few studies have investigated the direct contribution of STIM2 to TRPC-mediated SOCE. STIM1 has been proposed to regulate TRPC1 and TRPC3 channel function, whereas STIM2 regulated only TRPC1 function in HEK293 cells [117]. Modulation of the STIM1:STIM2 ratio appears to determine the store responsiveness of TRPC1 channel function in intestinal epithelial cells [118]. Thus, the exact role of STIM2 in TRPC channel function and regulation remains to be determined.

5.4 Orai1-TRPC Channel Interactions in SOCE

The pore-forming component of CRAC channels, Orai1, is indispensable for SOCE. A naturally occurring mutation of the channel, (R91W), which leads to loss of channel function, has been linked to severe combined immune deficiency (SCID) [119–121]. Orai1 has two closely related family members, Orai2 and Orai3, although there is a paucity of data regarding their contribution to SOCE when compared to Orai1 [122]. While endogenous Orai1 function is supported by endogenous

STIM1, exogenously expressed Orai1 does not by itself increase SOCE in cells unless STIM1 is co-expressed with it. The reason for this is not yet clear as cells appear to express STIM1 in excess of Orai1. Subsequent studies identified the pore region of Orai1 by showing that E106Q mutation generates a channel with a non-functional pore, while E106D changes Ca^{2+} selectivity [22, 110, 123, 124]. An additional interesting observation that has been reported is that STIM1 increases the Ca^{2+} selectivity of Orai1 [125]. Again the latter study was carried out with overexpressed protein and needs to be more fully examined using the endogenous channel.

Intriguingly, a number of studies demonstrate that Orai1 is also required for TRPC1 function. Knockdown of endogenous Orai1 abolished SOCE, despite the presence of endogenous or exogenously expressed STIM1 and TRPC1. Further, it was reported that Orai1 and STIM1 form a complex with TRPC1 in response to ER-Ca^{2+} store depletion in HSG cells [103], mouse pulmonary arterial smooth muscle cells [126], human parathyroid cells [127], human liver cells [128] rat kidney fibroblast [129], pancreatic acinar cells and salivary gland acinar cells [34, 39]. Notably assembly of the TRPC1-Orai1 complex requires STIM1 which also gates both channels. Co-localization of the three proteins in ER-PM junctions, as detected by TIRFM, suggests that TRPC1 is also localized in same ER-PM junctions where Orai1-STIM1 complex is assembled. The requirement of Orai1 in TRPC1 function was further revealed by data showing that non-functional Orai1 mutants, either Orai1E106Q or Orai1R91W, abrogated store-dependent activation of TRPC1 [87, 88, 92, 103]. Based on this, it was first proposed that TRPC1 and Orai1 assemble into a heteromeric channel where both proteins contribute to the channel pore. There was also the suggestion that TRPC channel forms the pore while Orai1 serves as a regulator. While this led to an extensive debate regarding the assembly of these putative channels, neither of these proposals was supported by conclusive data. Finally, the mechanism underlying the requirement of Orai1 in TRPC1 function was demonstrated in a study where Ca^{2+} influx mediated by Orai1 triggers plasma membrane insertion of TRPC1 [88]. The insertion presumably occurs within the same ER-PM junctions where the Orai1-STIM1 complex is assembled, to allow for TRPC1 gating by STIM1. Moreover, recruitment of TRPC1 into these junctions brings TRPC1 in close proximity to Orai1, such that Ca^{2+} entry via Orai1 can be sensed locally to trigger plasma membrane recruitment of TRPC1. This requirement of Orai1-mediated Ca^{2+} entry for TRPC1 insertion into the plasma membrane also accounts for the lack of TRPC1 activity when non-functional mutants of Orai1 are expressed. Importantly, Ca^{2+} entry mediated by TRPC1 and Orai1 are utilized by cells to regulate separate functions. Orai1-mediated SOCE is sufficient for activation of NFAT, whereas Ca^{2+} entry via both Orai1 and TRPC1 are required for NFκB expression and function, with TRPC1 contribution being predominant [88, 96]. Thus, Orai1 and TRPC1 form two separate STIM1-regulated channel complexes (Fig. 5.1). TRPC1 and STIM1 form a SOC channel that generates I_{SOC} while Orai1 and STIM1 form the highly Ca^{2+}-selective CRAC channel mediating I_{CRAC}. The smaller I_{CRAC} is masked by the larger I_{SOC} current and unmasked when TRPC1 function is suppressed. It should be noted that true TRPC1 currents

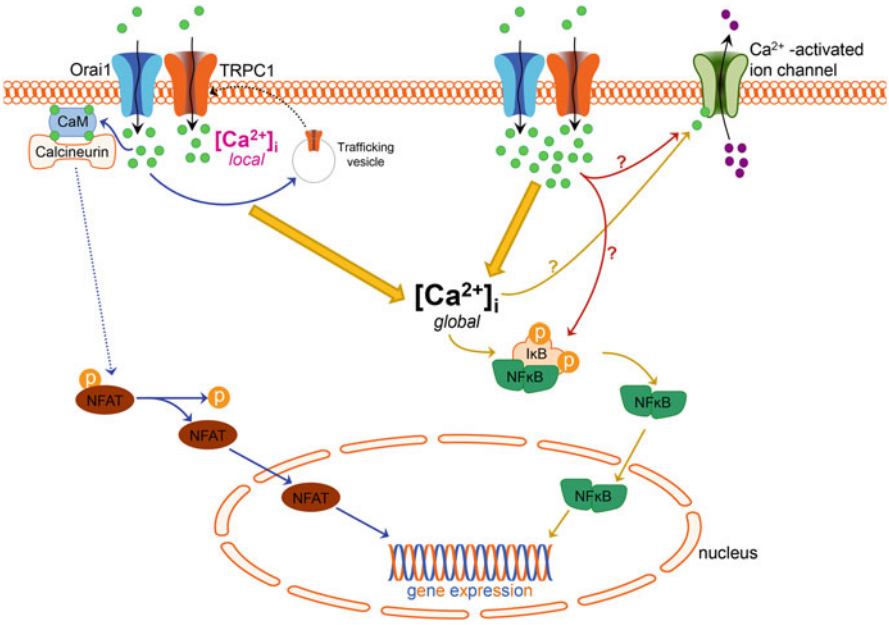

Fig. 5.1 Physiological function of Orai1 and TRPC1 in SOCE. Stimulation with agonists generates $[Ca^{2+}]_i$ changes that occur locally (i.e. close to the channel pore) and globally (i.e. throughout the cell cytosol). Local SOCE mediated by Orai1 has been shown to activate calcineurin, which subsequently induces NFAT translocation into the nucleus to drive gene expression. Local Orai1-SOCE also promotes insertion of TRPC1 into the plasma membrane. Ca^{2+} entry via both Orai1 and TRPC1 contribute to increase in global $[Ca^{2+}]_i$, which has been shown to activate NFκB and NFκB-driven gene expression. While the Ca^{2+}-activated ion channels in the plasma membrane are also activated by global $[Ca^{2+}]_i$, it is not clear whether the activating Ca^{2+} comes from those situated in the vicinity of neighboring Orai1 and TRPC1 channels and/or from the deeper regions of the cell cytosol

have not yet been described as most reported measurements of I_{SOC} include currents generated by both TRPC1+STIM1 and Orai1+STIM1 channels [88]. A requirement for Orai1 in other TRPC channels such as TRPC3 and TRPC6 [93], as well as heteromeric TRPC channels TRPC1/TRPC4 [130], have been reported. Whether TRPC channel trafficking is involved in these cases is not yet known. The exact proteins involved in regulating and mediating exocytosis of TRPC1 have not yet been elucidated.

One interesting suggestion which has been made is that Orai1 can regulate TRPC channels by determining their recruitment into specialized microdomains in the plasma membrane, such as the lipid raft domains (LRDs). This suggestion is consistent with previous studies showing that SOCE requires intact LRDs [39, 88, 90, 104, 131, 132]. Further, STIM1-TRPC1 interaction also takes place within LRDs as disruption of LRD leads to abrogation of STIM1-TRPC1 interaction and loss of SOCE [104]. Similarly, disruption of LRD in human platelets and HEK293 cells reduced interactions between Orai1, TRPC1, TRPC6 and STIM1 [90, 132, 133]. Orai1

interacts with the cytosolic termini of TRPC1 and TRPC6 to modulate their sensitivity to store depletion and STIM1 [93, 134, 135]. Thus, Lutz Birnbaumer and co-workers suggested the hypothesis that recruitment of Orai1, TRPC and STIM1 into LRD confers store-responsiveness to the channels [135]. At this stage, it remains unclear whether Orai1-STIM1 and TRPC-STIM1 complexes are initially formed outside the lipid rafts and subsequently recruited into these microdomains following store depletion or are maintained within this domain by interactions with Orai1 and STIM1. Presence of PIP_2-interacting domains in the C-terminus of STIM1 and STIM2 [132], which are proposed to enable anchoring of the proteins to the plasma membrane within ER-PM junctions, led to several studies examining the role of PIP_2 in SOCE. Effects of PIP_2 depletion on SOCE were inconsistent with some studies showing no effect on SOCE mediated by Orai1 while others demonstrated decreased function and STIM1 clustering [136–139]. Nevertheless, STIM1 or STIM2 lacking the polybasic tail domain do not form puncta within ER-PM junctional domains. However, when Orai1 is expressed with this mutant of STIM1, it rescues STIM1 clustering and CRAC channel activity. It has been suggested that the Orai1-STIM1ΔK complexes might be localized outside the ER-PM junctions, suggesting that the PIP_2 is not required for STIM1-dependent gating of Orai1 [140]. It is unclear whether TRPC-STIM1 interactions can also take place outside the junctional domains. A recent study suggests that dynamic changes in PIP_2 levels within ER-PM junctions mediated by proteins such as septin, impact not only assembly of the Orai1-STIM1 complexes but also regulation of CRAC channel activity [141–143]. It has also been recently reported that the ER-PM junctions might contain different PIP_2 microdomains. This study showed that Orai1-STIM1 complex assembled in ER-PM junctions is transferred from relatively PIP_2-poor to a PIP_2-rich microdomain which dictates the Ca^{2+}-dependent regulation of the channel. Interestingly, this recruitment is determined by Cav-1 and septin [143]. Further studies will be required to fully elucidate the dynamic lipid and protein remodeling that occurs with the ER-PM junctions that critically impact Orai1 and TRPC1 interaction with STIM1 and their function.

Trafficking of TRPC channels has been proposed as a major mode of regulation of their function in the plasma membrane. In addition to the trafficking proteins, scaffolding and regulatory proteins also modulate the magnitude and duration of TRPC-mediated SOCE. The main regulatory pathways that modulate surface expression and function of TRPC channels comprise of constitutive and regulated intracellular trafficking mechanisms. The enhancement of Ca^{2+} influx through TRPC channels can be due to increased exocytosis, retention via interaction with scaffolding proteins, and/or decreased channel endocytosis. As discussed above, TRPC1 function is dependent on LRD [144]. The cholesterol-binding LRD protein Cav-1 is reported to play a pivotal role in plasma membrane localization and activity of TRPC1. TRPC1 interacts with Cav-1 through binding sites located in its N- and C-terminal domains. The N-terminal Cav-1 binding site is involved in scaffolding and localization of TRPC1 in the plasma membrane while the C-terminal domain has been proposed to control channel function and/or inactivation. Knockdown of Cav-1, and mutations in Cav-1 or Cav-1 binding sites in TRPC1

resulted in mislocalization of TRPC1 and impairment of channel activity. Hence, Cav-1 is suggested as an LRD scaffolding protein for TRPC1 that determines plasma membrane localization [38, 39, 131, 145–149]. The current model proposes that in resting cells, constitutive trafficking mechanisms target TRPC1 to cellular regions close to the plasma membrane where the inactive channel interacts with Cav-1 and is retained at that location intracellularly. Following store depletion, STIM1 translocates to ER-PM junctions and activates Orai1. Ca^{2+} entry mediated by Orai1 is a pivotal step in TRPC1 insertion into the plasma membrane and channel activation [88], as it triggers the insertion of TRPC1 into the plasma membrane. Under these conditions, TRPC1 dissociates from Cav-1, interacts with and is gated by STIM1. Following ER-Ca^{2+} store refilling, SOCE is inactivated and TRPC1 disassembles from STIM1. LRDs are essential for STIM1 translocation to the ER-PM junctions as deleting the C-terminal lysine-rich region of STIM1, which contains a PIP_2-binding sequence, impairs puncta formation in these junctions and also alters partitioning of STIM1 into detergent insoluble fractions from cells. In addition, disruption of lipid rafts by cholesterol depletion also affects the ability of STIM1 to interact with TRPC1 [104]. These data demonstrate the importance of structural integrity for caveolar lipid rafts to act as scaffolding platforms for TRPC1-mediated SOCE. Based on the recent study that showed Cav-1 is required for recruitment of Orai1-STIM1 channel to a PIP_2-rich domain [143], it is possible that this event can bring TRPC1 in close proximity to Orai1 such that it can sense local $[Ca^{2+}]_i$ elevation due to Orai1-mediated Ca^{2+} entry. Indeed, Cav-1 might be of utmost importance in Orai1-dependent activation of TRPCs as almost all TRPC channels have once or more Cav-1 binding domains, some of which are fairly well conserved. Nonetheless, Ca^{2+} sensor proteins, as well as the identity of vesicles and intracellular compartments related to TRPC1 trafficking, remain to be determined.

In addition to Cav-1, another scaffolding protein that regulates TRPC1 function is Homer1. The C-terminus of TRPC1 (aa 644–650) forms a complex with Homer1 and IP_3R in resting cells. However, following store depletion, this complex dissociates to enable subsequent TRPC1 interaction with and gating by STIM1 [150, 151]. Further evidence for the contribution of Homer1 came from a study with knockout mice (Homer1$^{-/-}$) that reported impaired SOCE in skeletal muscle cells [47]. Soluble N-ethylmaleimide-sensitive factor attachment receptor (SNARE) proteins, such as synaptosome-associated protein (SNAP-25), are involved in membrane fusion within intracellular compartments or between vesicles and plasma membrane. Interaction of SNAP-25 with TRPC1 is vital for channel function as botulinum toxin treatment, which cleaves and inactivates SNAP-25, decreased SOCE in platelets [152]. Several cytoskeletal and microtubule proteins have also been shown to modulate the TRPC1 channel trafficking and activity. The monomeric GTPase protein, RhoA, regulates TRPC1 translocation to the plasma membrane in endothelial cells [29]. Interaction of β-tubulin with TRPC1 determines surface expression of TRPC1 retinal epithelial cells [153]. Disrupting TRPC1 interaction with either RhoA or β-tubulin significantly decreased SOCE. In aggregate, the data show that proper localization of TRPC1 in the plasma membrane, as well as trafficking to the

specific domains where SOCE is regulated, are vital for its interaction with Orai1-STIM1 and its activation.

5.5 Conclusions

The mechanism(s) underlying SOCE involves multiple interactions that allow cells to display dynamic regulatory modes for each physiological stimulus. The multiplicity of channel-protein and protein-protein interactions underscores the variety of signaling complexes that can be generated within a subregion of the cell. Indeed, TRPC channels interact with a wide range of channels and proteins involved in Ca^{2+} signaling, as well as scaffolding and trafficking processes. Such complexity underlies the physiological functions that have been ascribed to TRPC channels. Many studies have investigated the contributions of STIM1 and Orai1 to TRPC channel function. The functional relevance of STIM2, as well as Orai2 and Orai3, in SOCE remains to be resolved. It is worth noting that many cells and tissues express both STIM proteins and more than one Orai protein. Therefore, depending on the type and intensity of the cell stimulus, TRPC channels may also form dynamic signaling complexes with these STIMs and Orais to generate SOCE. Nonetheless, much remains to be elucidated to expand our current understanding of the exact sequence of molecular events involved in the regulation and function of TRPC channels in response to ER-Ca^{2+} depletion. As TRPC channels have been implicated in a number of human diseases, understanding the mechanism(s) involved in regulating and modulating channel function will provide potentially important information and lead to novel targets for the development of effective therapeutic interventions.

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