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Role of STIM1/ORAI1-mediated Store-Operated Ca^{2+} Entry in Skeletal Muscle Physiology and Disease

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Abstract

Store-operated Ca^{2+} entry (SOCE) is a Ca^{2+} entry mechanism activated by depletion of intracellular Ca^{2+} stores. In skeletal muscle, SOCE is mediated by an interaction between stromal-interacting molecule-1 (STIM1), the Ca^{2+} sensor of the sarcoplasmic reticulum, and ORAI1, the Ca^{2+}-release-activated-Ca^{2+} (CRAC) channel located in the transverse tubule membrane. This review focuses on the molecular mechanisms and physiological role of SOCE in skeletal muscle, as well as how alterations in STIM1/ORAI1-mediated SOCE contribute to muscle disease. Recent evidence indicates that SOCE plays an important role in both muscle development/growth and fatigue. The importance of SOCE in muscle is further underscored by the discovery that loss- and gain-offunction mutations in STIM1 and ORAI1 result in an eclectic array of disorders with clinical myopathy as central defining component. Despite differences in clinical phenotype, all STIM1/ORAI1 gain-of-function mutations-linked myopathies are characterized by the abnormal accumulation of intracellular membranes, known as tubular aggregates. Finally, dysfunctional STIM1/ORAI1-mediated SOCE also contributes to the pathogenesis of muscular dystrophy, malignant hyperthermia, and sarcopenia. The picture to emerge is that tight regulation of STIM1/ORAI1-dependent Ca^{2+} signaling is critical for optimal skeletal muscle development/function such that either aberrant increases or decreases in SOCE activity result in muscle dysfunction.

Keywords

Ca^{2+} signaling; Ca^{2+}-release-activated-Ca^{2+} (CRAC); muscle fatigue; tubular aggregate myopathy (TAM)

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1. Physiological Role of STIM1/ORAI1 Store-operated Ca^{2+} Entry in Skeletal Muscle.

Calcium (Ca^{2+}) is a ubiquitous second messenger that controls a plethora of cellular functions including proliferation, differentiation, apoptosis, exocytosis, neurotransmitter release, and muscle contraction. Ca^{2+} signaling occurs when cytoplasmic levels, kept at very low concentrations under resting conditions (~10^{-7} M), rise upon either the release of Ca^{2+} from intracellular stores and/or entry of Ca^{2+} into the cell from the extracellular space. Store-operated Ca^{2+} entry (SOCE), first discovered in salivary gland cells by James Putney in 1986 [1] and referred to as "capacitative Ca^{2+} entry," is one of the most important pathways for extracellular Ca^{2+} influx in non-excitable cells. After its initial discovery, SOCE in mast cells was shown to be mediated by Ca^{2+} release-activated calcium (CRAC) channels [2]. However, identification of the molecular components that coordinate SOCE remained elusive for two decades until it was shown that stromal-interacting molecule 1 (STIM1) was the Ca^{2+} sensor in the endoplasmic reticulum (ER) membrane [3] and ORAI1 [4] was the Ca^{2+}-permeable CRAC channel in the plasma membrane (Figure 1). The mechanism for SOCE activation was subsequently elucidated by a series of elegant studies conducted primarily in non-excitable cells [5]. Specifically, agonist-mediated Ca^{2+} release through activation of inositol-1,4,5trisphosphate receptor channels, sufficient to deplete ER Ca^{2+} stores, results in Ca^{2+} dissociation from luminal STIM1 N-terminal EF-hand domains. Subsequent global conformational changes in STIM1 promotes oligomerization of STIM1 proteins that then interact and activate highly, Ca^{2+}-selective ORAI1 channels localized in discrete junctional regions (~8–10 nm), or puncta, between the ER and plasma membrane [6]. While Ca^{2+} entry through activated ORAI1 channels is used to replenish ER Ca^{2+} stores, it is now clear that SOCE plays an important role in a wide range of Ca^{2+}dependent physiological functions including gene transcription, neurotransmitter release, and muscle contraction. Moreover, alterations in SOCE activity result in loss of fine control of Ca^{2+}-mediated processes that lead to pathological conditions including immunodeficiency and myopathy. In this section, we discuss the molecular mechanism and physiological role of SOCE in skeletal muscle.

1.1. Control of Ca^{2+} Signaling in Skeletal Muscle.

The primary function of skeletal muscle is to generate force for movement. Muscle contraction and relaxation are regulated by rapid (millisecond time frame) changes in myoplasmic free Ca^{2+} concentration. To produce a rapid increase in myoplasmic Ca^{2+} levels, muscle fibers utilize a highly-organized sarcotubular membrane apparatus termed the Ca^{2+} release unit (CRU) or "triad," which is composed of a transverse tubule (TT), a specialized invagination of the sarcolemma that runs transversally to the long axis of the muscle fiber, flanked by two terminal cisternae of the sarcoplasmic reticulum (SR). The SR and TT membranes of the CRU are closely opposed (~12–15 nm), thus providing the structural framework for excitation-contraction (EC) coupling, the process whereby an action potential in the TT is used to trigger Ca^{2+} release from the SR used to drive muscle contraction. At the molecular level, EC coupling in skeletal muscle is mediated by mechanical coupling between the dihydropyridine receptor (DHPR), the voltage sensor in the TT membrane, and ryanodine receptor type 1 (RYR1) Ca^{2+} release channel in the SR

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terminal cisternae [7]. Several other junctional proteins, including calsequestrin type 1 (CASQ1), triadin, junctin, JP-45, Stac3, and FK-506 binding protein 12 interact with the DHPR-RYR1 macromolecular machinery to influence Ca^{2+} release during EC coupling [8–10]. As one example, CASQ1, a highly acidic protein in the lumen of SR terminal cisternae that binds Ca^{2+} with moderate affinity, but high capacity [11–13], functions both as a luminal Ca^{2+} buffer and a regulator of RYR1 Ca^{2+} release channel activity [14, 15]. The SR also contains a high-level of sarco/endoplasmic reticulum Ca^{2+} ATPase-1 pumps that efficiently transport Ca^{2+} released during EC coupling back into the SR to terminate contraction and refill SR Ca^{2+} stores. The combination of both high capacity SR Ca^{2+} buffer (CASQ1) and robust Ca^{2+} reuptake makes it difficult to fully deplete SR Ca^{2+} stores in adult skeletal muscle fibers. As a result, a single twitch contraction results in only ~10% reduction of the releasable SR Ca^{2+} pool [16]; enabling twitch contractions to continue for long periods of time following complete removal of extracellular Ca^{2+} [17]. For many years it was believed that Ca^{2+} entry had no role in skeletal muscle. However, $^{45}Ca^{2+}$ tracer studies revealed that significant Ca^{2+} uptake from the extracellular space occurs during 40 Hz stimulation of intact muscles, in a manner that is not prevented by inhibitors of voltage-gated L-type Ca^{2+} channels [18]. In addition, muscle performance is reduced and muscle fiber types are altered in mouse models that reduce SOCE in skeletal muscle [19, 20]. Muscle specific force is also reduced during repetitive, high-frequency *ex vivo* stimulation under conditions that inhibit SOCE, particularly following acute exercise [21]. Finally, mutations in the STIM1 and ORAI1 genes result in human disorders that include a range of muscle phenotypes such as hypotonia, atrophy, and tubular aggregate myopathy (see Section 2.0). The following sections focus on recent advances in elucidating the molecular determinants, properties and physiological role of SOCE in muscle.

1.2 SOCE in Skeletal Muscle

Activation of a Ca^{2+} entry pathway in muscle by depletion of SR Ca^{2+} stores was first demonstrated in myotubes in 1996 by Steinhardt and colleagues [22]. Kurebayashi and Ogawa reported a similar process in adult muscle fibers five years later [23]. These findings motivated subsequent studies to identify the molecular determinants and physiological role of SOCE in muscle. Initial studies suggested that SOCE in muscle was determined by coupling of either RYRs or inositol-1,4,5-trisphosphate receptors in the SR membrane with transient receptor potential cation channels (TRPC) in the external membrane [24–29]. However, inositol-1,4,5-trisphosphate receptor expression in adult muscle is low and primarily restricted to the nuclear envelope [30] and SOCE persists in the absence of either RYR1 [27, 31] or TRPC3 [32]. Following the discovery that STIM1 and ORAI1 mediate SOCE in non-excitable cells [3, 4], subsequent work focused on assessing the roles of STIM1 and ORAI1 in skeletal muscle.

1.2.1. Molecular Components of SOCE—Several observations provide strong evidence for SOCE in muscle being coordinated by a functional interaction between STIM1 in the SR and ORAI1 in the TT. First, STIM1 and ORAI1 are abundantly expressed in both myotubes and adult skeletal muscle fibers [33, 34]. Second, using Ca^{2+} entry and Mn^{2+} quench assays, Lyfenko and Dirksen showed that SOCE is abolished by either knocking-down STIM1 or expressing a dominant-negative ORAI1 construct (E106Q) that eliminates

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ion permeation through the channel [31]. Third, myotubes from both global [33] and muscle-specific STIM1-knockout mice [35] lack SOCE, consistently with STIM1 being the SR Ca^{2+} sensor for SOCE activation in muscle. Fourth, SOCE is also abolished in adult muscle fibers from mice with either muscle-specific expression of dominant-negative ORAI1 [19] or muscle-specific ORAI1 knockout [20]. These studies provide compelling evidence that STIM1 and ORAI1 are required for SOCE in skeletal muscle. It should be noted that while ORAI1 functions in skeletal muscle as a SOCE channel, STIM1 has been proposed to be a multipurpose stress transducer activated by diverse stimuli (depletion, oxidation, temperature, hypoxia and acidification) that may regulate multiple downstream targets including different ion channels (e.g. ORAI1, ORAI2, ORAI3, TRPC channels), pumps/exchangers, adaptor proteins, ER chaperones, signaling enzymes and ER stress/remodeling proteins [36]. Finally, while transcripts for STIM2 [37], ORAI2 and ORAI3 [31] are also expressed in myotubes, the precise role(s) of these other isoforms in muscle Ca^{2+} homeostasis and function remain largely unresolved.

1.2.2. Properties of SOCE—In non-excitable cells, STIM1 and ORAI1 proteins are diffusely distributed throughout the ER and the PM, respectively, under resting conditions. Upon store depletion, STIM1 oligomerizes to form punctuate clusters in junctional regions between the ER and plasma membrane (of 10–25 nm gap). Within these puncta, STIM1 oligomers interact and activate highly Ca^{2+}-selective ORAI1 (CRAC) channels in the plasma membrane [6]. In T-lymphocytes, this entire process, from store depletion to CRAC channel activation, occurs over ~1 minute [38]. In muscle, however, some authors have proposed that Ca^{2+} influx can be activated very quickly (<1 second) following Ca^{2+} store depletion [16, 39]. This rapid activation of SOCE might in part be possible in muscle because highly-organized, pre-formed SR-TT junctions are already present. Under resting conditions with a Ca^{2+} replete SR, ORAI1 is located within the TT system [19, 21] and STIM1 is positioned both within the SR terminal cisternae and throughout the free SR within the I-band region of the sarcomere [19, 21, 33]. The localization of a fraction of STIM1 with ORAI1 within pre-existing triad junctions is proposed to underlie rapid SOCE activation in muscle since neither STIM1 redistribution nor SR remodeling upon store depletion are required [40]. Consistent with functional STIM1/ORAI1 localization within the triad junction, muscle fibers from mice lacking mitsugumin-29, a synaptophysin protein that contributes to triad formation and maintenance, exhibit swollen and irregular TTs, altered triad structure, and a marked impairment of SOCE [27, 41].

1.2.3. Proposed Roles of STIM1S and STIM1L—Although the above studies provide evidence for pre-localization of ORAI1 and a fraction of STIM1 to the triad in resting muscle, the precise nature and role of STIM1 present within the free SR at the I-band require more investigation. Stiber and colleagues [33] suggested that muscle contains two functionally distinct pools of STIM1 proteins: i) one pool located at the triad that mediates rapid SOCE activation and ii) a reserve pool within the free SR at the I-band that is recruited following store depletion to produce graded SOCE. A recent study provides a potential molecular explanation for these two different pools of STIM1 [42]. This work discovered a STIM1 splice variant highly expressed in skeletal muscle, STIM1L (L for long, as it encodes an extra 106 amino acids), that is the consequence of alternative splicing of exon 11. The

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unique residues in STIM1L were found to interact with cytoskeletal actin in a manner that results in the formation of permanent clusters with ORAI1 even under conditions of fully replete Ca^{2+} stores [42]. On the other hand, the more common, shorter STIM1 variant (STIM1S, S for short) was more diffusely distributed throughout the SR at rest and required >1 min following store depletion to form clusters [42, 43]. As the rate-limiting-step for SOCE activation in non-excitable cells involves the time required for STIM1S oligomers to migrate into clusters and then interact/activate ORAI1 channels [43–45], pre-formed STIM1L-ORAI1 clusters within the triad junction could account for rapid SOCE activation upon sustained or repetitive Ca^{2+} release sufficient to transiently deplete Ca^{2+} within the terminal SR. Conversely, as STIM1S is localized throughout the free SR and is not pre-localized with ORAI1, STIM1S might mediate graded recruitment of additional SOCE activity when needed.

1.2.4. Effect of Exercise on SOCE—What conditions might drive graded recruitment of STIM1Smediated SOCE in skeletal muscle? A recent study found that a single period of acute treadmill exercise triggers a reorganization of the sarcotubular membrane system in *extensor digitorum longus* muscle fibers of wild type male mice. The sarcotubular reorganization results in the formation of new junctional contacts between the SR and TT membrane within the I-band of the sarcomere [21]. The width of the junctional gap in these new SR/TT junctions is only ~7–8 nm, narrower than that of triads containing RYR1 feet (12–15 nm). In contrast to the translocation of STIM1 oligomers toward ORAI1 in the plasma membrane following store depletion in non-excitable cells, in skeletal fibers exercise drives the TT membrane containing ORAI1 to elongate into the I-band, toward the Z-line, to form junctions with elongated stacks of free SR membranes that contain STIM1 proteins (Figure 2). Immunofluorescence and immuno-gold for electron microscopy studies found that, following exercise, STIM1 localization remains largely within the Iband, while a fraction of ORAI1 moves toward the Z-line, promoting a significant increase in STIM1/ORAI1 co-localization in the I-band. Prior studies reported that overexpression of STIM1 in non-muscle cells triggers a similar remodeling of ER membranes to form stacks of flat-parallel cisternae [46, 47]. Following acute treadmill exercise, *extensor digitorum longus* muscles were more resistant to fatigue during repetitive, high-frequency stimulation in the presence of extracellular Ca^{2+}, a difference abolished by experimental interventions that reduce SOCE (e.g. 0 Ca^{2+} or the addition of the SOCE inhibitors BTP-2 or 2-APB) [21]. Together, these results indicate that acute exercise triggers the formation of new SR-TT junctions within the I-band that enable recruitment of additional STIM1/ORAI1 interactions needed to enhance SOCE and muscle performance during rigorous activity.

Given the potential role for these junctions in mediating STIM1/ORAI1 SOCE after acute exercise, they were referred to as *Calcium Entry Units* (CEUs) in order to differentiate them from classical CRUs (Figure 2). In contrast to rapid activation of SOCE in muscle following store depletion [16, 39], exercise-induced formation of CEUs occurs over a relatively long period time (minutes/hours). It is also important to note that CEUs similar to those formed after exercise are also present in muscle fibers from mice not subjected to acute exercise, although they are less frequent and smaller in size [21]. Several unanswered issues regarding CEUs remain to be addressed. For example, the relative roles of STIM1S, STIM1L, and

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ORAI1 in exercise-dependent sarcotubular remodeling, CEU formation and SOCE in muscle remain unclear. Second, the relative contribution of STIM1/ORAI1 coupling within the triad (i.e. CRUs) versus CEUs to SOCE in muscle at rest and after exercise also remains to be determined.

1.3. Physiological Role of SOCE in Skeletal Muscle Development and Function

Recent evidence indicates that SOCE plays an important role in both muscle development and maintaining contractile activity during periods of prolonged, high-frequency stimulation.

1.3.1. Role of SOCE in Muscle Development—STIM1/ORAI1 coupling regulates long-term muscle function (e.g. differentiation, development and growth) through activation of downstream Ca^{2+}-dependent signals including nuclear factor of activated T-cells (NFAT), mitogen-activated protein (MAP) kinase, and extracellular signal-regulated kinase 1 and 2 (ERK 1/2) [48, 49]. The role of STIM1/ORAI1 SOCE in muscle development is supported by studies showing increased expression of both proteins and enhanced SOCE activity during differentiation of myoblasts to myotubes [33, 49–51]. In addition, global STIM1 KO mice exhibit delayed muscle development and a lethal congenital myopathy [33, 35], while muscle-specific STIM1 KO results in reduced activation of multiple Ca^{2+}-dependent signal transduction pathways (including calcineurin, MAP kinase, ERK1/2, and AKT) involved in muscle maturation and growth [35]. Muscle-specific STIM1 KO mice and transgenic mice with muscle-specific expression of dominant negative E108Q ORAI1 (dnORAI1 mice) both exhibit reductions in whole-body and muscle mass, which are due in part to a marked decrease in muscle fiber cross-sectional area [19, 35]. Consistent with these findings, mice with constitutive, muscle-specific knockout of ORAI1 (cORAI1 KO mice), in which ORAI1 is absent throughout development, exhibit parallel reductions in both body/muscle mass and muscle fiber cross-sectional area [20]. Slow twitch soleus muscles from cORAI1 KO mice exhibit reduced content and cross-sectional area of oxidative, fatigue-resistant type I fibers [20]. Together, these studies indicate that STIM1/ORAI1-dependent signals promote muscle fiber maturation, growth and specification of oxidative, fatigue-resistant fibers. However, as muscle mass, fiber cross-sectional area, and fatigue-resistant fiber content are not altered following postnatal, muscle-specific ORAI1 ablation [20], the impact of ORAI1 on muscle fiber specification and growth occurs during an early developmental time point. Taken together, these studies provide strong evidence for STIM1/ORAI1-dependent activation of Ca^{2+}-dependent downstream signaling cascades that promote muscle fiber growth and differentiation during early development.

1.3.2. Role of SOCE in Maintaining Contractile Function—In addition to playing a role in muscle development and growth, STIM1/ORAI1-dependent SOCE also promotes sustained force generation during periods of prolonged activity. Under these conditions, muscle is activated by repetitive, high-frequency train of action potentials (e.g. 150 Hz) to produce tetanic force. Such sustained stimulation triggers massive Ca^{2+} release that can result in a transient depletion of SR Ca^{2+} content, especially at sites of active Ca^{2+} release. As the Ca^{2+} current through ORAI1 channels exhibits strong inward rectification [52], significant Ca^{2+} influx through activated ORAI1 channels would be expected to occur

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primarily during intervals between succeeding high-frequency trains of action potentials after the membrane potential has returned to a negative value (e.g. −90 mV). The ability of muscle fibers to recover Ca^{2+} ions from the extracellular space via STIM1/ORAI1-mediated SOCE represents one mechanism to promote SR store refilling needed to maintain Ca^{2+} release during periods of repetitive, high-frequency stimulation. Consistent with this, removal of extracellular Ca^{2+} and addition of SOCE channel inhibitors (e.g., 2-APB, BTP-2) reduce the ability of skeletal muscle to maintain contractile force during prolonged stimulation [21, 27]. Muscles from mitsugumin-29 knockout mice, which display reduced SOCE activity, exhibit an increased susceptibility to fatigue [27]. Conversely, mice that lack sarcalumenin, a Ca^{2+}-binding protein in the free SR, display increased mitsugumin-29 expression, increased SOCE activity, and enhanced resistance to muscle fatigue [53]. More recently, Stretye and colleagues reported that myostatin-deficiency is accompanied by parallel reductions in STIM1 and ORAI1 expression, SOCE activity, SR Ca^{2+} content and depolarization-evoked Ca^{2+} release [54], while Boncompagni and colleagues found that exercise-induced formation of CEUs correlates with an increased ability of muscle to maintain force during sustained contractions in the presence of extracellular Ca^{2+} [21]. Together, these studies support a close relationship between STIM1/ORAI1-dependent SOCE, SR Ca^{2+} content, and resistance to fatigue.

Studies using STIM1 and ORAI1 loss-of-function mouse models provided important additional insights into the physiological role of STIM1/ORAI1-dependent Ca^{2+} entry on muscle contractile function [19, 20, 33, 35]. STIM1-deficient myotubes lack SOCE and exhibit a marked reduction in the ability to maintain myoplasmic Ca^{2+} transients during repetitive KCl-induced depolarization as a consequence of reduced SR Ca^{2+} content [33]. Muscle-specific STIM1 ablation results in loss of SOCE and the inability of muscle fibers to maintain Ca^{2+} transient amplitude during repetitive stimulation in spite of EC coupling being unaffected [35]. However, as neither global nor muscle-specific STIM1 knockout mice survive into adulthood, these studies do not provide insight into the physiological role of STIM1/ORAI1 coupling in adult muscle. On the other hand, muscle-specific dnORAI1 transgenic mice lack SOCE in muscle and thrive into adulthood [19]. Thus, dnORAI1 transgenic mice provided the first opportunity to assess the physiological role of ORAI1-dependent SOCE in adult skeletal muscle. Adult dnORAI1 mice exhibit increased susceptibility to exhaustion during rotarod and treadmill exercise. Single muscle fibers from dnORAI1 mice show decreases in both SR Ca^{2+} store content and ability to maintain Ca^{2+} transient amplitude during repetitive stimulation. Consistent with this, *extensor digitorum longus* muscles exhibit a reduced ability to maintain contractile force when subjected to the same repetitive stimulation protocol [19]. Subsequent studies using cORAI1 KO mice confirmed the physiological role of STIM1/ORAI1mediated SOCE in promoting SR Ca^{2+} refilling and sustained muscle activity during high-frequency stimulation. [20]. Interestingly, while cORAI1 KO mice exhibit reduced performance in treadmill and rotarod endurance tests, this was not observed following muscle-specific ablation of ORAI1 in adult mice using tamoxifen-inducible ORAI1 KO mice [20]. This finding suggests that the reduced endurance observed in cORAI1 KO mice primarily results from the reduction in both cross-sectional area and fractional contribution of fatigue-resistant type I fibers observed with early developmental ablation of ORAI1 (section 1.3.1).

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2. Mutations in *STIM1* and *ORAI1* Genes Cause Muscle Disease

Since their discovery over a decade ago, mutations in STIM1 and ORAI1 have been linked to multiple human diseases including various forms of immunodeficiency and myopathy (Table 1 and Figure 1). The fact that mutations in STIM1 and ORAI1 result in disorders characterized by clinical myopathy is consistent with the discussion above that STIM1/ORAI1-mediated SOCE plays an important role in muscle function.

2.1. Loss-of-Function Mutations in *STIM1* and *ORAI1* Genes

The involvement of SOCE dysfunction in skeletal muscle disease became clear with the initial identification of ORAI1 as the pore-forming subunit for CRAC activity [4]. Using a modified linkage analysis with single-nucleotide polymorphism arrays and *Drosophila* RNA interference screen approaches, a loss-of-function missense mutation in ORAI1 (p.R91W) was identified in patients with combined immunodeficiency (CID) with severe skeletal muscle myopathy [4, 55]. A subsequent clinical report from a patient with this mutation also revealed a predominance of type I fibers and atrophic type II fibers, consistent with ORAI1 exhibiting a critical role in fiber type differentiation/maintenance [56]. Similarly, a gastrocnemius muscle biopsy taken from a patient with an ORAI1 p.V181SfsX9 loss-of-function mutation exhibited an almost complete absence of type II muscle fibers [57].

To date, 13 different loss-of-function mutations in the *STIM1* and *ORAI1* genes, which result in a marked reduction of SOCE function, have been described (Figure 1). Loss-of-function mutations in the *STIM1* gene have been reported to result in severe, early-onset immunodeficiency with muscle hypotonia, mydriasis, iris hypoplasia, ectodermal dysplasia, splenomegaly, lymphadenopathy, and multiple auto-immune manifestations including thrombocytopenia and hemolytic anemia (Table 1). As one example, patients homozygous for the E136X (p.E128RfsX9) mutation in STIM1 exhibit CID coincident with progressive muscular hypotonia as a consequence of a lack of SOCE [58]. Similarly, significant muscular hypotonia was reported in patients with a loss-of-function p.R429C point mutation in STIM1 [59], a conserved residue in the third coiled-coil domain required for oligomerization of STIM1 dimers and subsequent binding/activation of ORAI1 channels [60]. In many cases, individuals with loss-of-function mutations in *STIM1* and *ORAI1* exhibit a common clinical phenotype. For example, patients carrying *STIM1* (p.E128RfsX9, p.P165Q, p.R426C, or p.R429C) and *ORAI1* (p.A88SfsX25, p.R91W, p.G98R, p.H165PfsX1, p.V181SfsX8, p.L194P) mutations experience CID, atrophy/hypotonia of skeletal muscle, myopathy and a severe chronic pulmonary problem due to respiratory muscle weakness [49, 57, 61] (Table 1).

2.2. Gain-of-Function Mutations in *STIM1* and *ORAI1* Genes

Recently, multiple gain-of-function mutations in both the *STIM1* and *ORAI1* genes (Figure 1), which result in constitutively activated SOCE, were found to be linked to three overlapping diseases with presentations ranging from non-syndromic tubular aggregate myopathy (TAM) [62, 63] to more complex pathologies such as Stormorken and York Platelet syndromes [64–66] (Table 1).

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2.2.1. Tubular Aggregate Myopathy (TAM)—TAM is a relatively rare skeletal muscle disorder characterized by progressive muscle weakness, cramps, and myalgia [67] that exhibits both autosomal dominant and recessive modes of inheritance [68]. Despite differences in clinical phenotype and symptomatology among TAM patients, a consistent histopathological feature is the presence of tubular aggregates (TAs). TAs are abnormal structures in muscle composed of an unusual accumulation of highly-ordered and tightly packed SR tubule membranes (Figure 3) that contain CASQ1, SERCA, and sarcalumenin [67, 69]. The first identification and characterization of TAs were made in 1970 by Engel and colleagues using electron microscopy to observe TAs in muscle biopsies from dyskalemic patients [70]. Under electron microscopy and freeze fracture, TAs appear as single- or double-walled parallel aligned tubules in longitudinal sections (Figure 3A-C) and as honeycomb-like structures in cross-sections (Figure 3D-F). The tubules can either appear empty or containing electron-dense material. Under light microscopy, TAs are detected using two distinct staining procedures: 1) as organized inclusions of bright red materials located either in the center or periphery of the fiber upon Gomori trichrome staining or 2) as dark stained regions with NADH-tetrazolium reductase staining. Interestingly, TAs stain negatively for succinate dehydrogenase, consistent with their SR, rather than mitochondrial, origin.

Subsequent to their description in dyskalemic patients, TAs were found in a variety of other pathological conditions affecting muscle including hypoxia [71], periodic paralysis, congenital myasthenic syndromes, and myotonic disorders [72–74]. Thus, TAs are a relatively non-specific structural alteration present in patients across a wide variety of neuromuscular disorders. Although having not yet been confirmed in humans with age, TAs are abundant in fast twitch muscle of aged (>24 months old) male mice and stain positively for CASQ1 and SERCA (Figure 3) [67, 75].

A relationship between altered Ca^{2+} homeostasis and the formation of TAs has long been suggested [69, 73]. The hypothesis that TAs are formed as a consequence of altered Ca^{2+} handling in skeletal muscle fibers, is strengthened by the fact that gain-of-function mutations in both STIM1 and ORAI1 result in myopathies characterized by the presence of TAs (see sections **2.2.2** and **2.2.3** below). Thus, increased SOCE via constitutively-active STIM1/ORAI1 proteins likely serves as an upstream trigger for TA formation. While the precise downstream cellular and molecular mechanisms that underlie TA assembly remain to be elucidated, several hypotheses have been advanced. One possibility is that enhanced SOCE promotes an aggregation and fusion of free SR vesicles/membranes into TAs. Alternatively, TAs may represent an adaptive mechanism triggered by constitutive SOCE designed to limit Ca^{2+}-mediated muscle fiber hypercontraction and necrosis.

A second hypothesis is that a dysfunction in Ca^{2+} homeostasis could result in protein misfolding and aggregation due to altered proteostasis, which in turn, drives morphological changes in the SR structure that lead to TA formation [76]. In this regard, protein N-glycosylation plays a critical role in the correct maintenance of ER proteostasis, such that a reduction in protein N-glycosylation can induce ER/SR stress and increase the accumulation of unfolded proteins [77, 78]. Recessive mutations in the glutamine-fructose-6-phosphate transaminase 1 gene, an enzyme that produces UDP-N-acetylglucosamine needed for N-

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linked glycosylation in the ER/SR, results in congenital myasthenic syndromes with a limb-girdle dystrophy phenotype that are associated with TAs [79]. Interestingly, mutation of an N-glycosylation site in STIM1 correlates with strong activation of ORAI1 channels that could drive TAs formation in skeletal muscle [80]. It is also possible that TAs are driven by conditions (e.g. hypoxia, aging, constitutive SOCE) that promote abnormal clustering of STIM1 oligomers. Consistent with this idea, EM images of TAs reveal the presence of discrete, evenly spaced electron-dense bridges within the gap between adjacent tubules (Figure 3 E). Similar bridging structures were described in TAs of patients with TAM [67] and between stacks of flat parallel cisternae in CEUs following exercise [21]. The molecular nature of these electron-dense strands remains unknown, though aggregates of STIM1 oligomers represent a reasonable candidate.

This possibility is supported by immuno-gold detection of STIM1 in the SR stacks following exercise in adult skeletal muscle [21] and in the ER stacks after STIM1 overexpression in HeLa cells [46]. In addition, Endo and colleagues showed that TAs in skeletal muscle from TAM patients are positive for STIM1 and ORAI1 immunostaining, consistent with the two proteins being sequestered in TAs [63]. However, a separate study found that STIM1 is not included in TAs, but rather is co-localized with RYR1 around the TA periphery, in muscle biopsies of TAM patients with STIM1 gain-of-function mutations [62]. Thus, while a relationship between altered SOCE function and Ca^{2+} homeostasis in TA formation in muscle is clear, additional studies are needed to more precisely determine the precise molecular components of TAs and the cellular/molecular mechanisms involved in their formation.

2.2.2. *STIM1* Gain-of-Function Mutations—The majority of autosomal dominant mutations in STIM1 linked to TAM are located in the N-terminal luminal cEF-hand or hEF-hand (EF1/2) domains (Figure 1). These domains function as a sensor for the Ca^{2+} concentration in the SR lumen and are critical for initiating a complex series of conformational changes that lead to STIM1 oligomerization and ORAI1 channel activation following SR Ca^{2+} depletion. Bohm and colleagues were the first to describe four heterozygous dominant missense mutations in four families with dominant TAM, each affecting a highly-conserved EF1/2 hand amino acid residue [62]. Members from these families displayed a clinical spectrum of myopathic features including elevated serum creatine kinase levels, wrist contractures, ophthalmoplegia, miosis, as well as mild and slowly progressive lower-limb muscle weakness [62] (Table 1). Ten different STIM1 EF-hand mutations, five each in both the cEF1- and hEF2-hands, have been reported to date. By disrupting the ability of EF1/2 hands to bind Ca^{2+} and/or destabilizing the interaction with the sterile α-motif (SAM) domain, these mutations promote STIM1 oligomerization and ORAI1 channel activation even in the absence of SR Ca^{2+} depletion. Consistent with this, in contrast to wild type STIM1, the STIM1 EF-hand mutants promote clustering of STIM1 monomers independently from thapsigargin-induced store depletion following expression in C2C12 myoblasts. Moreover, myoblasts obtained from a patient with one of these mutations (p.D84G) were shown to exhibit elevated levels of resting Ca^{2+} and increased thapsigargin-induced and thapsigargin-independent Ca^{2+} influx compared to that of control myoblasts [62].

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Similar to TAM, patients affected by Stormorken disease, a rare autosomal-dominantly inherited disorder characterized by a complex clinical picture including thrombocytopenia, platelet defects, congenital miosis, and proximal muscle weakness (Table 1), also exhibit increased serum levels of creatine kinase and skeletal muscle fibers with histological evidence of myopathy with TAs [81, 82]. A mutation in the first cytosolic coiled-coil domain of STIM1 (p.R304W), a domain that plays a critical role in maintaining STIM1 in a closed, inactive state until SR Ca^{2+} levels are reduced enough to dissociate Ca^{2+} from the EF-hand domains, was shown to be associated with Stormorken disease [64, 65, 83]. The p.R304W mutation is proposed to disrupt the conformation of an inhibitory helix in the first coiled-coil domain that unlocks the inhibitory state of STIM1, thus resulting in a gain-of-function effect on STIM1 function [83]. Indeed, the p.R304W mutation promotes formation of STIM1 puncta and CRAC channel activation even in the absence of thapsigargin-induced store depletion [64, 65, 83]. In addition, a recent study reported a muscle degenerative phenotype in p.R304W knock-in mice [84].

2.2.3. *ORAI1* Gain-of-Function Mutations—To date, four autosomal dominant inherited gain-of-function mutations in ORAI1 have been reported in families with TAM (p.G98S and p.L138F) and Stormoken-like disease (p.S97C and p.245L) (Figure 1). The two TAM mutations, p.G98S and p.L138F, located in transmembrane domains 1 and 2, respectively, result in constitutively activatedORAI1 channels that permit Ca^{2+} influx independently of Ca^{2+} store depletion and STIM1 oligomerization [63]. The p.P245L mutation, located in transmembrane domain 4, results in a Stormorken-like phenotype characterized by myopathy with TAs and congenital miosis, but in the absence of thrombocytopenia and platelet defects [64]. Heterologous co-expression of STIM1 and either wild type or p.P245L ORAI1 in HEK 293 cells revealed that this mutation markedly reduces Ca^{2+} dependent inactivation of ORAI1, and thus, enhances SOCE, but still requires STIM1 to be activated [64]. The p.S97C mutation in ORAI1, located in the transmembrane domain 1, is associated with mild, late-onset TAM with congenital miosis, consistent with a Stormorken-like syndrome in the absence of thrombocytopathy (Table 1). Similar to the adjacent p.G98S TAM mutation, the p.S97C mutation results in a constitutively active channel that increases Ca^{2+} influx both in the absence and presence of store depletion [85]. Functional assays conducted in both transfected HEK 293 cells and patient-derived myotubes revealed that the p.S97C mutation in ORAI1 increases the rate of SOCE, consistent with a gain-of-function effect on the channel. The reason(s) for the markedly earlier onset and more severe clinical presentation observed in TAM patients possessing the p.G98S mutation compared to those with milder Stormorken-like syndrome of patients with the p.S97C mutation is not entirely clear. As one possibility, the difference in phenotypic expression could be due to a larger effect of the p.G98S mutations on heterotypic ORAI1 channel function and/or other genetic or environmental factors that influence the clinical phenotype [85].

3. SOCE Activity as a Modifier of Skeletal Muscle Disorders.

In addition to loss-of-function and gain-of-function mutations in STIM1 and ORAI1 directly causing muscle disease, altered STIM1/ORAI1 function also indirectly contributes to or

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amplifies the pathogenesis of other muscle disorders including muscular dystrophy, malignant hyperthermia, and sarcopenia.

3.1. SOCE and Muscular Dystrophy

Muscular dystrophy (MD) comprises a heterogeneous group of muscle diseases characterized by weakness and progressive muscle degeneration. The most common MD is Duchenne muscular dystrophy (DMD), an incurable X-linked disorder resulting from loss-of-function mutations to the gene that encodes dystrophin [86]. Dystrophin, a 427 KDa structural protein on the cytoplasmic face of the sarcolemma [87], anchors actin filaments and microtubules to a group of proteins collectively known as the dystrophin-associated protein complex [88]. The dystrophin-associated protein complex stabilizes sarcolemmal integrity during mechanical stress [89] by linking the cytoskeleton to laminin in the extracellular matrix [90]. While disruption of sarcolemmal integrity is a common feature among different MDs, the exact mechanism(s) that underlies progressive muscle fiber degeneration remains controversial. A longstanding hypothesis for muscle fiber degeneration in DMD is that alterations in the sarcolemma stability promote excessive Ca^{2+} entry that triggers calpain- and mitochondrial-mediated cell death [91]. Consistent with this hypothesis, defective Ca^{2+} homeostasis has been shown to play a role in the pathogenesis of the dystrophic phenotype. For example, both Ca^{2+} influx and total Ca^{2+} content are increased in muscle biopsies from DMD patients and in skeletal muscle fibers from *mdx* mice (a murine dystrophin-deficient model of DMD) [92, 93]. Myoplasmic Ca^{2+} overload could trigger an array of intracellular pathways/mechanisms responsible for the dystrophic phenotype including: mitochondrial Ca^{2+} overload, enhanced oxidative stress, and activation of the Ca^{2+}-dependent proteases [94–96]. However, the mechanisms for enhanced Ca^{2+} influx in dystrophic fibers, including through “microtears” in the sarcolemma or specific ion channels, remain uncertain and continue to be debated. Over the past two decades, increased activity of several different classes of Ca^{2+} channels (e.g. Ca^{2+} leak channels, stretch-activated channels, receptor-operated channels and SOCE channels) have all been proposed to promote the dystrophic phenotype in DMD [97–104].

A growing number of reports provide evidence for a modulatory role of SOCE in the pathogenesis of DMD. Early studies found that SOCE activity is upregulated in muscle from *mdx* mice [93], though the molecular components at that time remained unknown. Prior to the identification of STIM1 and ORAI1 in coordinating SOCE in muscle (see section 1.2.1 above), Vandebrouck and colleagues found that upregulation of TRPC1 and TRPC3 voltage-independent Ca^{2+}-permeable channels sensitive to thapsigargin- and caffeine-mediated store depletion increases Ca^{2+} influx in muscle fibers from *mdx* mice [100]. Consistent with these results, overexpression of TRPC3 in muscle enhanced, while dominant negative TRPC4 expression reduced, the dystrophic phenotype of *mdx* and δ-sarcoglycan-deficient (*Sgcd−/−*) mice [101]. A similar reduction in the dystrophic phenotype was also observed following overexpression of dominant negative stretch-activated TRPV2 channels [105]. Moreover, different levels of stretch-activated TRPC1 channel activity correlates with DMD in mice [106] and muscle damage following eccentric contractions is reduced in TRPC1 knockout mice [107].

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Several studies provide evidence for a modulatory contribution of STIM1/ORAI1-dependent Ca^{2+} influx to the dystrophic phenotype of *mdx* mice. First of all, muscle fibers from *mdx* mice exhibit increased STIM1/ORAI1 expression and SOCE function, including a shift in SOCE activation and deactivation thresholds to higher SR luminal Ca^{2+} concentrations [39, 108]. In line with these findings, Zhao and colleagues found an increase in both ORAI1 mRNA and protein levels coincident with enhanced SOCE activity and SR Ca^{2+} storage in muscle from *mdx* mice, although STIM1 levels were unaltered in this study [102]. This enhanced SOCE and SR Ca^{2+} storage were reduced by either shRNA-mediated ORAI1 knockdown or treatment of animals with BTP-2, a potent CRAC channel inhibitor. Together, these studies suggest that increased STIM1/ORAI1dependent SOCE contributes to Ca^{2+}-mediated muscle fiber degeneration in *mdx* mice. Consistent with this idea, muscle-specific STIM1 overexpression enhances SOCE and promotes a dystrophic phenotype (e.g. increased inflammation, fibrosis, necrosis, mitochondrial swelling, and serum CK levels) similar to that observed in *mdx* and *Sgcd*$^{-/-}$ mice [103]. Importantly, both SOCE and MD of *mdx* and *Sgcd*$^{-/-}$ mice are reduced by crossing with transgenic mice with muscle-specific expression of dominant-negative ORAI1 (dnORAI1) [103]. These findings support a modulatory role for STIM1/ORAI1-mediated Ca^{2+} entry in the pathogenesis of MD.

3.2. SOCE and Malignant Hyperthermia

Malignant hyperthermia (MH) susceptibility is an inherited pharmacogenetic disorder characterized by a life-threatening response to halogenated anesthetics (i.e. halothane, isoflurane) and certain muscle relaxants (e.g. succinylcholine) commonly used during surgical procedures [109]. The exposure of susceptible individuals to these agents triggers a hypermetabolic reaction characterized by skeletal muscle rigidity, rise in core body temperature (e.g. hyperthermia), rupture of skeletal muscle fibers (e.g. rhabdomyolysis) and dangerous increases in serum levels of creatine kinase and potassium. MH crises can be lethal if not immediately corrected by suspension of triggering agents, cooling and administration of dantrolene, the only FDA-approved drug to treat MH reactions. At the molecular level, exposure of MH susceptible individuals to triggering agents induces an uncontrolled sustained rise in myoplasmic Ca^{2+} concentration as a result of activation of RYR1 Ca^{2+} release channels in the SR [109]. In ~70% of cases, MH susceptibility is caused by mutations in the *RYR1* gene [110, 111]. Mutations in the α_{1S}-subunit of the DHPR account for another ~1% of cases [112, 113]. The genetic cause of the remaining ~30% of cases remains unknown. While mice lacking CASQ1 (CASQ1-null) exhibit a phenotype resembling MH in humans [114, 115], mutations in CASQ1 were not identified in a large North American cohort of MH patients [116]. An *in vitro* caffeine-halothane contracture test (IVCT or CHCT), which measures the sensitivity of a muscle biopsies to caffeine- and halothane-induced contractures, was developed as a diagnostic assay for MH susceptibility in the late 1980s and continues to be the gold standard for MH diagnosis [117, 118].

For many years it was assumed that the sustained rise in myoplasmic Ca^{2+} during an MH event was solely the consequence of an uncontrolled activation of RYR1 Ca^{2+} release from the SR. However, early optimization studies for the diagnostic IVCT/CHCT found that the assay only worked when extracellular Ca^{2+} is included in the solution bathing the muscle biopsy [119–121], implicating a critical role for extracellular Ca^{2+} in the enhanced

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sensitivity of MH susceptible muscle. More recently, MH triggering agents were proposed to promote sustained RYR1-dependent Ca^{2+} release sufficient to deplete SR Ca^{2+} stores [114, 122–124], which in turn, activates SOCE channels to trigger Ca^{2+} influx from an essentially infinite extracellular compartment. The combined effects of sustained SR Ca^{2+} release, store depletion, and massive SOCE-dependent Ca^{2+} influx result in the myoplasmic Ca^{2+} overload, hypercontractures, heat generation and rhabdomyolysis that occur during an MH event. The first direct evidence for a role of SOCE in MH pathogenesis was provided by Steele and colleagues who used mechanically-skinned fibers from normal and MH susceptible individuals to show that therapeutic levels of halothane induce SR Ca^{2+} release and store depletion sufficient to activate STIM1-dependent Ca^{2+} influx in muscle fibers from MH susceptible, but not normal, individuals [125]. Consistent with this, Cully et al (2018) used a skinned fiber approach to show that muscle fibers from MH-susceptible individuals exhibit enhanced RYR1 Ca^{2+} leak, persistent SOCE activity, and a compensatory increase in capacity to extrude Ca^{2+} across the TT system compared with that observed for muscle fibers from control individuals [126].

Evidence from validated mouse models of MH susceptibility (*Ryr1*$^{Y522S/+}$ and *Ryr1*$^{R163C/+}$ RYR1 knock-in mice) provides additional support for a role of SOCE in MH pathogenesis. As is observed for other MH-causative mutations in RYR1, the Y522S and R163C promote RYR1 Ca^{2+} leak and increased sensitivity of the release channel to be opened by a wide variety of activators (including halothane, caffeine, 4-chloro-m-cresol, DHPR voltage sensor) [109]. Following homologous expression in RYR1-null myotubes, the Y522S MH mutation produces the highest degree of RYR1 Ca^{2+} leak, sensitization and SR Ca^{2+} store depletion of the MH-causative mutations studied in this system [127, 128]. Consistent with these findings, RYR1 channel permeability is increased (>2fold) and resting SR Ca^{2+} store content reduced (~50%) in muscle fibers from *Ryr1*$^{Y522S/+}$ mice [129], which would be expected to increase SOCE and explain the elevation in resting Ca^{2+} levels [130, 131]. A similar increased RYR1 Ca^{2+} leak linked to massive reduction in SR Ca^{2+} content is observed in muscle fibers from CASQ1-null mice [114, 132, 133]. Consistent with an increased loss of SR Ca^{2+} via RYR, the rate of SOCE activation is accelerated in myotubes from both *Ryr1*$^{Y522S/+}$ and CASQ1-null mice [134]. Dantrolene directly inhibits RYR1 channel activity in a calmodulin- [135] and Mg^{2+}-dependent manner [136], but does not directly inhibit SOCE channels [134].

However, as SOCE activation lies downstream of store depletion, dantrolene indirectly inhibits SOCE by protecting stores from becoming depleted as a result of reducing RYR1 Ca^{2+} leak.

Myotubes derived *Ryr1*$^{R163C/+}$ mice exhibit increased basal sarcolemmal divalent cation influx that results in a chronically elevated resting Ca^{2+} concentration [137]. Both elevated basal divalent cation influx and resting Ca^{2+} levels were reduced by inhibitors of ORAI1-dependent SOCE (BTP2, Gd^{3+}, expression of dominant-negative ORAI1) and TRPC channels (Gd^{3+}, GsMTx-4). Importantly, elegant *in vivo* measurements of resting Ca^{2+} levels in *vastus lateralis* muscles of control and *Ryr1*$^{R163C/+}$ mice during exposure to 1.5% halothane vapor, revealed that local application of BTP-2, Gd^{3+} or GsMTx-4 all markedly reduced halothane-induced elevations in resting Ca^{2+} [137]. Taken together, studies

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conducted in muscle from MH susceptible individuals and validated murine models of MH support a paradigm by which SOCE serves as a modifier or amplifier of MH pathogenesis such that STIM1/ORAI1 coupling could represent a potential therapeutic target for the treatment of MH in humans.

3.3. SOCE and Age-related Muscle Dysfunction

Aging is a complex, irreversible process characterized by morphological alterations and progressive decline of multiple biological/physiological functions. Age-related loss of skeletal muscle function (sarcopenia) is characterized by a marked reduction in muscle mass, lowered muscle strength, increased susceptibility to fatigue, and reduced velocity of contraction [138, 139]. The underlying causes of sarcopenia includes loss of muscle mass (atrophy) due to reduced fiber number and size [140, 141], muscle stem cell depletion that leads to neuromuscular junction degeneration [142], and loss (1015%) and remodeling of motor units [143]. However, these effects alone are not sufficient to account for the degree of muscle weakness observed with aging. Impairments in intrinsic muscle fiber capacity for Ca^{2+} release and mitochondrial ATP production contribute to a reduction in specific force production. A decrease in DHPR expression leads to an uncoupling between DHPR and RYR1 proteins that results in a reduction in Ca^{2+} available to activate the contractile filaments [144, 145]. A decrease in number/area and altered morphology of CRUs also contributes to the reduction in electrically-evoked Ca^{2+} release and skeletal muscle force production [146, 147]. Finally, alterations in mitochondrial structure, function, and number also play a role in age-related decreases in muscle performance [148–150]. Thus, impairments in Ca^{2+} release and mitochondrial energy production contribute to the observed age-dependent decline in muscle specific force.

A reduction in STIM1/ORAI1-mediated SOCE is also proposed to contribute to the decline in muscle contractile force and increase in susceptibility to fatigue in aging. In support of this idea, muscle fatigue during repetitive, high-frequency stimulation is accelerated [27] and SOCE is reduced in skeletal muscle from aged (2 year old) mice [151]. Interestingly, the reduction of SOCE in muscle from aged mice was reported to occur in the absence of a change in transcript levels for either STIM1 or ORAI1 [151]. However, a significant reduction in the expression levels of mitsugumin-29 was reported in aged muscles [151], consistent with reduced mitsugumin-29 expression causing a disruption of triad architecture and decrease in SOCE [27]. Thornton and colleagues showed that SOCE is required to maintain contractile force during repetitive contractions in *soleus* muscles from young mice, but not from aged mice [152]. Together, these studies suggest that an inability to recover Ca^{2+} ions from the extracellular space via SOCE during periods of intense activity contributes to a reduction in force generation and increase in susceptibility to fatigue in aging. This idea is further supported by the fact that pharmacological inhibition of SOCE in muscles from young mice similarly results in a reduction in force generation and increase in susceptibility to fatigue [21, 27, 152]. However, the potential role of altered SOCE in sarcopenia is controversial. For example, Payne and colleagues reported that while sustained contraction during high-frequency stimulation depends on extracellular Ca^{2+} in a subpopulation of muscle fibers from aged mice, this was due to an effect of extracellular Ca^{2+} on excitability rather than insufficient SOCE [153]. In addition, Edwards and

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colleagues concluded that in spite of a 40% reduction in STIM1 expression (in the absence of a change in ORAI1 expression), SOCE is unaltered in muscle fibers from aged mice [154]. Thus, the relative role of STIM1/ORAI1-dependent SOCE in the age-dependent decline of skeletal muscle performance remains enigmatic. Clearly, additional studies are needed to resolve this issue.

4. Conclusions and Future Directions

Over the past two decades, the importance of Ca^{2+} entry in skeletal muscle has garnered significant attention. As a result, STIM1/ORAI1-mediated SOCE in muscle has unequivocally been demonstrated, shown to promote muscle growth/differentiation and limit force decay during sustained muscle activity. In addition, defects in STIM1/ORAI1-mediated SOCE both directly and indirectly contribute to a wide range of different clinical myopathies. Nevertheless, several important unresolved issues and open questions remain to be addressed.

Boncompagni and colleagues reported that acute treadmill exercise triggers a remodeling of sarcotubular membranes that results in an elongation of the TT from the triad into the I-band, toward the Z-line, to form junctional contact with flat-parallel stacks of SR cisternae [21]. As STIM1 and ORAI1 proteins are present within these newly formed regions of SR-TT contact, the junctions were termed CEUs. However the precise molecular mechanisms that control exercise-dependent remodeling of SR and TT membranes are unknown. For example, future studies will need to determine the specific exercised-induced signals, as well as the relative roles of STIM1S, STIM1L and ORAI1, in both remodeling of the free SR into well-ordered flat-parallel stacks of cisternae and extensions of the TT into these stacks of membranes. The potential role of proteins known to be involved in TT biogenesis and maintenance (e.g. junctophilins, myotubularin-1, dysferylin, BIN-1; [155]), in exercise-induced elongation of the TT and CEU formation, as well as the time course for the formation and disassembly of CEUs, need to be determined. Finally, although *extensor digitorum longus* muscles from mice subjected to exercise exhibit an increased frequency of CEUs containing STIM1 and ORAI1 proteins and enhanced resistance to fatigue [21], the relative impact of CEUs on the magnitude and properties of SOCE after exercise, as well as opposing Ca^{2+} efflux mechanisms, compared to that observed under resting conditions needs to be determined. Such an analysis would also provide insight into the relative contribution of STIM1/ORAI1 coupling from CRUs versus CEUs in SOCE in muscle at rest and after exercise.

Another major unresolved issue involves the precise relationship between SOCE function and the formation of TAs in skeletal muscle. It is now clear that gain-of-function mutations in both STIM1 and ORAI1 result in clinical myopathies with TAs being a central defining histopathological characteristic. However, the mechanism(s) by which constitutively active SOCE leads to the formation of TAs is unknown. Another unresolved issue is whether the formation and properties of TAs resulting from gain-of-function STIM1 and ORAI1 mutations are similar or fundamentally distinct from those observed in aging in which SOCE may be reduced. In addition, it is unclear if TAs contribute to the hypotonia and muscle weakness experienced by individuals with TAM or rather if their formation is a protective

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compensatory response designed to limit Ca^{2+} induced damage (e.g. increased proteolysis, oxidative stress, activation of the mitochondrial permeability transition pore). Alternatively, analogous to how physiological hypertrophy may initially be protective to the heart while later being detrimental, TAs could initially be protective by providing a sink for constitutive SOCE, but over time, become detrimental as larger and more extensive TAs begin to interfere with the EC coupling and myofilament apparatus. In any event, answers to these questions will require animal models that faithfully recapitulate the clinical and histopathological phenotype of human TAM patients. Finally, as loss- and gain-of-function mutations in both STIM1 and ORAI1 directly cause several muscle pathologies (see section 2.0) and SOCE dysfunction contributes to the pathogenesis of other muscle disorders (see section 3.0), STIM1/ORAI1-mediated SOCE in muscle could emerge as an intriguing potential new therapeutic target to treat a wide range of debilitating human myopathies in the future, though potential side effects of inhibiting ORAI1 channels in muscle (e.g. iris sphincter dysfunction) would need to be appropriately managed.

List of frequently used abbreviations:

Ca^{2+}	calcium
CID	combined immunodeficiency
CASQ1	calsequestrin-1
CRAC	Ca^{2+}-released-activated-Ca^{2+}
CEU	Ca^{2+} entry unit
CRU	Ca^{2+} release unit
DHPR	dihydropyridine receptor
EC coupling	excitation-contraction coupling
DMD	Duchenne muscular dystrophy
ER	endoplasmic reticulum
MH	malignant hyperthermia
MD	muscular dystrophy
RYR1	ryanodine receptor type-1
SOCE	store-operated Ca^{2+} entry
SR	sarcoplasmic reticulum
STIM1	stromal interaction molecule-1
TA	tubular aggregates
TAM	tubular aggregate myopathy

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TRP	transient receptor potential cation
TT	transverse tubule.

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Highlights

- STIM1 and ORAI1 coordinate SOCE in skeletal muscle.
- STIM1/ORAI1 SOCE promotes muscle development/growth and maintains Ca^{2+} store content during periods of prolonged, high-frequency stimulation.
- Loss-of-function and gain-of-function mutations in STIM1 and ORAI1 result in an eclectic array of disorders with clinical myopathy as a central defining component.
- Dysfunctional STIM/ORAI1 SOCE also contributes to the pathogenesis of other muscle disorders including muscular dystrophy, malignant hyperthermia, and sarcopenia.
- Tight regulation of STIM1/ORAI1 SOCE is critical for optimal skeletal muscle function.

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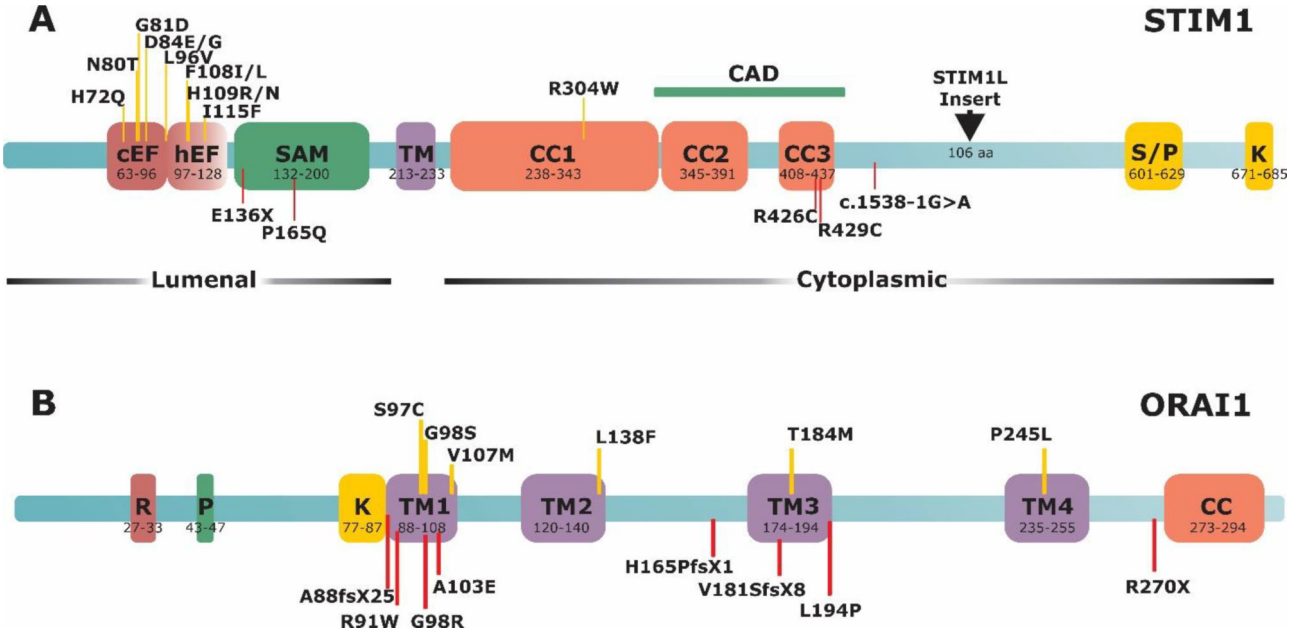

Figure 1. Schematic representation of STIM1 and ORAI1 proteins and location of associated disease mutations.

A) STIM1 protein structure. cEF, canonical EF-hand; hEF, hidden EF-hand; SAM, sterile α-motif; TM, transmembrane; CC, coiled-coil region; S/P serine-proline-rich domain; K, lysine-rich domain; CAD, channel activation domain. B) ORAI1 protein structure. R/P, arginine-proline-rich domain; TM, transmembrane domain; CC, coiled-coil domain. Upper, yellow lines indicate gain-of-function mutations. Lower, red lines indicate loss-of-function mutations.

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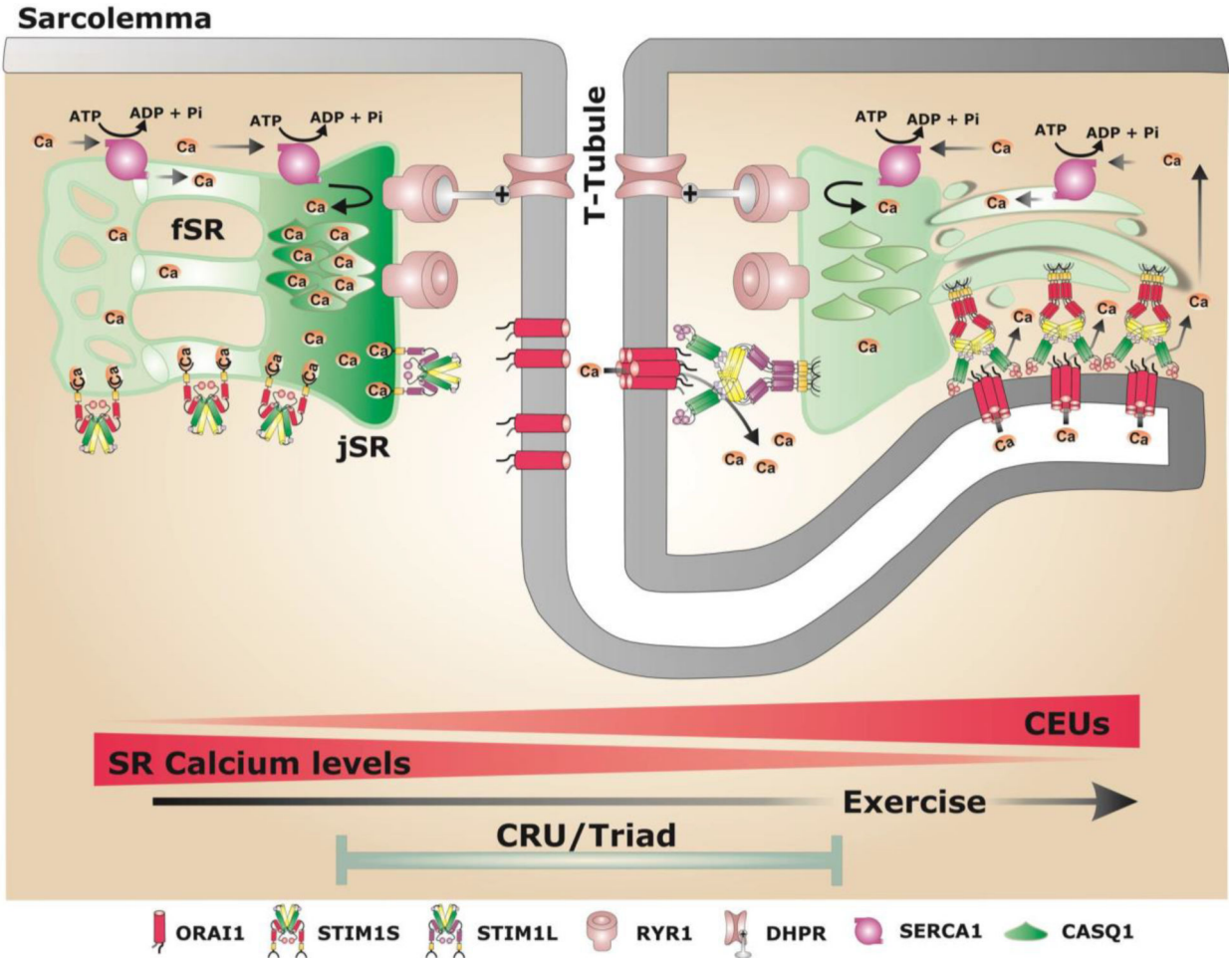

Figure 2. Schematic model showing potential sites of STIM1/ORAI1 coupling in skeletal muscle under resting conditions and after exercise.

The SR of adult fibers is divided in two compartments: i) the junctional SR (jSR, or SR terminal cisternae) that contains CASQ1 and RYR1 and is closely associated with the T-tubule (TT) that contains DHPR, to form the triad (or CRU), the site of excitation-contraction (EC) coupling; ii) the free SR (fSR) that does not interact with TT and is localized throughout I band. Both jSR and fSR contain high levels of the sarco/endoplasmic Ca^{2+} ATPase-1 (SERCA1), a Ca^{2+} ATPase that pumps Ca-$^{2+}$ ions Ca^{2+} released during EC coupling from the myoplasm back into the lumen of the SR. Two different splice variants are expressed in skeletal muscle: STIM1S and STIM1L. Under resting conditions (left side), ORAI1 is located within the TT system at the triad, while STIM1S and STIM1L are located in the fSR and jSR, respectively. After exercise (right side): i) the fSR and TT undergo a striking remodeling to form new junctions composed by multiple layers of flat parallel stacks of fSR cisternae and an extension of the TT from the triad into the I-band toward the Z-line [21]. These new junctions promote increased STIM1/ORAI1 colocalization at the I-band as TT elongation allows ORAI1 to interact with STIM1S proteins in the fSR. These new junctions are proposed to function as *Calcium Entry Units* (CEUs) [21].

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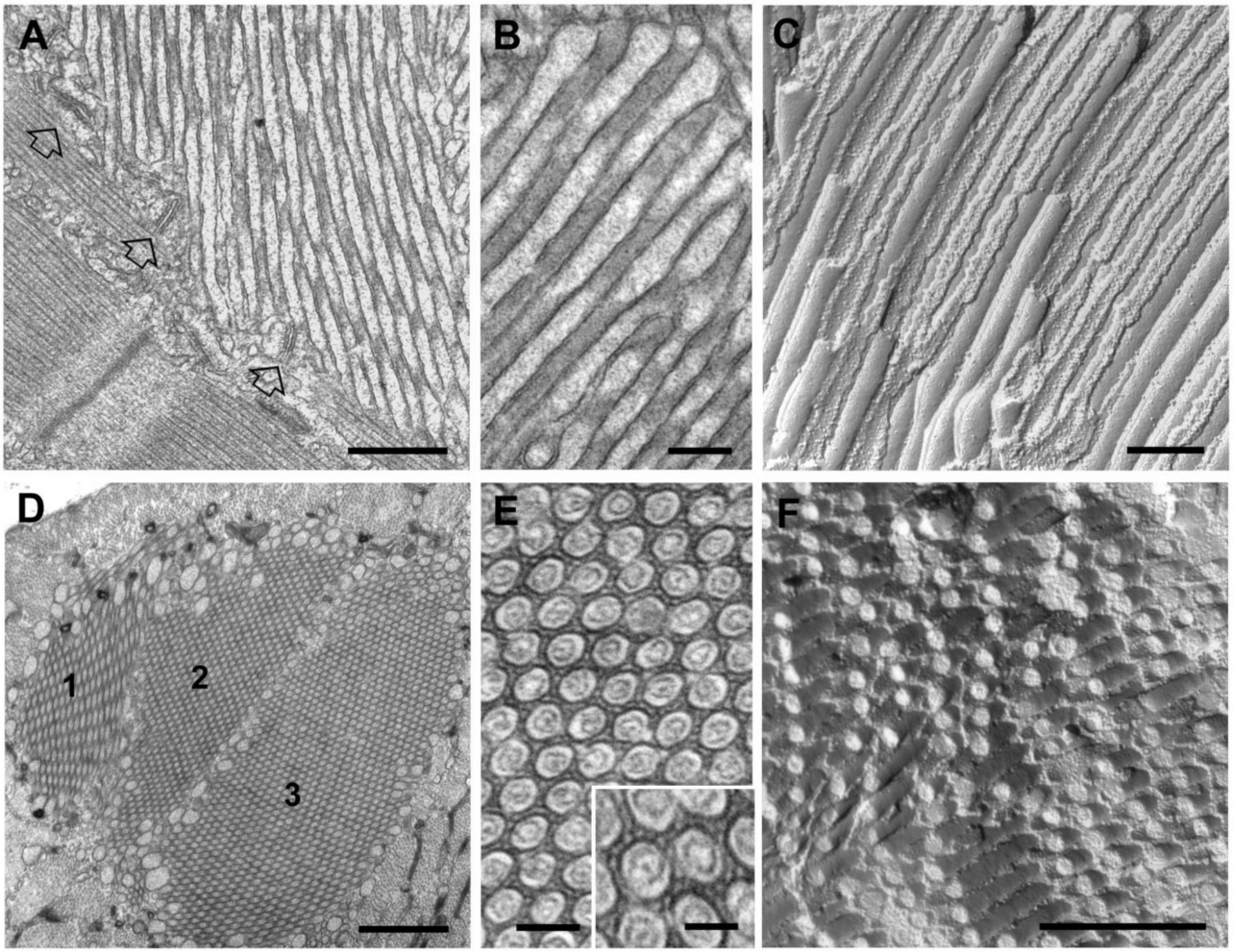

Figure 3. Tubular aggregates (TAs) in *extensor digitorum longus* fibers from 2 year old male wild type mice.

A-C) EM images of longitudinal views of TAs in thin sections (A and B) and freeze fracture (C). Empty arrows in panel A point to jSR-TT junctions (or triads) located at the periphery of a TA. Tubes of TAs are typically filled with electron-dense material, most likely CASQ1 (B). The regular and straight shape of the tubules are emphasized in freeze fracture replicas, where tubules appear as long cylinders showing alternated views of the luminal and cytoplasmic leaflets (see [75] for additional detail). D-F) EM images of cross-sectional views of TAs in thin sections (D and E) and freeze fracture (F). Large TAs often result from the association of multiple TAs of smaller size (panel D: 1–3). In the core of each domain, tubes forming the TA display uniform diameters and appear ordered in a hexagonal pattern (E). Note the presence of small linkages that bridge the gap between membranes of adjacent tubules (E, inset). Bars: A, D and F: 0.5 μm; B and C: 0.2 μm; E: 0.1 μm (inset: 0.05 μm)

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Table 1.

Genetic, mechanistic, histological, and clinical muscle phenotypes of patients with loss-of-function and gain-of-function *STIM1* and *ORAI1* mutations.

CID, combined immunodeficiency; CAD, channel activation domain; CC, coiled-coil domain; CK, creatine kinase; cEF, canonical EF-hand domain; hEF, hidden EF-hand domain; ER, endoplasmic reticulum; GF, gain-of-function mutation; LF, loss-of-function mutation; ND, not determined; CID, severe combined immunodeficiency; SOCE, store-operated Ca^{2+} entry; STIM1, stromal interaction molecule-1; TA, tubular aggregates; TAM, tubular aggregate myopathy; YPS, York platelet syndrome.

Clinical and Histological Muscle Features Resulting from STIM1 and ORAI1 Gene Mutations						
Disease	**Gene/Position**	**Mutation**	**Lost or gain of function/others**	**Histological features**	**Muscle phenotype**	**Reference**
CID	STIM1/SAM	p.E128RfsX9(or E136X)	LF Abolishes STIM1 expression	No abnormalities	No progressive muscular hypotonia, partial iris hypoplasia, mydriasis Onset: early	[58]
	STIM1/SAM	p.P165Q	LF Reduces STIM1 protein expression	ND	No progressive muscular hypotonia Onset: early	[156]
CID	STIM1/CAD	p.R426C	LF Impairs STIM1/ORAI1 co-localization	ND	No muscular hypotonia Onset: early	[157, 158]
	STIM1/CAD	p.R429C	LF Normal STIM1 expression, impairs STIM1-ORAI1 interaction	ND	Mild muscular hypotonia, mydriasis Onset: early	[59, 60, 159]
	STIM1/Exon8	c. 1538–1G>ASplice-site mutation	LF Low STIM1 mRNA levels, abolishes STIM1 protein expression	ND	ND Onset: early	[160]
CID	ORAI1/TM1	p.R91W	LF Abolishes ORAI1 channel conductance	Predominance of type I fibers, atrophic type II fibers, fiber size variations	Muscular hypotonia Onset: early	[4, 56]
	ORAI1/TM1	p.G98R	LF Normal ORAI1 mRNA Abolish ORAI1 protein expression	No abnormalities by H&E Mitochondrial damage by EM	Muscular hypotonia, mydriasis, partial iris hipoplasia Onset: early	[57]
	ORAI1/TM1	p.A88SfsX25	LF Abolishes ORAI1 mRNA/ protein expression	ND	Muscular hypotonia Onset: early	[56]

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Clinical and Histological Muscle Features Resulting from STIM1 and ORAI1 Gene Mutations						
Disease	**Gene/Position**	**Mutation**	**Lost or gain of function/others**	**Histological features**	**Muscle phenotype**	**Reference**
	ORAI1/TM1	p.A103E	LF Abolishes ORAI1 protein expression	ND	Muscular hypotonia Onset: early	[56]
	ORAI1/TM3	p.V181SfsX8	LF Normal ORAI1 mRNA Abolish ORAI1 protein expression	Predominance of type I fibers and atrophic type II fiber	Muscular hypotonia, esotropia Onset: early	[57]
	ORAI1/TM3	p.L194P	LF Normal ORAI1 mRNA Abolishes ORAI1 protein expression	No abnormalities by H&E Mitochondrial damage by EM	Muscular hypotonia Onset: early	[56, 57]
	ORAI1/2nd loop	p.H165PfsX1	LF Abolishes ORAI1 protein expression	ND	Muscular hypotonia Onset: early	[161]
	ORAI1/C-terminus	p.R270X	LF Impairs ORAI1 association with STIM1	ND	Hypotonia Onset: early	[162]
YPS/Stormorken syndrome	STIM1/CC1	p.R304W	GF Constitutive SOCE Impairs STIM1 inhibition Increase in basal Ca^{2+} levels Decreases ER Ca^{2+} content	TAs, predominance of atrophic type II fibers	Muscle weakness Cramps Miosis Elevated CK levels Onset: early, mild and late	[64–66, 83]
Stormorken-like syndrome/TAM	STIM1/hEF	p.I115F	GF	TAs, type I fiber prevalence, type II fiber hypotrophy Mild increase in internal nuclei Fiber size variability Fatty infiltration and muscle atrophy	Slowly progressive, girdle muscle weakness and contractures of ischiocrural muscles. Elevate CK levels Onset: early	[66, 163]
	ORAI1/TM4	p.P245L	GF Not constitutively activated Impairs slow Ca^{2+} dependent inactivation Requires STIM1 association	TAs in type I & II fibers Fiber size variation Fibro fatty infiltration Internal nuclei	Progressive proximal of distal upper limbs, proximal lower limb weakness Cramps Miosis Elevate CK levels Onset: late	[64, 164]
TAM TAM	STIM1/cEF	p.D84E	Constitutive STIM1 activation (clusters)	TAs in type I fibers, type I fiber prevalence, type II fiber atrophy, fiber size variation Internal nuclei	Proximal muscle weakness with lower limb predominance Diffuse cramps Elevate CK levels Hypocalcemia Onset: late	[165]

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Clinical and Histological Muscle Features Resulting from STIM1 and ORAI1 Gene Mutations						
Disease	**Gene/Position**	**Mutation**	**Lost or gain of function/others**	**Histological features**	**Muscle phenotype**	**Reference**
	ORAI1/TM1	p.G98S	GF Constitutive SOCE Increase in basal Ca^{2+} levels Normal ORAI & STIM1 protein expression (1/6 patient analyzed)	TAs in Type I & II fibers Single internal nuclei Type I fiber predominance Fiber size variation	Slowly progressive muscle weakness, lower and upper proximal limbs, myalgia, cramps, stiffness Marked replacement of soleus and gastrocnemius muscles with fat Severe atrophy and fat infiltration of trapezius, latissimus dorsi, gluteus medius, hamstrings and adductor thigh muscles Bilateral ankle joint contractures, rigid spine and hypocalcemia Elevate CK levels Onset: early	[63, 166]
TAM TAM	ORAI1/TM2	p.L138F	GF Constitutive SOCE Increase in basal Ca^{2+} levels	TAs in type I & II fibers Single/multiple internal nuclei Type I fiber predominance Fiber size variation	Slowly progressive, diffuse muscle weakness. Modest increase in CK levels Onset: mild	[63]
	ORAI1/TM1	p.S97C	GF Constitutive SOCE Ca^{2+} oscillations	TAs in type I & II fibers with predominance in type II fibers Type I fiber prevalence	Weakness in proximal and distal lower limbs and proximal upper limbs Cramps Miosis Elevate CK levels Onset: mild & late	[85]
	ORAI1/TM1	p.V107M	GF Constitutive SOCE Increase in basal Ca^{2+} levels	TAs in type I & II fibers Fiber size variability Internal nuclei	Proximal lower limb and upper limb weakness Stiffness, cramps, and myalgia Calf hypertrophy Elevate CK levels Onset: early	[166]
	ORAI1/TM3	p.T184M	GF No constitutive SOCE Requires STIM1 association Increase in basal Ca^{2+} levels	TAs in type I & II fibers Fiber size variability Internal nuclei	Mild general weakness Cramps and myalgia	[166]
	STIM1/cEF	p.D84G	GF Constitutive STIM1 activation Impairs STIM1 Ca^{2+} sensing Increase in basal Ca^{2+} levels Normal STIM1 expression	TAs in type I & II fibers Fiber size variation Type I fiber prevalence	Mild-slowly progressive Proximal lower limb weakness, mild and diffuse upper limb weakness Elevate CK levels Onset: early & mild	[62]

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Clinical and Histological Muscle Features Resulting from STIM1 and ORAI1 Gene Mutations						
Disease	**Gene/Position**	**Mutation**	**Lost or gain of function/others**	**Histological features**	**Muscle phenotype**	**Reference**
	STIM1/cEF	p.H72Q	GF Constitutive STIM1 activation Impaired STIM1 Ca^{2+} sensing	TAs in type I & II fibers Fiber size variation Type I fiber prevalence Type II fiber atrophy	No muscle weakness Elevate CK levels Onset: asymptomatic	[62]
	STIM1/cEF	p.G81D	GF Constitutive SOCE Increase in basal Ca^{2+} levels Impairs STIM1 Ca^{2+} sensing	TAs with prevalence in type I fibers Type II fiber atrophy	Lower and upper limb muscle weakness, Mild-severe contractures, rigid spine, stiff neck, scapular winging, muscle atrophy Elevate CK levels Onset: early	[167]
	STIM1/hEF	p.H109Rp.H109N	GF Constitutive STIM1 activation Impairs STIM1 Ca^{2+} sensing	TAs in type I & II fibers Type I fiber prevalence Type II fiber atrophy	Proximal lower limb weakness, mild proximal upper limb weakness Elevate CK levels Onset: early, mild & late	[62, 163, 168]
	STIM1/cEF	p.N80T	GF Constitutive STIM1 activation (clusters) Impairs STIM1 Ca^{2+} sensing	TAs with prevalence in type II fibers Fiber size variability Internal nuclei and fibrosis	Proximal and lower limb muscle weakness Myalgia Heel contractures Eye movement defects Elevate CK levels Onset: early & late	[168]
	STIM1/cEF	p.L96V	GF Constitutive STIM1 activation (clusters) Impaired STIM1 Ca^{2+} sensing	TAs with prevalence in type II fibers Fiber size variability Internal nuclei	Muscle weakness in lower limbs Myalgia Elevated CK levels Onset: early	[168]
	STIM1/hEF	p.F108I	GF Constitutive STIM1 activation (clusters) Impairs STIM1 Ca^{2+} sensing	TAs Fiber size variability Type I fiber prevalence Internal nuclei, fibrosis	Proximal muscle weakness Myalgia Elevated CK levels Onset: early	[168]
	STIM1/hEF	p.F108L	GF Moderate constitutive STIM1 activation (clusters) Impairs STIM1 Ca^{2+} sensing	TAs Atrophy of Type II fibers	No muscle weakness Myalgia Normal CK levels Onset: late	[168]