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Forms and Functions of Store-operated Calcium Entry Mediators, STIM and Orai

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Abstract

Calcium signals arise by multiple mechanisms, including mechanisms of release of intracellular stored Ca^{2+}, and the influx of Ca^{2+} through channels in the plasma membrane. One mechanism that links these two sources of Ca^{2+} is store-operated Ca^{2+} entry, the most commonly encountered version of which involves the extensively studied calcium-release-activated Ca^{2+} (CRAC) channel. The minimal and essential molecular components of the CRAC channel are the STIM proteins that function as Ca^{2+} sensors in the endoplasmic reticulum, and the Orai proteins that comprise the pore forming subunits of the CRAC channel. CRAC channels are known to play significant roles in a wide variety of physiological functions. This review discusses the multiple forms of STIM and Orai proteins encountered in mammalian cells, and discusses some specific examples of how these proteins modulate or mediate important physiological processes.

Introduction

Aberrant Ca^{2+} signaling underlies or contributes to numerous pathological conditions (Berridge, 1994; Feske, 2007; Missiaen et al., 2000; Mooren and Kinne, 1998). In particular, and pertinent to the theme of this volume, numerous studies implicate Ca^{2+} signaling in the development and progression of cancer cells (Baldi et al., 2003; Bodding et al., 2003; El Boustany et al., 2008; Flourakis et al., 2010; Jaffe, 2005; Kohn et al., 1995; Kohn et al., 1996; Lee et al., 2006; McAndrew et al., 2011; Tannheimer et al., 1997; Trump and Berezesky, 1996; Wissenbach et al., 2001; Yang et al., 2009; Zhuang et al., 2002). Virtually all mechanisms and pathways of Ca^{2+} signaling have been implicated in either the pathology or potential therapy of diseases, including Ca^{2+} pumps, intracellular Ca^{2+} mobilization, and Ca^{2+} channels. One widely encountered signaling mechanism involves the phosphoinositide-derived second messenger, inositol 1,4,5-trisphospate (IP_3) (Mikoshiba, 2015). This mode of signaling involves IP_3-induced activation of a receptor-channel on the endoplasmic reticulum resulting in release of stored Ca^{2+} and activation of downstream Ca^{2+}-sensitive pathways. A large number of physiological processes, and disease states can be associated with IP_3-induced signaling (Mikoshiba, 2015). Calcium signals can also result from the

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opening of Ca^{2+} channels in the plasma membrane. One specific and widely distributed Ca^{2+} channel, and the focus of this chapter, is the store-operated or calcium-release-activated-Ca^{2+} (CRAC) channel, implicated in a number of diseases (Feske, 2007; Feske, 2010), including cancer (Chen et al., 2011; Davis et al., 2014; McAndrew *et al.*, 2011; Motiani et al., 2013; Yang *et al.*, 2009).

Store-operated Ca^{2+} channels are activated when the Ca^{2+} concentration in the endoplasmic (or sarcoplasmic) reticulum is low (Parekh and Putney, 2005; Putney, 1986). Physiologically, this generally occurs through activation of a Ca^{2+} release signaling mechanism, usually inositol 1,4,5-trisphospate-induced release, or Ca^{2+}-induced Ca^{2+} release through the ryanodine receptor. Experimentally, influx through store-operated channels results in a rise in steady-state Ca^{2+}, a process sometimes referred to as store-operated Ca^{2+} entry (SOCE). In electrophysiological studies, SOCE presents as a small inwardly rectifying current termed calcium-release activating Ca^{2+} current (I_{crac}) (Hoth and Penner, 1992). The level of Ca^{2+} in the endoplasmic reticulum is sensed by a transmembrane endoplasmic reticulum resident protein, STIM1, and to a less well defined extent, its homolog STIM2 (Liou et al., 2005; Roos et al., 2005). STIM1 is a single pass transmembrane protein with an EF hand Ca^{2+} binding motif in the N-terminus directed to the lumen of the endoplasmic reticulum. When free Ca^{2+} in the endoplasmic reticulum falls, Ca^{2+} dissociates from STIM1 resulting in its aggregation into multimers and consequent confirmation change. This confirmation change exposes sequences that can interact with and activate store-operated Ca^{2+} channels, composed of Orai1 subunits, in the plasma membrane ((Feske et al., 2006; Vig et al., 2006; Zhang et al., 2006), reviewed in (Fahrner et al., 2009; Frischauf et al., 2008; Hogan et al., 2010; Prakriya, 2009)). In addition, Ca^{2+} entering through Orai1 channels can recruit some members of the TRPC cation channel family to the plasma membrane where they interact with STIM1 producing additional, albeit less specific, Ca^{2+} entry (Cheng et al., 2011).

STIM

STIM, or STromal Interacting Molecule, was first identified as a gene linked to certain tumors (Parker et al., 1996; Sabbioni et al., 1997) and almost simultaneously as a stromal cell derived plasma membrane protein capable of interacting with B-lymphocytes (Oritani and Kincade, 1996). Limited screens of *Drosophila* (Roos *et al.*, 2005) and mammalian (Liou *et al.*, 2005) siRNA libraries identified STIM proteins as requisite for SOCE. *Drosophila* has a single STIM, while mammalian cells express, to varying degrees, two proteins, STIM1 and STIM1. Both proteins contain Ca^{2+} binding EF hand motifs directed to the lumen of the endoplasmic reticulum. STIM1 is also expressed in the plasma membrane, but its function there remains poorly defined. In the endoplasmic reticulum, both proteins bind Ca^{2+} in the endoplasmic reticulum and lose the bound Ca^{2+} when luminal Ca^{2+} drops below a certain level. By far, much more work has been done with STIM1 (together with the Ca^{2+} channel subunit Orai1) than STIM2. Overexpression of STIM1 with Orai1 produces huge CRAC currents in response to Ca^{2+} store depletion, whether by phospholipase C-activating agonists or by the endoplasmic reticulum Ca^{2+} ATPase inhibitor, thapsigargin (Mercer et al., 2006; Peinelt et al., 2006; Soboloff et al., 2006). STIM2 on the other hand, when co-expressed with Orai1, produces constitutively active Ca^{2+} influx (Bird et al., 2009; Brandman et al., 2007; Parvez et al., 2008), consistent with one view that its function is

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largely maintenance of endoplasmic reticulum Ca^{2+} levels (Brandman *et al.*, 2007). However, there also appears to be a role for STIM2 in producing Ca^{2+} signal-dependent activation of downstream pathways as well (Kar et al., 2012; Oh-Hora et al., 2008).

At least one additional splice variant each of STIM1 and STIM2 has been identified. A longer version of STIM1, STIM1L, arises from splicing into the C-terminus of an additional 106 amino acids (Darbellay et al., 2011). The additional sequence in STIM1L contains an actin-binding domain that anchors STIM1L to the actin cytoskeleton and concentrates STIM1L at the endoplasmic reticulum-plasma membrane contact sites for rapid Orai1 activation (Darbellay *et al.*, 2011). STIM1L was found to be necessary for maintenance of intracellular stores when Ca^{2+} signaling involved brief spikes of Ca^{2+} release in myotubes, leading to the conclusion that anchoring of STIM1L resulted in faster and more efficient store refilling (Darbellay *et al.*, 2011). However, a subsequent study found that STIM1L, while somewhat pre-localized to near plasma membrane junctions, was still further recruited upon Ca^{2+} store depletion with thapsigargin (Sauc et al., 2015). STIM1L and STIM1S supported SOCE equally well and at similar speeds in a paradigm utilizing cyclopiazonic acid to slowly deplete endoplasmic reticulum stores (Sauc *et al.*, 2015). STIM1L differed from STIM1S in that the latter, but not the former, recruited and enlarged cortical endoplasmic reticulum cisternae when overexpressed (Sauc *et al.*, 2015). In comparing the rates of these two STIM1 forms in moving to the plasma membrane junctions and activating SOCE, it is worth noting that both the aforementioned studies were carried out at room temperature. An earlier publication demonstrated that at physiological temperatures, STIM1 is pre-clustered at endoplasmic reticulum junction suggesting that the apparent diffuse distribution of STIM proteins when stores are full, seen in room temperature experiments, may be artifactual (Xiao et al., 2011).

By database mining, Miederer *et al.* (Miederer et al., 2015) found a splice variant of STIM2 (STIM2.1) that contains an eight amino acid sequence inserted in the STIM-Orai Activating Region (SOAR (Yuan et al., 2009)). STIM2.1 failed to activate Orai1 in an overexpression protocol, and appears to negatively regulate SOCE. STIM2.1 expression relative to the more common STIM2 (STIM2.2) varied among tissues and cell type, indicating that it can contribute to shaping SOCE signaling.

STIM1 activity can be modified by post-translational modifications. STIM1 contains two N-linked luminal glycosylation sites, and STIM2 contains one. Mutation of the sites in STIM1 can lead to either decreased or increased SOCE, likely due to alterations in STIM1 oligomerization (Kilch et al., 2013; Miederer *et al.*, 2015; Mignen et al., 2007). A small amount of STIM1 gets to the plasma membrane where it is required for activation of non-store-operated Arachidonate-Regulated Ca^{2+} current (I_{crac} (Mignen *et al.*, 2007; Shuttleworth et al., 2007). Mutants of STIM1 that cannot be glycosylated can still activate CRAC channels, but do not go the plasma membrane and thus fail to activate ARC channels. It is not clear, however, whether alterations in the glycosylation state of STIM proteins is regulated or varies in any way *in vivo*.

STIM1 is phosphorylated *in vivo* although the specific sites are unclear (Manji et al., 2000). However, it is clear that the phosphorylation state of STIM1 and STIM2 changes during the

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cell cycle and this change in phosphorylation alters the function of STIM1 in two significant ways. It is a relatively old observation, dating prior to the discoveries of STIM and Orai, that SOCE is diminished or absent in cells undergoing mitosis (Preston et al., 1991; Volpi and Berlin, 1988). Smyth *et al.* (Smyth et al., 2009) demonstrated that STIM1 is phosphorylated on multiple sites during mitosis, and mutation or deletion of candidate sites restores SOCE in mitotic cells (Smyth et al., 2012; Smyth *et al.*, 2009).

There is an additional consequence of the phosphorylation of STIM1 during mitosis. In interphase cells, STIM1 associates with the growing tips of microtubules, through interaction with the microtubule growing tip protein, EB1 (Honnappa et al., 2009; Mimori-Kiyosue et al., 2000), and thus plays a role in remodeling of cortical endoplasmic reticulum (Honnappa *et al.*, 2009). However, mutation of a specific EB1 binding site in STIM1 had no effect on its ability to support SOCE (Honnappa *et al.*, 2009). During mitosis, the function of microtubules is dramatically altered, and microtubules rearrange and organize in the pro-nucleus to form the mitotic spindle that direct appropriate chromosomal segregation during cell division (Inoue, 1981). Phosphorylation of STIM1 prevents association with EB1, and thus with the mitotic spindle, allowing for appropriate segregation of STIM1 to the periphery during mitosis (Smyth *et al.*, 2012). Mutation of candidate phosphorylation sites results in continued association of endoplasmic reticulum with microtubules during mitosis such that endoplasmic reticulum elements can be seen to decorate the mitotic spindle (Smyth *et al.*, 2012). However, cells overexpressing this mutant form of STIM1 undergo normal cell division and the rate of cell division appears unaffected. Thus, it is not yet clear which, if either, of the underlying effects of STIM1 phosphorylation are functionally more important, the shutting down of SOCE, or the segregation of endoplasmic reticulum from the mitotic spindle. Likely more subtle experimental models, such as mutations in phosphorylation sites in model organisms may provide answers to this enigmatic question.

Orai

In mammals, there are three Orai gene products, Orai1, 2 and 3 (Feske *et al.*, 2006). By far the most is known of the functions and regulation of Orai1, null mutations of which produce severe phenotypes in humans and mice (Feske *et al.*, 2006; Vig et al., 2008). All three forms produce enhanced SOCE when co-expressed with STIM1, although quantitatively, Orai2 is much weaker than Orai1 in this regard, and Orai3 much weaker still. Mice lacking Orai1 die perinatally, likely due to poor skeletal muscle development, but can survive in less than Mendelian numbers in a mixed genetic background (Gwack et al., 2008; Vig *et al.*, 2008). T-cells from Orai1 knockout mice have only partial loss of SOCE, and compensatory increased expression of Orai2 may account for this (REF**).

Orai1 can function in other signaling pathways other than SOCE. A subfamily of the large Transient Receptor Potential (TRP) family includes 7 Canonical TRPPs, or TRPC channels. These channels are known to be activated downstream of phospholipase C coupled receptors, and can clearly be activated independently of calcium store depletion (DeHaven et al., 2009; Vazquez et al., 2004). However, as mentioned above, Orai1 can interact with TRPC channel subunits in a poorly understood manner to produce a moderately selective Ca^{2+} current termed I_{soc} (Cheng *et al.*, 2011; Cheng et al., 2008; Ong et al., 2007).

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Following Ca^{2+} store depletion, Ca^{2+} entering through CRAC channels recruits TRPC (in particular TRPC1) to the plasma membrane. There, TRPC1 interacts with STIM1 via a domain distinct from that which interacts with Orai1. However, it is unclear how prevalent this mode of signaling is *in vivo*. Mice lacking all 7 TRPC channel subunits show a significantly milder phenotype than mice lacking Orai1, and cells from these mice have apparent normal SOCE (http://grantome.com/grant/NIH/ZIA-ES101684-12).

Orai1 is also a necessary pore-forming subunit for a non-store-operated channel activated by arachidonic acid (I_{arc}) (Mignen et al., 2008)or a metabolite of arachidonic acid, leukotriene C4 (Gonzalez-Cobos et al., 2013). The Shuttleworth laboratory demonstrated that ARC channels are a pentamer of three Orai1 and two Orai3 subunits (Mignen et al., 2009). STIM1 is required for ARC channel activation; however, Ca^{2+} dissociation is unnecessary (Mignen *et al.*, 2007). Rather, a pool of STIM1 targeted to the plasma membrane is required (Mignen *et al.*, 2007). This scenario was called into question by Zhang *et al.* (Gonzalez-Cobos *et al.*, 2013; Zhang et al., 2014). These authors identified a similar current in vascular smooth muscle cells activated by arachidonic acid, but more potently by its metabolite, leukotriene C4 (I_{larc}). A comparison of the arachidonic acid and leukotriene currents in both HEK293 cells and vascular smooth muscle cells indicated that the two currents are essentially the same channels (Gonzalez-Cobos *et al.*, 2013). Interestingly, STIM1 in the plasma membrane was required for channel activation when recording currents in whole-cell mode, but with perforated patch STIM1 in the ER was sufficient (Zhang *et al.*, 2014).

In mammary glands, Orai1 appears to play a role in mediating basal flux of Ca^{2+} into milk (Feng et al., 2010; Ross et al., 2013). This Ca^{2+} flux appears to be independent of intracellular Ca^{2+} stores, does not depend on STIM1 or STIM2, but rather results from a constitutive interaction by a form of a Golgi Ca^{2+} pump, SPCA2 (Cross et al., 2013; Feng *et al.*, 2010).

Much less is known of the functions of Orai2 and Orai3 in comparison to Orai1, owing in part to less experimental work with these Orai forms. Both Orai2 and Orai3 can be activated by store-depletion when overexpressed with STIM1, but the resulting currents are substantially less than those seen with Orai1 (Lis et al., 2007; Mercer *et al.*, 2006). In the majority, knockdown or knockout seems to fully prevent SOCE (for example, (Davis et al., 2016; Davis et al., 2015; Hwang et al., 2012; Hwang and Putney, 2012; Steinckwich et al., 2015; Xing et al., 2013)). However, mast cells (Vig *et al.*, 2008) show significant but incomplete loss of SOCE in Orai1 knockout mice. T-cells are even less affected (Gwack *et al.*, 2008; Vig *et al.*, 2008), and a recent report demonstrates roles for both Orai1 and Orai2 in T-cell function (Vaeth et al., 2017). Additionally, although there have been few studies of SOCE in the central nervous, Orai2 appears to be the major Orai form in the brain (Chauvet et al., 2016). A major role for Orai3 appears to be as a pore-forming subunit of the non-store-operated ARC channels. However, Saul et al. (Saul et al., 2016) provided evidence that Orai3 can function as a subunit of SOC channels, together with Orai1, and the presence of Orai3 reduces the redox sensitivity of the channels. In addition, Motiani et al. (Motiani *et al.*, 2013) demonstrated SOCE in breast cancer cells mediated by Orai3, and also showed that estrogen receptor alpha activation led to increased expression of Orai3 and increased SOCE.

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A more detailed discussion of potential roles of Orai2 and Orai3 can be found in a review by Hoth and Niemeyer (Hoth and Niemeyer, 2013).

In humans and presumably other mammals, Orai1 protein is expressed in a long and short form termed Orai1α and Orai1β (Fukushima et al., 2012). The longer Orai1α when deglycosylated runs as a 33 kD protein, corresponding to the molecular size predicted from the coding sequence. The shorter Orai1β runs at 23 kD, and arises from alternative translation initiation at methionine 64. Deletion of the first 63 amino acids in Orai1 results in the loss of potentially important signaling domains, including a caveolin binding site (Yu et al., 2010), an adenylyl cyclase 8 binding site (Willoughby et al., 2012), a potential phosphatidylinositol 4,5-bisphosphate binding site, two potential protein kinase C phosphorylation sites (Kawasaki et al., 2010), and a recognition site for the membrane skeletal protein 4.1 (GASCARD et al., 1993) (Figure 1). Examination of the Kozak sequences at methionine 1 and 64 reveal that at methionine 1 the Kozak sequence is rather weak, while at methionine 64 it is strong. Strengthening of the Kozak sequence at methionine 1 results in formation of Orai1α exclusively indicating that the shorter Orai1β arises from skipping of the first initiation site. When overexpressed together with STIM1, the two forms appear to coalesce into puncta with STIM1 equally well, and produce similarly large CRAC currents and large SOCE (Fukushima *et al.*, 2012). However, fluorescence recovery after photobleaching (FRAP) measurements indicated that plasma membrane mobility of Orai1α was considerably slower than Orai1β. Consistent with this finding, Orai1α was shown to distribute and traffic to intracellular structures to a greater extent than did Orai1β (Fukushima *et al.*, 2012). This may result from the presence of a caveolin binding domain in the extended sequence of Orai1α (Yu et al., 2010). Interestingly, discreet segregation of Orai1α-like mobilities from Orai1β mobilities suggests that the two forms do not associate with one another to form heteromeric channels.

The cell biology and channel properties of Orai1α and Orai1β channels suggest they may subtend somewhat distinct physiological functions. (Desai et al., 2015). In experiments employing murine embryonic fibroblasts (MEFs) from Orai1-null mice (Vig *et al.*, 2008), both Orai1α and Orai1β were capable of rescuing SOCE and I_{crac}. Extensive overexpression of Orai1 produces diminished SOCE (Mercer *et al.*, 2006), presumably due to inappropriate stoichiometry, and so for these rescue experiments it was necessary to utilize constructs driven by the moderately active thymidine kinase promoter (Korzeniowski et al., 2010). The function of Orai1 forms in the TRPC-dependent current I_{soc} was assessed by transfection of HEK293 cells with TRPC1, STIM1 and wild-type Orai1, Orai1α or Orai1β. In each case, store depletion resulted in relatively non-selective inward currents, reminiscent of I_{soc}, and the currents in cells expressing the different Orai1 constructs were quantitatively and qualitatively similar (Desai *et al.*, 2015). Omission of TRPC1 resulted in inwardly rectifying I_{crac}, similar in magnitude for all three constructs, consistent with the findings in MEFs (Desai *et al.*, 2015).

Orai1-dependent CRAC currents undergo complex regulation by Ca^{2+}, including a rapid negative feedback inhibition involving Ca^{2+} action in close proximity of the mouth of the channel termed fast inactivation (Fierro and Parekh, 1999; Hoth and Penner, 1993). In

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HEK293 cells co-transfected with STIM1 and either Orai1α or Orai1β, only cells transfected with Orai1α showed fast inactivation (Desai *et al.*, 2015).

The relative ability of Orai1 forms to support the non-store-operated current, I_{arc}, was evaluated by using HEK293 cells, a line known to express endogenous I_{crac} and I_{arc}. Knockdown of Orai1 by siRNA essentially eliminated both endogenous currents. Transfection with constructs coding specifically Orai1α or Orai1β fully rescued store-operated I_{crac}. However, only Orai1α was capable of rescuing the non-store-operated I_{arc} (Desai *et al.*, 2015).

Physiological Functions of Store-operated Channels

Despite the various roles for STIM and Orai dependent channels, it is primarily the store-operated channels for which there is information regarding roles in physiological processes. For example, to the author's knowledge, no publications have appeared utilizing animal models to investigate the importance of ARC channels or SOC channels at the organ system or organism level. Animal models with TRPC channel deletions have revealed numerous physiological functions subtended by these channels, but without experimentally demonstrating that these involve the store-operated activation mode.

Mouse Models

Orai1 knockout mice die perinatally, but survive for prolonged periods in mixed genetic backgrounds (Gwack *et al.*, 2008; Vig *et al.*, 2008). As is the case for humans lacking functional Orai1, Orai1 knockout mice are deficient in multiple aspects of the immune system (Feske, 2009; Gwack *et al.*, 2008; Vig *et al.*, 2008). The mice are small in stature, which likely results from deficient muscle development (Lyfenko and Dirksen, 2008), and possibly also in deficient development of bone (Hwang *et al.*, 2012; Robinson et al., 2012). The precursor cells for both osteoclasts (bone resorbing cells) and osteoblasts (bone forming cells) have reduced SOCE, and the differentiation and functions bone are impaired, such that the mice exhibit osteopenia (decreased bone density) (Hwang *et al.*, 2012; Robinson *et al.*, 2012).

SOCE is well known to play a prominent role in the immune system (Feske et al., 2003). Much of the research in this area has involved acquired immunity despite the fact that the original discovery of I_{crac} was in mast cells (Hoth *et al.*, 1992). Mast cells from mice lacking either Orai1 (Vig *et al.*, 2008) or STIM1 (Baba et al., 2008) exhibited a deficiency in SOCE and loss of mast cell function.

Neutrophils play a major role in innate immunity (McDonald and Kubes, 2011). Neutrophils migrate to sites of infection and inflammation by sensing gradients of small molecules, a process of chemotaxis (Maxfield, 1993). The well-studied chemoattractant, fMLF, has long been known to require Ca^{2+} to function. The tripeptide fMLF activates a plasma membrane G-protein-coupled receptor that is linked to phospholipase C and the production of the Ca^{2+} releasing signal molecule, IP_3 (Dougherty et al., 1984; Jaconi et al., 1988). The Ca^{2+} requirement for chemotaxis apparently involves entry of Ca^{2+}, and that entry mechanism seems to be SOCE (Alvarez et al., 1994; Andersson et al., 1986; Demaurex et al., 1992).

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Reduction of Orai1 or STIM1 expression in HL-60 neutrophils significantly impaired Ca^{2+} signaling and chemotaxis in response to fMLF (Steinckwich *et al.*, 2015). Not surprisingly, when neutrophils become polarized in a chemoattractant gradient, it appears that SOCE signaling also distributes itself in an asymmetric manner. What is surprising is that STIM 1 seems to distribute to the rear of the cells (Putney et al., 2017).

Psoriasis is a skin disease resulting from a complex autoimmunity involving, among other components, neutrophils (Toichi et al., 2000). In mice exhibiting the symptoms of psoriasis, knockout of STIM1 increased the speed of reversal of psoriasis symptoms (Steinckwich *et al.*, 2015). Thus, SOCE might be a useful pharmacological target for treatment of psoriasis and other autoimmunity-involved disorders.

The maintenance and development of the epidermis requires calcium, and Ca^{2+} signaling controlled primarily by a calcium sensing receptor (Tu et al., 2004). An extracellular calcium gradient in some manner signals differentiation of keratinocytes to their differentiated state. In HaCaT keratinocytes, increasing extracellular Ca^{2+} induced expression of keratinocyte-associated genes, , and slowed cell growth in the process of terminal differentiation (Tu *et al.*, 2004). A calcium sensing receptor, signaling through phospholipase C, mediates this process (Hofer and Brown, 2003). Reduced expression of either Orai1 or STIM1 diminished SOCE, I_{crac} and $[Ca^{2+}]_i$ signaling in response to elevation of extracellular Ca^{2+} (Numaga-Tomita and Putney, 2013).

1. Exocrine Glands

SOCE has been investigated with Orai1 knockout mice in two different exocrine glands, mammary glands and lacrimal glands. Calcium signaling is essential for mammalian oocyte fertilization in mammals (Miao and Williams, 2012; Miyazaki et al., 1993; Swann and Yu, 2008). Intracellular IP_3 is generated through the action of sperm-delivered phospholipase C zeta, resulting periodic intracellular Ca^{2+} oscillations (Kashir et al., 2017). There is evidence implicating a role for Orai1 and SOCE as playing a role in mammalian oocyte fertilization (Gómez-Fernández et al., 2012). But surprisingly, female Orai1 knockout female mice are fertile, and with normal size litters. However, pups are small and survive only about four days, unless transferred to a wild type for fostering (Davis *et al.*, 2015). The indication then is a failure of adequate lactation. Mammary glands secrete milk by a mechanism that differs from most other exocrine glands. At or around birth, hormones stimulate constitutive secretion of milk calcium and nutrients into alveoli. Through a mechanism involving oxytocin receptors, suckling stimulates contraction of alveolar basket myoepithelial cells (Crowley and Armstrong, 1992; Shennan and Peaker, 2000). Milk from Orai1 knockout females had a Ca^{2+} concentration of only about 50% of controls (Davis *et al.*, 2015). Thus an additional function of Orai1 involves transporting Ca^{2+} into alveoli (Feng *et al.*, 2010). However, this decrease in milk Ca^{2+} is unlikely to account for the observed phenotype. Engorged mammary glands of Orai1 knockouts suggested that constitutive milk formation was normal but discharge of milk was inhibited. In support of this interpretation, Ca^{2+} oscillations induced by oxytocin in myoepithelial cells were reduced substantially in Orai1 knockout mice. When alveolar contractions were examined microscopically, the alveolar contractions due to oxytocin were also substantially diminished (Davis *et al.*, 2015). Thus,

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lactation in Orai1 knockout female mice likely fails due to a loss of Ca^{2+} entry in myoepithelial cells.

The original concept of SOCE emerged from Ca^{2+} signaling studies in exocrine glands, both parotid gland and lacrimal acinar cells (Putney and Bird, 2014; Putney et al., 1998; Takemura et al., 1989; Takemura and Putney, 1989). lacrimal gland acinar cells from Orai1 knockout mice do not show SOCE in response to muscarinic receptor activation or to the Ca^{2+} pump inhibitor, thapsigargin, and exhibit no detectable I_{crac} (Xing *et al.*, 2013). Lacrimal secretion activated by pilocarpine *in vivo* was significantly reduced in knockout animals. Histological analysis of the lacrimal glands revealed that development and structure of the glands were normal. Secretion of peroxidase from wild-type lacrimal gland fragments was increased in response to the muscarinic agonist, methacholine, in the presence of Ca^{2+} and to a lesser degree in when Ca^{2+} was absent. When fragments from Orai1 knockout mice were utilized, peroxidase secretion in the presence of Ca^{2+} was decreased to that in the absence of Ca^{2+}. However, secretion in the absence of extracellular Ca^{2+}, resulting from IP_3-induced Ca^{2+} release, as well as constitutive secretion, were unaffected in the cells from knockout mice (Xing *et al.*, 2013). This illustrates how highly specific is the role of Orai1 in signaling calcium entry. Lacrimal glands of Orai1 mice lacking Orai1 also lack SOCE, I_{crac}, and the component of exocytotic secretion that depends on external Ca^{2+}. However, the morphology and size, as well asCa^{2+}-independent secretion remain unaffected. Thus, the basic mechanism of storage and synthesis and storage of secretory granules product, as well as the mechanism of Ca^{2+}-dependent exocytosis, and signaling through the IP_3 and release of intracellular Ca^{2+} are quantitatively unchanged.

2. Conclusions

This review focused on distinct forms of the major molecular players in store-operated Ca^{2+} entry, STIM1 and Orai1. A graphic summary of the mechanisms of action of these key molecules is shown in Figure 2. To better understand the physiological functions of these key molecules, mouse models lacking a specific molecule in the store-operated Ca^{2+} entry pathway have been developed. To illustrate the utility of such models, this review has discussed some key findings from such mouse models, providing new insights into the roles of SOCE in mammalian physiology. Hopefully such an approach will eventually allow modulation of this pathway to ameliorate any of the number of diseases known to result from aberrant Ca^{2+} signaling (Missiaen *et al.*, 2000; Mooren *et al.*, 1998; Targos et al., 2005).

Supplementary Material

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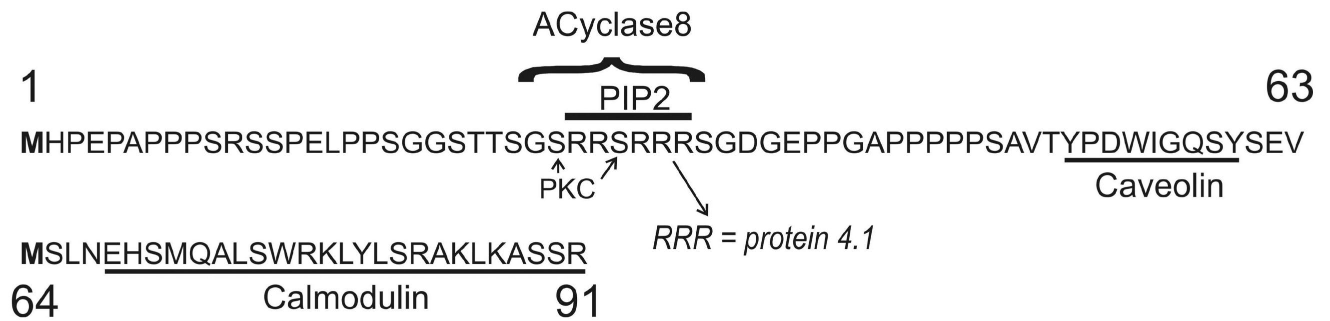

Figure 1. N-terminal sequence of Orai1

Two methionines in the N-terminus can serve as initiation sites, at position 1 and position 64, resulting in two forms of Orai1. Potential sequences in the longer version include a caveolin binding site (Yu *et al.*, 2010), an adenylyl cyclase 8 binding site (Willoughby *et al.*, 2012), a potential phosphatidylinositol 4,5-bisphosphate binding site, two potential protein kinase C phosphorylation sites (Kawasaki *et al.*, 2010), and a recognition site for the membrane skeletal protein 4.1 (GASCARD *et al.*, 1993).

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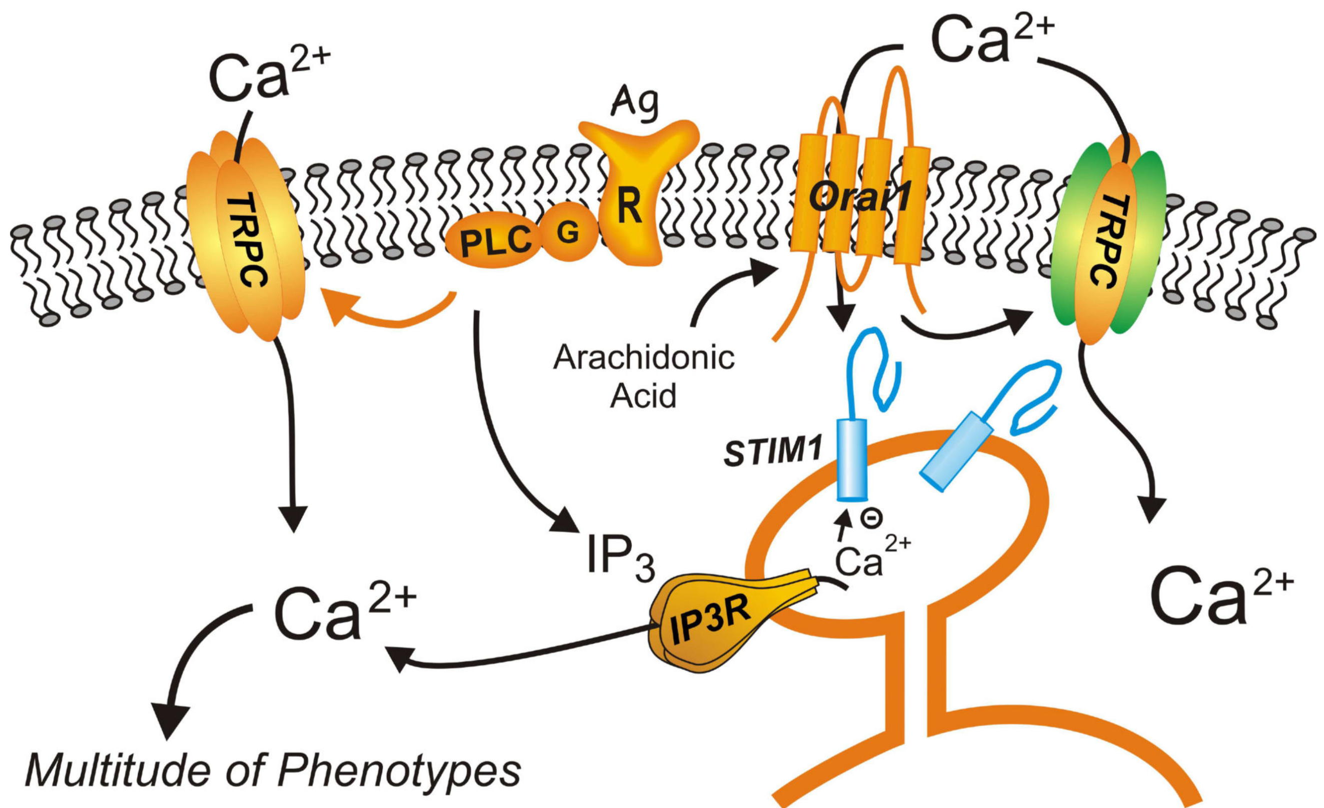

Figure 2. Actions of the key SOCE mediators, STIM1 and Orai1

Signaling is generally initiated by agonist (Ag) acting through a receptor (R) and G-protein (G) to activate phospholipase C (PLC) and produce the Ca^{2+}-mobilizing messenger, inositol 1,4,5-trisphosphate (IP_3). IP_3 in turn activates the IP_3 receptor (IP3R) in the endoplasmic reticulum. The fall in Ca^{2+} in the endoplasmic reticulum activates STIM1 to aggregate and migrate to specific sites near the plasma membrane where Orai1 channels are activated resulting in SOCE. Channels composed of Orai1 and Orai3 (not shown) subunits can also be activated in a non-store-operated mode by arachidonic acid or a metabolite, leukotriene C4. Calcium entering through Orai1 channels can recruit and together with STIM1 activated certain members of the TRPC cation channel family. Some members of the TRPC cation family can also be activated more directly by products of phospholipase C. Calcium entering the cytoplasm through all of these routes regulates and activates a myriad of cell responses, some of which were discussed in the current review.