Published in final edited form as:

Microcirculation. 2013 May ; 20(4): 330–336. doi:10.1111/micc.12042.

What Role for Store-Operated Ca^{2+} Entry in Muscle?

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Abstract

Store-operated Ca^{2+} entry (SOCE) is a receptor-regulated Ca^{2+} entry pathway that is both ubiquitous and evolutionarily conserved. SOCE is activated by depletion of intracellular Ca^{2+} stores through receptor-mediated production of inositol 1,4,5-trisphosphate (IP_3). The depletion of endoplasmic reticulum (ER) Ca^{2+} is sensed by stromal interaction molecule 1 (STIM1). On store depletion, STIM1 aggregates and moves to areas where the ER comes close to the plasma membrane (PM; within 25nm) to interact with Orai1 channels and activate Ca^{2+} entry. Ca^{2+} entry through store-operated Ca^{2+} (SOC) channels, originally thought to mediate the replenishment of Ca^{2+} stores, participate in active downstream signaling by coupling to the activation of enzymes and transcription factors that control a wide variety of long-term cell functions such as proliferation, growth and migration. SOCE has also been proposed to contribute to short-term cellular responses such as muscle contractility. While there are significant STIM1/Orai1 protein levels and SOCE activity in adult skeletal muscle, the precise role of SOCE in skeletal muscle contractility is not clear. The dependence on SOCE during cardiac and smooth muscle contractility is even less certain. Here, we will hypothesize on the contribution of SOCE in muscle and its potential role in contractility and signaling.

From the Oxford English Dictionary

hy·poth·e·sis

noun \h - 'pä-thə-səs\

A proposition or principle put forth or stated (without any reference to its correspondence with fact) merely as a basis for reasoning or argument, or as a premiss from which to draw a conclusion; a supposition.

Introduction

Store-operated Ca^{2+} entry (SOCE) is a ubiquitous receptor-regulated Ca^{2+} entry route that has been long appreciated for its prominence in non-excitable cells(38, 39). Ligation of a variety of phospholipase C (PLC)-coupled receptors leads to the hydrolysis of phosphatidylinositol4,5-bisphosphate (PIP_2) into two second messengers, diacylglycerol (DAG) and inositol1,4,5-trisphosphate (IP_3)(4). Intracellular activation of IP_3 receptors by IP_3 efficiently mobilizes Ca^{2+} from the endoplasmic reticulum (ER) intracellular Ca^{2+} stores resulting in Ca^{2+} store depletion. The depletion of ER Ca^{2+} is sensed by stromal interaction molecule 1 (STIM1) which results in STIM1 aggregation and movement to areas where the

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ER comes close to the plasma membrane (PM; within 25nm) to physically interact with Orai1 channels to activate Ca^{2+} entry(18) (Fig. 1).

STIM1 and Orai1 recapitulate the archetypical SOC current termed Ca^{2+} release-activated Ca^{2+} (CRAC) channel first identified in mast cells(19). A number of earlier studies suggested that canonical transient receptor potential channels (TRPC) were candidates for SOC channels based mainly on the ability of ectopically expressed TRPC channels to mediate ion conductances downstream of PLC-coupled receptor activation (Fig. 1). The involvement of TRPC in the SOCE pathway remains, to this day, a highly contentious and unresolved issue. However, there is not a single instance where a TRPC channel has been able to recapitulate the biophysical properties of CRAC. This topic has been discussed thoroughly elsewhere(18, 37, 46, 51).

Ca^{2+} entry through SOC channels was originally thought to mediate replenishment of ER Ca^{2+} stores. However, it is now clear that SOCE participate in active downstream signaling by coupling to the activation of enzymes and transcription factors that control a wide variety of long-term cell functions such as proliferation, growth and migration. While in non-excitabile cells SOCE and its long term physiological outcomes have been relatively easier to pinpoint, the precise role of STIM1/Orai1-mediated SOCE in muscle contractility is not clear. Here, we will take advantage of the knowledge accumulated on the SOCE mechanism in three independent muscle types to hypothesize on the contribution of SOCE to muscle function and its potential role in contractility and signaling.

SOCE in Skeletal Muscle

During excitation-contraction (EC) coupling of fast-twitch skeletal muscle, the voltage-activated L-type Ca^{2+} channel isoform Cav1.1 senses voltage and induces opening of ryanodine receptor (RyR) Ca^{2+} release channels in the terminal cisternae of the sarcoplasmic reticulum (SR). Compared to smooth or cardiac muscle, skeletal muscle fibers are unique such that their contractility does not cease when extracellular calcium is chelated with EGTA(40). In fact, Ca^{2+} currents through voltage-gated L-type Ca^{2+} channels accounts for less than 5% of the intracellular Ca^{2+} transients(40), and the kinetics of activation of L-type Ca^{2+} channels, in the order of ~50-100 ms, are too slow to effectively contribute any significant Ca^{2+} entry during a fast-twitch skeletal muscle action potential (lasting 2-5 ms; (10)). Unlike cardiac and smooth muscle, the bulk of Ca^{2+} required for skeletal muscle contractility comes from the SR, reflecting the physiological requirement for fast kinetics of EC coupling during skeletal muscle fiber contraction compared to the monotonous or tonic contractilities of cardiac or smooth muscle. Skeletal muscle fibers display SOC activity upon depletion of internal Ca^{2+} stores(23), and more recent data demonstrated that SOC activity in skeletal muscle fibers is mediated through the interaction between STIM1 and Orai1(28). SOCE in skeletal muscle has different properties than in non-excitabile cells. In non-excitabile cells, SOC activation develops slowly and requires tens of seconds for full activation. In skeletal muscle however, SOC is activated much more rapidly, within a second(25). The fast kinetics of SOC in skeletal muscle are likely due to: i) pre-aggregated STIM1 molecules that are pre-coupled to Orai1 channels in the absence of store depletion(10); and ii) an alternatively spliced longer version of STIM1 found predominantly in skeletal muscle, STIM1L that shows association with actin(8).

What is the role of SOCE in skeletal muscle contractility? In addition to the fact that SOCE is inhibited by PM depolarization, the enhanced kinetics of SOC in skeletal muscle remain too slow (even slower than L-type Ca^{2+} channels) to account for any significant contribution of Ca^{2+} entry through SOCE to skeletal muscle twitch contraction *per se*, during a brief action potential. One might think then that SOCE function in skeletal muscle with its

relatively faster kinetics could be required for SR Ca^{2+} refilling during repolarization cycles, to complement Ca^{2+} recycling to the SR by the sarcoplasmic/endoplasmic reticulum Ca^{2+} -ATPase (SERCA) and keep up with SR Ca^{2+} release. However, as was discussed in great detail earlier, direct contribution of SOCE to cytoplasmic Ca^{2+} and the contractile apparatus during contraction as well as its indirect contribution through SR refilling in active fast-twitch muscle appears minimal at best(24). SOCE has emerged as a PM-associated signaling mechanism in non-excitable cells as recent experiments suggest that SOCE-mediated Ca^{2+} signals are spatially encoded within the Ca^{2+} influx site at the plasma membrane(33). A similar and perhaps more specialized signaling function for SOCE in skeletal muscle can be envisioned especially that STIM1 and Orai1 are pre-coupled in skeletal muscle and appear uniformly distributed along the junctional membranes. A modulatory role of SOCE on RyR function during skeletal muscle contractility has been suggested(24). One can envision the role of SOCE expanding to the activation of transcription programs to support the mid- and long-term adaptive changes to the muscle during extended periods of activity. Another possibility could be that SOCE provides the necessary Ca^{2+} to maintain mitochondrial Ca^{2+} homeostasis necessary for sustained ATP production during extended periods of muscle activity. Indeed, mitochondria takes up cytoplasmic Ca^{2+} both indirectly by buffering Ca^{2+} released from the endoplasmic reticulum through IP_3 receptors, and directly by buffering Ca^{2+} that enters through SOCE, thus reducing Ca^{2+} -dependent slow inactivation of SOC channels(2, 35). While the precise role of SOC in skeletal muscle contractility remains elusive, the subtle differences in SOC mechanism of activation in skeletal muscle compared to non-excitable cells are consistent with a signaling role of SOC during long-term contractility which could explain the skeletal muscle hypotonia and weakness that are characteristics of STIM1- and Orai1-deficient patients and mice(12, 13). One universal observation in all instances of STIM and Orai knockout or knockdown in various cell types is the lack of any effect on ER Ca^{2+} stores, arguing that other Ca^{2+} entry routes can fulfill the function of store refilling, and that perhaps all Ca^{2+} entry routes contribute to store refilling. Indeed, previous data in non-excitable cells showed that when SOC channels are blocked, an artificially introduced store-independent Ca^{2+} entry channel (TRPC3) equally fulfills the task of store repletion(5). Therefore, the primary function of SOCE in all cell types, including muscle, is likely active PM-associated cell signaling. Furthermore, as argued earlier(44), STIM and Orai functions in skeletal muscle -and other cell types- do not have to be exclusively associated with store depletion and/or EC-coupling as Orai channels can encode store-independent Ca^{2+} channels activated by second messengers and STIM1 regulates an increasing and additional number of channels and pumps.

SOCE in Cardiac and Smooth Muscle

What about cardiac muscle and smooth muscle, is there a role for SOCE in contractility? The relatively larger contribution of L-type Ca^{2+} channels to Ca^{2+} entry during contractility and the lower expression of STIM1 and Orai1 in these cell types argue for a minimal role for SOCE in contractile cardiac and smooth muscle. STIM1- and Orai1-deficient patients and mice do not show any obvious cardiac or smooth muscle-related phenotypes consistent with the idea that the SOCE pathway is more prominent or necessary during skeletal muscle development and/or contractility under normal physiological conditions. In fact, skeletal muscle expresses higher levels of STIM1 and Orai1 than cardiac muscle(22, 47). Adult cardiomyocytes and contractile smooth muscle express low levels of STIM1 and Orai1(3, 6, 27, 36). SOC activity is prominent in neonatal cardiomyocytes and is undetected in adult cardiomyocytes(27). An independent study previously reported minimal SOCE activity in adult cardiomyocytes(21). It is tempting to hypothesize that in contractile cardiac and smooth muscle, where the contribution of extracellular influx through voltage-gated L-type Ca^{2+} channels is substantial, L-type Ca^{2+} channels might contribute to long-term signaling, supporting increased energy demands and the adaptive changes required for long-term

contractility. In contrast, STIM1/Orai1 signaling complexes would have a somewhat smaller contribution. However, as discussed elsewhere(45), STIM1/Orai1 would gain prominence as their expression increases during the physiological and pathological processes of remodeling.

It is quite possible that STIM1/Orai1-mediated SOC are more relevant in cardiomyocytes during extreme physical activity that requires enhanced cardiac output and/or during “fight or flight” responses. A cardiac or smooth muscle phenotypes in STIM1- and Orai1-deficient mice and patients might become apparent with long-term processes such as aging, stressful stimuli or enduring exercise; though, neither patients nor mice lacking STIM1/Orai1 live long enough to know for sure. Mammalian cardiac muscle was shown to express some level of STIM1L (8, 27) but the potential pre-coupling between STIM1 and Orai1 in primary cardiomyocytes has not been reported. Luo et al further showed that neonatal hearts express significant amounts of STIM1 and STIM1L, which decrease with cardiomyocyte maturation(27). Consistent with the idea of a prominent role of STIM1 in cardiomyocytes under stressful situations, the same authors showed that STIM1L expression in mature cardiomyocytes reappear with agonist- or afterload-induced cardiac stress(27). One alternative possibility that could explain the lack of a prominent role of STIM1 in adult cardiomyocytes and contractile smooth muscle basal physiological contractility would be that STIM2 and Orai2/3 contribute to signaling and thus compensate for STIM1 and Orai1 in STIM1- and Orai1-deficient patients and mice. In our view, this is a less likely possibility since there is not one instance of STIM1 or Orai1 knockdown or knockout where other endogenous STIM/Orai isoforms were fully capable of functionally replacing the altered protein, suggesting lack of redundancy of these molecules. One recent report showed that Orai1-deficient zebrafish are prone to severe heart failure, have reduced ventricular systolic function and bradycardia, in addition to the typical skeletal muscle weakness that was previously described in mammals(49). Electron micrographs of skeletal and cardiac muscle from Orai1-deficient zebrafish showed abnormal organization of z-discs. This phenotype in Orai1-deficient zebrafish hearts suggests a requirement for Orai1 in zebrafish muscle development. Such a developmental requirement is perhaps partially or fully fulfilled in mammalian hearts by the exclusively mammalian gene, Orai3 (that apparently arose from Orai1 rather than Orai2;(7)) or a channel contributed by Orai3 such as Arachidonate-regulated Ca^{2+} (ARC) channels(41, 42).

Smooth muscle structure and contractility are quite distinct from skeletal and cardiac muscles. For example, a major smooth muscle type, vascular smooth muscle displays basal level of tonic contractility that can be further increased upon stimulation of membrane receptors by neuronal, humoral, and endothelial factors. This receptor-mediated increase in contractility develops somewhat slowly and can be sustained over extended periods of time. Similar to the heart, the bulk of Ca^{2+} entry during EC-coupling in smooth muscle comes through L-type Ca^{2+} channels. Protein levels of STIM1 and Orai1 (and Orai2/3) in contractile vascular smooth muscle cells are very low compared to hematopoietic cells (3, 6, 36). Furthermore, SOCE activity is essentially absent in contractile smooth muscle cells (36, 50). Collectively, these data argue for a minor role, if any, for SOCE in smooth muscle contractility.

Taking into account the physiological function of skeletal, cardiac and smooth muscle, it is tempting to propose that the SOCE pathway would be more important in supporting long-term contractility in fast-twitch skeletal muscle where uniform expression and co-localization of STIM1 and Orai1 at the junctional membranes would support active membrane delimited signaling to assist in long-term muscle work. In cardiac and smooth muscle, this function would be mainly supported by L-type Ca^{2+} channels. Consistent with this idea, STIM1-deficient patients show atrophy of type II skeletal fibers (fast-twitch)(30).

Skeletal muscle with larger proportion of slow-twitch fibers such as the diaphragm and soleus that express the cardiac isoform of L-type Ca^{2+} channels (Cav1.2) (15, 34) and have enhanced sarcolemmal permeability to Ca^{2+} compared to fast-twitch muscle(14), might thus display a minor requirement for SOCE similar to that of cardiac or smooth muscle.

STIM1/Orai1 Channels in Muscle Remodeling

Consistent with a role for SOC in cell signaling as opposed to solely store repletion, there is evidence that STIM1/Orai1 signaling is required during development and, as we argued elsewhere(45), could gain prominence during the processes of physiological or pathological muscle remodeling. For instance, during smooth muscle remodeling, the activation of the STIM/Orai signaling units upon membrane receptor ligation, either through store depletion or store-independent mechanisms, would activate transcription programs that would support physiological and pathological phenotypic modulation of smooth muscle in response to environmental cues, increasing demands or injury. It is now clearly established that SOCE is essential for driving nuclear translocation and activity of Nuclear Factor for Activated T cells (NFAT) in muscle and non-excitable cells such as hematopoietic cells(17, 43, 52). As will be discussed below, we propose that all major types of muscle involve STIM1/Orai1-dependent SOCE and -likely- store-independent pathways in signaling supporting long-term processes such as development, growth, proliferation and remodeling.

Skeletal Muscle

The importance of STIM1 in skeletal muscle development is highlighted by the fact that most STIM1-deficient mice die perinatally(31, 43). STIM1 and Orai1-mediated SOC channel activity is critical for human myoblast differentiation(9). STIM1 is required for NFAT activation in skeletal muscle and STIM1-deficient mice show impaired skeletal muscle differentiation(43), suggesting that STIM1-dependent signaling is required for the activation of gene programs that control long-term skeletal muscle functions such as differentiation and remodeling. Upregulation of STIM1, Orai1 and SOCE activity is observed during differentiation of C2C12 myoblasts into myotubes(22, 43). Impairment of Ca^{2+} signaling in muscle pathologies has been described; SOCE activity is enhanced in Duchenne muscular dystrophy and skeletal muscle fibers from *mdx* dystrophic mice show altered SOCE function and upregulation of STIM1/Orai1 protein levels(11, 22). Therefore, it appears that a certain physiological level of STIM1/Orai1-mediated SOCE activity in skeletal muscle is required for differentiation and development while further increase in SOCE activity might contribute to skeletal muscle dystrophy. Using conditional skeletal muscle STIM1^{-/-} knockout mice, data by Li et al supports a role for STIM1-mediated Ca^{2+} signaling in skeletal muscle hypertrophic growth(26). Although still unexplored, it is possible that strength training and the ensuing adaptive physiological muscle hypertrophy might be characterized by a reversible modulation of STIM1/Orai1 protein levels and SOCE activity.

Cardiac Muscle

Rat neonatal cardiomyocytes in culture were shown to express STIM1 while STIM1 knockdown inhibited SOCE activity and hypertrophic response in this cell culture model(32). Subsequent studies showed that Orai1 and STIM1 fulfill the role of SOC channels upon Ca^{2+} store depletion in rat neonatal cardiomyocytes (21, 48). A surprising finding was that STIM1 knockdown reduced diastolic Ca^{2+} levels and caffeine-mediated Ca^{2+} release from the SR while Orai1 knockdown did not(48). However, both Orai1 and STIM1 knockdown inhibited basal ERK1/2 and calmodulin kinase II (CamKII) activation. This suggests that while STIM1/Orai1-mediated Ca^{2+} entry controls the activation of some downstream signaling pathways, some contribution of STIM1 to SR refilling exists at least

in neonatal cardiomyocytes and may occur through Orai1-independent mechanisms. Using the phenylephrine (PE)-induced hypertrophy of neonatal rat cardiomyocytes, Voelkers et al showed that both Orai1 and STIM1 knockdown inhibited cardiomyocyte growth and increased expression of natriuretic factor through inhibition of GPCR-mediated activation of CamKII and ERK1/2 (48). Importantly, SOCE activity is absent in adult cardiomyocytes but was significantly enhanced (along with STIM1 expression) upon exposure to pathological stress(21, 27). Hulot et al demonstrated upregulation of STIM1 and enhanced SOCE activity in adult rat cardiomyocytes that developed compensated cardiac hypertrophy after abdominal aortic banding. Using patch clamp electrophysiology, these authors reported STIM1-dependent plasma membrane currents in hypertrophic cardiomyocytes; these currents were evident under basal conditions in the absence of store depletion. Significantly, *in vivo* STIM1 knockdown by adeno-associated viruses-mediated gene transfer protected rats from pressure overload-induced cardiac hypertrophy (21). These results were confirmed by a subsequent study from Luo et al that further showed STIM1 contributes to agonist-induced hypertrophy through activation of the calcineurin-NFAT pathway(27).

Smooth Muscle

The evidence for a role for STIM1/Orai1-mediated SOCE in smooth muscle phenotypic modulation has been recently reviewed (45) and will be only briefly discussed here. Proliferative migratory smooth muscle cells show increased STIM1/Orai1 protein expression and display robust SOCE by comparison to contractile smooth muscle. STIM1 and Orai1 are required for increased NFAT nuclear translocation and activity in response to store depletion and proliferative migratory agonists such as the platelet-derived growth factor (PDGF)(29, 52). STIM1 and Orai1 are also upregulated in response to *in vivo* vessel injury in medial and neointimal smooth muscle. Prevention of this upregulation using *in vivo* transduction of shRNA inhibits smooth muscle remodeling and neointima formation(1, 16, 52). Furthermore, recent data show that smooth muscle-specific STIM1 knockout mice are resistant to smooth muscle remodeling upon vascular injury (29).

Conclusions

Here we hypothesized that SOCE in muscle (and non-muscle cells) is involved in active spatial signaling at the PM to support a variety of mid- and long-term cell functions. Unlike the situation in contractile smooth muscle and cardiomyocytes, STIM1 and Orai1 are prominently expressed and SOCE appears functional in skeletal muscle. However, SOCE contribution to cytoplasmic Ca^{2+} or SR refilling during skeletal muscle contractility does not appear to be significant (24). The expression of STIM1/Orai1, their pre-coupling and distribution in the junctional membranes and the specialized nature of SOCE in skeletal muscle argue for a role in signaling to support long-term contractility and adaptation to increasing muscle work. This function might potentially be fulfilled in contractile smooth muscle and cardiomyocytes by Ca^{2+} entry through L-type Ca^{2+} channels. We also argued that in smooth muscle and heart, STIM1/Orai1 and SOCE might be “turned on” during physiological or pathological muscle remodeling such as during cardiac hypertrophy or when vascular smooth muscle switch to a proliferative and migratory phenotype. As argued earlier, proliferative migratory smooth muscle ion channel profile is more reminiscent of non-excitable cells(20). In fact, as is the case in non-excitable cells, STIM1/Orai1 signaling in this dedifferentiated smooth muscle phenotype supports proliferation and migration(45). SOCE is known to contribute to mitochondrial Ca^{2+} homeostasis and to couple to a number of downstream signaling pathways and transcription factors including *c-fos* and NFAT(12, 17, 33). As research continues in this field, depending on the cell type and the physiological function or pathophysiological situation considered, we might discover different signaling pathways activated by either SOCE or by specific STIM/Orai isoforms through SOCE-

independent mechanisms. This will likely bring us closer to a better understanding of the role these proteins during normal cell functions and their changing expression, regulation and role in the processes of remodeling, aging and disease.

Acknowledgments

Work in our laboratory is supported by grant HL097111 from NHLBI/NIH.

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Figure 1. Store-operated Ca^{2+} entry (SOCE) pathway. 1)

Binding of a variety of physiological agonists to their specific Phospholipase C (PLC)-coupled receptors triggers the generation of the second messengers, inositol1,4,5-trisphosphate (IP_3) and diacylglycerol (DAG). **2)** Diffusible IP_3 binds to the IP_3 receptors in the membrane of the endoplasmic reticulum (ER) to cause Ca^{2+} release and subsequent store depletion. **3)** Ca^{2+} store depletion is then sensed by the ER-resident STIM1 proteins. **4)** Dissociation of Ca^{2+} from STIM1 results in STIM1 oligomerization into punctate structures and translocation to junctional ER regions of close apposition with the plasma membrane (PM). **5)** Physical interactions between the C-terminus of STIM1 and C- and N-termini of Orai1 results in CRAC channel opening and increased Ca^{2+} entry. TRPC channels were also proposed to act as SOC channels regulated by electrostatic interactions with STIM1(51).