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With the greatest care, stromal interaction molecule (STIM) proteins verify what skeletal muscle is doing

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Skeletal muscle contracts or relaxes to maintain the body position and locomotion. For the contraction and relaxation of skeletal muscle, Ca^{2+} in the cytosol of skeletal muscle fibers acts as a switch to turn on and off a series of contractile proteins. The cytosolic Ca^{2+} level in skeletal muscle fibers is governed mainly by movements of Ca^{2+} between the cytosol and the sarcoplasmic reticulum (SR). Store-operated Ca^{2+} entry (SOCE), a Ca^{2+} entryway from the extracellular space to the cytosol, has gained a significant amount of attention from muscle physiologists. Orai1 and stromal interaction molecule 1 (STIM1) are the main protein identities of SOCE. This mini-review focuses on the roles of STIM proteins and SOCE in the physiological and pathophysiological functions of skeletal muscle and in their correlations with recently identified proteins, as well as historical proteins that are known to mediate skeletal muscle function. [BMB Reports 2018; 51(8): 378-387]

INTRODUCTION

Skeletal muscle makes up 36 to 42% of human body mass (the percentage of skeletal muscle in the body depends on gender, age, and various environmental factors), and its main task is to maintain the position of the body and locomotion via contraction and relaxation (1). Skeletal muscle contraction is achieved via excitation-contraction (EC) coupling, and Ca^{2+} ions from the sarcoplasmic reticulum (SR, an intracellular

organelle corresponding to the endoplasmic reticulum (ER) in other types of cells) work as a switch to activate a series of contractile proteins during skeletal muscle contraction (2-5). The initiation of skeletal muscle contraction is different from maintenance (i.e., the duration of the skeletal muscle contraction with a high cytosolic Ca^{2+} level, and is considered one of the significant parameters of skeletal muscle strength). When elucidating the maintenance of skeletal muscle contraction, skeletal muscle physiologists study classical EC coupling and pay significant attention to extracellular Ca^{2+} entry (6-8). One of the avenues for extracellular Ca^{2+} entry in skeletal muscle fibers is store-operated Ca^{2+} entry (SOCE) (6, 7). Orai1 (a Ca^{2+} entry channel protein) and stromal interaction molecule 1 (STIM1, a Ca^{2+} sensor protein) form a unit that is the main mediator in skeletal SOCE, as well as in other types of cells (9-18). This mini-review focuses on the roles of STIMs and SOCE in the physiological or pathophysiological functions of skeletal muscle and on the correlations with recently identified proteins, as well as historical EC coupling-mediating proteins.

SKELETAL EC COUPLING

In skeletal muscle fibers during EC coupling (2-5), acetylcholine receptors, i.e., ligand-gated Na^+ channels, in the sarcolemmal membrane (corresponding to the plasma membrane in other types of cells) are activated by acetylcholine that is released from motor neurons (skeletal muscle fibers are often called 'myotubes' in *in vitro* culture conditions). Na^+ influx into the cytosol through acetylcholine receptors induces depolarization of the sarcolemmal membrane ('excitation' of the skeletal muscle fibers). The spreading of the membrane depolarization to the interior of the skeletal muscle fibers via invagination of the sarcolemmal membrane (transverse (t)-tubules) activates dihydropyridine receptors (DHPRs) that is a voltage-gated Ca^{2+} channel on the t-tubule membrane. T-tubule membranes are closely juxtaposed with the SR membrane, which is more specialized than the ER in storing a massive amount of Ca^{2+} ions (3, 4, 19-22). Collectively, this membrane complex is referred to, either as the triad junction, or as the junctional membrane complex. Physical stimulation

induces the active DHRP to activate ryanodine receptor 1 (RyR1), which is a ligand-gated Ca^{2+} channel on the SR membrane. Ca^{2+} ions that are stored in the SR are released to the cytosol via the activated RyR1. The Ca^{2+} ions in the cytosol bind to troponin C, which activates a series of contractile proteins to induce contraction in skeletal muscle fibers. Interestingly, during the skeletal EC coupling, DHPRs serve as activating ligands for RyR1 (2-5). Accordingly, Ca^{2+} entry via DHPRs is not a necessary factor for skeletal EC coupling, although Ca^{2+} entry via DHPR does exist, which is one of the critical differences between skeletal and cardiac EC coupling processes. Skeletal EC coupling is an outside-in signal from the DHPRs on t-tubule membranes to the internal RyR1 on the SR membrane and is regarded as an orthograde signal compared with other recently discovered signals.

A totally different protein is required to remove and recycle the Ca^{2+} ions from the cytosol during skeletal muscle relaxation − a reverse action to skeletal muscle contraction. During relaxation of the skeletal muscle, sarcoplasmic/endoplasmic reticulum Ca^{2+}-ATPase 1a (SERCA1a, a Ca^{2+} pump on the SR membrane) uptakes cytosolic Ca^{2+} ions into the SR in order to reduce the cytosolic Ca^{2+} level to that at rest as well as to refill the SR with Ca^{2+} ions (3, 23). SERCA1a is the major isoform in adults (24). Calsequestrin (CSQ), a luminal protein of the SR, has a Ca^{2+}-buffering ability that prevents the SR from swelling or bursting by osmotic pressure due to the high Ca^{2+} concentrations in the SR following skeletal muscle relaxation (i.e., at rest) (25).

EMERGING PROTEINS RELATED TO SKELETAL EC COUPLING

Modern physiologists who study skeletal muscle have steadily searched for and discovered new proteins with exclusive functions in skeletal muscle and have established their interactive mechanisms with EC coupling-mediating proteins. The triad junction supports an efficient arrangement of the EC coupling-mediating proteins on the SR and t-tubule membranes, which allows for the rapid and frequent delivery of Ca^{2+}, depending on the purpose and on the appropriate retention of Ca^{2+} in skeletal muscle fibers (3, 4). Junctophilin 1 (JP1, also known as mitsugumin 72), JP2, or mitsugumin 29 (MG29) contributes to the formation and maintenance of the triad junction (3, 4, 19-22, 26).

The activity of the EC coupling-mediating proteins is regulated by other proteins. STIM1 on the SR membrane negatively regulates Ca^{2+} release from the SR through a direct interaction of its C-terminus with DHPRs (27). The activity of RyR1 is increased by the binding of the FK506-binding protein 12 (FKBP12) or JP1 (28-32). Triadin on the SR membrane interacts with RyR1 via its KEKE motifs and is required for typical RyR1 activity (33-35). SERCA1a activity is regulated, either by MG53 or STIM1: MG53 binds to SERCA1a via its TRIM-PRY domain and attenuates SERCA1a activity (36);

STIM1 binds to SERCA1a via its C-terminal portion, and is required for the full activity of SERCA1a (37). On the other hand, there are several proteins that do not directly bind to the EC coupling-mediating proteins but regulate the gain of EC coupling. Canonical-type transient receptor potential cation channel type 3 (TRPC3) is required to sustain high Ca^{2+} levels in the cytosol for the full gain of EC coupling (3, 38). For other proteins or factors that regulate skeletal EC coupling, either directly or indirectly, refer to primary review articles by Endo *et al.* (1977) and Zucchi *et al.* (1997) (2, 5).

BREAKING FRESH GROUND IN SKELETAL MUSCLE RESEARCH

Recent advances in the deep understanding of Ca^{2+} movements during skeletal muscle contraction and relaxation have established the involvement of extracellular Ca^{2+} in the various functions of skeletal muscles, including both contraction and relaxation; this has demonstrated the importance of Ca^{2+} entry from the extracellular space to the cytosol of skeletal muscle fibers. Extracellular Ca^{2+} entry into skeletal muscle fibers has gained significant attention over the past decade, although its existence was reported a long time ago (6-8).

SOCE is one of the methods for extracellular Ca^{2+} entry, and is also known as Ca^{2+} release-activated Ca^{2+} (CRAC) in mast cells (6, 7). The proteins required for SOCE have been identified over a 20-year period, since its discovery in the 1980s (6, 7). Orai1 (also known as CRACM1) works as the Ca^{2+} entry channel in plasma/sarcolemmal membranes during SOCE (14-18). The gating of Orai1 depends on the state of the STIM1 located in the ER/SR membrane. STIM1 is a subunit-like protein of Orai1, rather than a regulatory protein (9-13), as described in the next section. STIM1 functions as a Ca^{2+} sensor for the amount of Ca^{2+} ions that are stored in the ER/SR. In skeletal muscle, SOCE contributes to the Ca^{2+} supply that is required for the maintenance of skeletal muscle contraction (8, 39). However, note that SOCE is not for the initiation of skeletal muscle contraction, as mentioned in the *Introduction* section; rather, SOCE is required for the fine-tuning of skeletal muscle functions, particularly for events taking place over a long period or with repetition. Furthermore, SOCE is believed to be one of the common tools that mediate various cellular events, including the progression of diseases, as well as physiological functions in skeletal muscle (8, 39).

GENERAL OVERVIEW OF SOCE

Generally speaking, Ca^{2+} depletion of the ER is the initiation signal that evokes SOCE. The Ca^{2+} depletion is sensed by the N-terminus of STIM1, which induces the dimerization of STIM1s and the relocation of dimeric STIM1s to the ER membrane near the plasma membrane (10 to 25 nm gap

between the two membranes) (40, 41). At the same time, some portions of the ER are rearranged towards the plasma membrane where the dimeric STIM1s relocate (42). It remains unclear, however, what initiates the ER rearrangement and STIM1 relocation, and in what order. In response to the ER rearrangement and STIM1 relocation, monomeric Orai1 on the plasma membrane simultaneously oligomerizes to form a hexameric and functional Ca^{2+} channel and relocates to the plasma membrane near the ER membrane containing the dimeric STIM1s; this allows for the formation of heteromeric oligomers that are composed of STIM1s and Orai1s (called 'puncta') (43). The formation of puncta allows an extracellular Ca^{2+} entry through Orai1 (44, 45). The entire process of SOCE starting from ER Ca^{2+} depletion to extracellular Ca^{2+} entry takes several seconds, depending on the types of cells (46). Two independent research teams have reported on the interaction of the domain of STIM1 to Orai1 in the puncta: the CRAC activation domain (CAD) and the STIM1-Orai activating region (SOAR) (44, 45). CAD and SOAR overlap with one another and are referred to as CAD/SOAR, which is highly conserved and binds directly to the N- and C-termini of Orai1.

SOCE IN THE SKELETAL MUSCLE

In skeletal SOCE, the SR and t-tubule membranes substitute for the ER and plasma membranes, respectively, and Orai1 and STIM1 are also the main proteins that are responsible for skeletal SOCE (47-49). Interestingly, skeletal SOCE has exclusive properties that compare to properties in other types of cells or tissues. Orai1 and STIM1 in skeletal muscle form puncta even during resting periods (i.e., puncta formations without the Ca^{2+} depletion from the SR) (Fig. 1A) (26, 27, 39). As mentioned in the Introduction section, skeletal muscle fibers have a specific membrane structure that is referred to as the triad junction. Closely juxtaposed t-tubule and SR membranes in the triad junction allow skeletal muscle to skip both the rearrangement of the SR membrane near the t-tubule membrane and the relocation of STIM1s or Orai1s to the rearranged SR or t-tubule membranes during skeletal SOCE. The formation of pre-puncta occurs during the development of skeletal muscle fibers (i.e., myogenesis) and during terminal differentiation, which is a process whereby skeletal myoblasts fuse and form multi-nucleated mature myotubes; myoblasts are the proliferative form of satellite cells, and these are also referred to as skeletal muscle stem cells (26, 27, 39). The pre-puncta reside in an almost-ready-to-go state, and the conformational changes of Orai1 and/or STIM1 seem to be required in order to evoke skeletal SOCE (26, 27, 50). An advantage of the pre-puncta formation in the skeletal SOCE is faster kinetics (an immediate and rapid delivery of extracellular Ca^{2+} to the cytosol during the skeletal SOCE). The skeletal SOCE occurs in less than a second i.e., millisecond activation, which is significantly faster than in other types of cells that can require up to several seconds (39, 49, 51). While skeletal SOCE is fast, it is relatively slower than classical Ca^{2+} movements in skeletal muscle fibers, such as intracellular
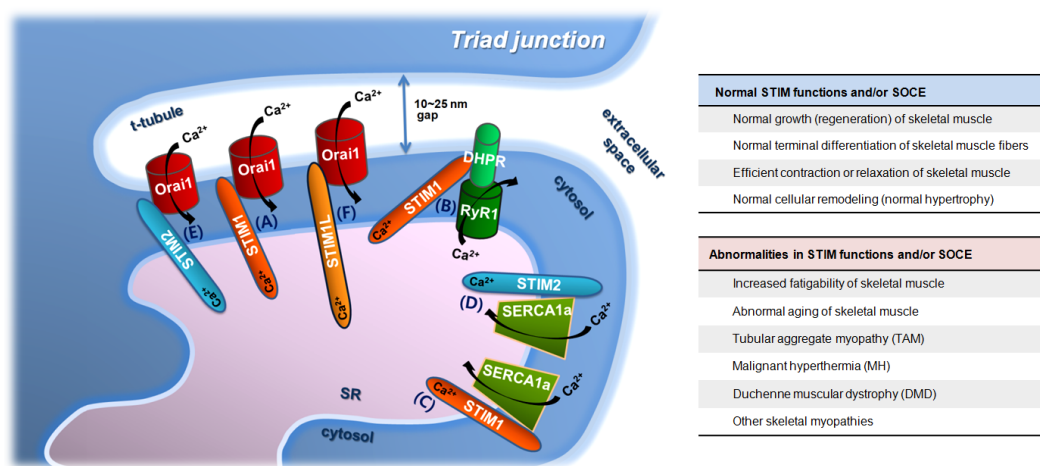
Fig. 1. Ca^{2+} movements involving STIMs and/or skeletal SOCE in skeletal muscle, and proteins that either regulate or are otherwise related to the Ca^{2+} movements. A triad junction with proteins that either regulate or are related to STIMs and skeletal SOCE is depicted, and the involvement of STIM proteins in the Ca^{2+} movements of skeletal muscle fibers is presented (A to F). DHPR, dihydropyridine receptors; RyR1, ryanodine receptor 1; STIM1, stromal interaction molecule 1; STIM2, stromal interaction molecule 2; STIM1L, a long form of STIM1; SERCA1a, sarcoplasmic/endoplasmic reticulum Ca^{2+}-ATPase 1a; SR, sarcoplasmic reticulum; and, t-tubule, transverse-tubule. The direction of Ca^{2+} movements via the proteins is presented by black arrows. STIMs and/or skeletal SOCE participate in various skeletal muscle functions, ranging from short to long and from physiological to pathophysiological phenomena (summarized in the right-hand panel). Proteins that contribute to the formation and maintenance of the triad junction (JP1, JP2, or MG29) are not depicted, despite their significance.

Ca^{2+} release to the cytosol during contraction or Ca^{2+} uptake to the SR during relaxation.

The SR in skeletal muscle fibers is subdivided by location (5). Junctional SR is also referred to terminal cisternae and participates in the formation of the triad junction, which is where STIM1 in other types of cells exist during SOCE. Longitudinal SR is not juxtaposed with t-tubule membranes. STIM1 in the skeletal muscle fibers is found in both types of the SR (39). The existence of graded SOCE, which is also referred to as delayed SOCE, has been reported in skeletal muscle, and STIM1 in the longitudinal SR could be responsible for the graded SOCE (52-54). Therefore, STIM1-mediated SOCE in skeletal muscle follows different time-courses according to the location of STIM1 in the SR, which could contribute to various functions involving the skeletal SOCE, with a delayed onset or an extended period.

Skeletal SOCE is one of the retrograde signals in terms of the working direction (Ca^{2+} depletion from the SR is a signal from the internal SR that triggers activation of Orai1 in the t-tubule membrane) (42, 55). Therefore, the skeletal SOCE fundamentally differs from the movement of Ca^{2+} during orthograde EC coupling in terms of both the working direction and the source of Ca^{2+}.

DOMAINS OF STIM1

STIM1 has a short intra-luminal N-terminus (with a signal peptide, a canonical EF-hand, a hidden EF-hand (pseudo EF-hand), and a sterile α-motif (SAM) domain), a single transmembrane domain, and a cytosolic C-terminus (with three coiled-coil (CC) domains, a CAD/SOAR, a di-arginine consensus site, and a lysine-rich domain) (9, 13, 56). The signal peptide is composed of 22 amino acids and directs STIM1 to the ER, which amounts to an ER retention signal (12, 57, 58). The CC domains, the lysine-rich domain, and the di-arginine consensus site also contribute to ER retention (57, 58). The D76, D84, and E87 residues in the canonical EF-hand are critical for sensing the amount of Ca^{2+} in the ER (11, 27, 59, 60). The EF-hands and SAM domain are responsible for the self-oligomerization and the relocalization of STIM1 during SOCE (61, 62). The first CC domain (CC1) participates in the oligomerization of STIM1 at rest (63). CAD/SOAR is the binding site to the N- and C-termini of Orai1 (44, 45). The lysine-rich domain is responsible for the Orai1-independent plasma membrane targeting of STIM1 (44).

STIMs IN THE SKELETAL MUSCLE

The domain arrangement and the function of each domain of STIM1 in the skeletal muscle are the same as those of STIM1 found in other types of cells. STIM1 binds to CSQ in hetrologous expression systems and the binding interferes with STIM1 dimerizations, with the binding between STIM1 and Orai1, and with the skeletal SOCE (64-67). STIM1 plays important roles in Ca^{2+} release and uptake during skeletal muscle contraction and relaxation, as well as in skeletal SOCE. STIM1 binds to DHPR and attenuates DHPR activity, which reduces intracellular Ca^{2+} release in response to contractile stimuli by way of DHPR, such as membrane depolarization during the EC coupling (Fig. 1B) (27). STIM1 also binds to SERCA1a via its C-terminal portion (amino acids from 449 to 671) and maintains the full activity of SERCA1a at a high cytosolic Ca^{2+} level. One such example is during skeletal muscle relaxation following contraction (Fig. 1C) (37). Therefore, STIM1 functions as an all-around player in Ca^{2+} movements in the skeletal muscle. It acts a faithful guardian of SR Ca^{2+} storage by sensing SR Ca^{2+} depletion during skeletal SOCE (Fig. 1A) and an attenuator of DHPR activity during skeletal muscle contraction (Fig. 1B). It also balances SERCA1a activity during skeletal muscle contraction and relaxation (Figs. 1C and 1D; for this, see the next paragraph).

In addition to the role of STIM1 in a single event, such as skeletal SOCE, it is also involved in long-term events such as terminal differentiation as well as neonatal muscle growth (68, 69). STIM1 expression has been detected in myoblasts before terminal differentiation. It gradually increases initially during the terminal differentiation until differentiation day 2 and is maintained during further differentiation days after a small decrease (27, 39). These changes in the expression level of STIM1 accompany the enhancement of skeletal SOCE during terminal differentiation (27, 39, 70). STIM2 is also required for terminal differentiation (71, 72). STIM1L, in conjunction with TRPC1 and TRPC4, participates in the formation of larger myotubes during terminal differentiation (73).

STIM2 and STIM1L have been identified as homologues of STIM1 (13, 52, 74). The physiological roles of the homologues are not as well defined as those for STIM1. STIM2 plays a role in SOCE in mild Ca^{2+} depletion of the ER, and regulates basal Ca^{2+} levels in a storage-independent manner in heterologous expression systems (75, 76). STIM1 and STIM2 are functionally redundant to some degree in skeletal muscle, such as in the case of positive controls in SOCE (Fig. 1E). Either STIM1 or STIM2 can correct most of the impact of STIM2- and STIM1-silencing in skeletal SOCE and in terminal differentiation (71, 72, 77). STIM2 acts similarly to STIM1 i.e., it also binds to SERCA1a via a C-terminal portion (amino acids from 453 to 729) (Fig. 1D) and contributes to intracellular Ca^{2+} distribution between the cytosol and the SR. However, the regulation of SERCA1a activity by STIM2 is in opposition to that by STIM1, and attenuation of SERCA1a activity by STIM2 is the reason STIMs work as balancers of SERCA1a activity (77). Thus, STIM1 and STIM2 function as fine-tuners that regulate SERCA1a activity in skeletal muscle fibers. Overall, the roles of STIM2 in skeletal muscle bear similarities and also differences to those of STIM1. This functional redundancy makes it difficult to discriminate the roles of STIM1 from those of STIM2. STIM1L is an alternatively spliced, longer variation of STIM1 (47, 52). It is abundantly expressed in skeletal muscle,

but much less so in non-excitable cells (47, 52). STIM1L generates faster and repetitive skeletal SOCE through formation of permanent puncta (Fig. 1F) (52).

Taken together, STIMs and skeletal SOCE in the skeletal muscle play various roles in the integration of signals during growth, terminal differentiation, contraction and relaxation of skeletal muscle. These functions rely on spatial, temporal, and additional resources to utilize STIMs and skeletal SOCE.

DOMAIN STRUCTURES IN STIM1

Crystallographers have examined each domain of human STIM1, but not that of full-length STIM1. The 3-dimensional (3D) structure of SOAR that is capable of activating Orai1 shows four helixes (78). Dimeric SOARs are necessary to activate Orai1 (78). The CC1 domain has an adjacent inhibitory helix (CC1-IH, amino acids from 237 to 340), and CC1-IH show a long helix and contributes to the oligomerization of STIM1 (79). The binding of IH to SOAR induces an inactive STIM1 dimer (78, 79). The CC1 and CC2 regions homo-dimerize in an antiparallel fashion and form a U-shaped structure (80). A trimer of the dimers of CC1 and CC2, which results in a hexameric STIM1 homomer, activates a hexameric Orai1 with a central ion-permeating pore (41, 81, 82).

The canonical EF-hand is paired with a hidden EF-hand, and the EF-hand pair is then composed of ten short helixes that mediate mutually hydrophobic interactions between the EF-hand pair and the SAM domain (EF-SAM) (56). Ca^{2+} depletion makes the EF-SAM unstable by exposing several hydrophobic residues, and the unstable EF-SAM oligomerizes at the luminal portion of the SR to be energetically favorable. The 3D structure of the EF-SAM in STIM2 is not much different from that in STIM1, except for an expanded non-polar cleft (62). This suggests the possibility that other domains of STIM2 are not much different from those of STIM1, although the 3D structure of STIM2 remains unknown.

It is interesting that the 3D-structure of Orai1 differs markedly from that of other ion channels, and the functional Orai channel of *Drosophila melanogaster* exists as a hexameric assembly (a tetramer is common in other channels) (81, 82).

SKELETAL MUSCLE FATIGUE OR AGING THAT INVOLVES SKELETAL SOCE

The involvement of STIM1 and/or SOCE in relatively longer-term events of the skeletal muscle, such as fatigue and aging, is briefly mentioned in this section. Correlations between skeletal muscle fatigue and skeletal SOCE have been reported. Skeletal muscle fibers from transgenic mice with dominant-negative Orai1 display a lack of skeletal SOCE and an increased susceptibility to skeletal muscle fatigue (50). MG29-deficient mice also show an increased susceptibility to skeletal muscle fatigue due to abnormal triad junctions and severe dysfunctions in skeletal SOCE (83-85). Skeletal muscle

fibers from sarcalumenin-deficient mice show increases in skeletal SOCE and fatigue resistance (86). Transgenic mice with sarcolipin are more resistant to skeletal muscle fatigue, and skeletal muscle fibers from these mice show an increase in skeletal SOCE (87). Exercising mice show extra junctions that are composed of the SR and t-tubule membranes containing Orai1 and STIM1 (88). The mice with the extra junction show increased resistance to skeletal muscle fatigue, and SOCE inhibitors abolish the increased resistance to skeletal muscle fatigue. Therefore, SOCE could be one of the fatigue-regulating factors in skeletal muscle.

Skeletal muscle fibers from aged mice (26-27 months corresponding to old age in humans) show severe reductions in skeletal SOCE (89). However, the reduction in the skeletal SOCE is not the result of a change in either STIM1 or Orai1 expression levels. In accordance with this fact, the expression levels of neither STIM1 nor Orai1 are changed during skeletal muscle aging in humans, mice, or flies (90). It is possible that changes in the functional properties of STIM1 and Orai1, possibly in conjunction with the regulatory proteins, could govern the aging processes of skeletal muscle. Unlike cardiac muscle, hypertrophy in skeletal muscle is related to healthy phenomena such as muscle growth, repair, or regeneration (i.e., cellular remodeling) (91, 92). Healthy hypertrophy in skeletal muscle involves increases in skeletal SOCE (69, 93). For both a broader and a deeper understanding of the fundamental aspects of aging in skeletal muscle, readers are encouraged to refer to a study by Zahn *et al*. (90), where the transcriptional profiling of aging in human, mouse, and fly muscle is well defined using common aging signature sets.

SKELETAL MUSCLE DISEASES THAT INVOLVE STIM1 AND/OR SKELETAL SOCE

Skeletal muscle diseases are extremely complex issues in terms of their causes, onsets, levels of progress, symptoms, and prognoses. In this section, the involvement of STIM1 and/or skeletal SOCE in skeletal muscle diseases are briefly mentioned. However, as far as we could ascertain, there are no reports on the involvement of either STIM2 or STIM1L in skeletal muscle diseases.

Patients with a loss-of-function mutation of STIM1, E136X, show severe combined immunodeficiency (SCID) and congenital myopathies such as non-progressive muscular hypotonia due to lack of skeletal SOCE (94). Patients with another type of STIM1 mutation, R429C, also show muscular hypotonia (95). STIM1 deficiency in mice results in a perinatally lethal condition, which is characterized by a failure to show skeletal SOCE, a significant reduction in body weight, skeletal-muscle hypotonia, and a significant increase in susceptibility to skeletal muscle fatigue (39). STIM1 transgenic mice show a significant increase in skeletal SOCE, as observed in dystrophic muscle fibers (96). These reports suggest that STIM1 in skeletal muscle is involved in diseases such as skeletal

muscle dystrophies as well as in physiological phenomena such as growth, terminal differentiation, and contraction and relaxation of skeletal muscle.

Tubular aggregate myopathy (TAM), a genetically heterogeneous disease, is characterized by tubular aggregates within skeletal muscle fibers (97). These tubular aggregates are among the secondary features that are representative markers of various human myopathies (97). Mutations in STIM1 have been found in patients with TAM (N80T, G81D, L96V, F108I, H109R, I115F, or I484R) (98-101). In particular, patients with one of four STIM1 mutations in the EF-hands or a region near the hidden EF-hand (H72Q, D84G, H109N, or H109R that are constitutively active forms of STIM1) also show atrophy of skeletal muscles and progressive muscle weaknesses involving excessive levels of skeletal SOCE and a significantly higher cytosolic Ca^{2+} level (102). Therefore, STIM1 is among the genetic causes of TAM.

When volatile anesthetics are administered to patients with malignant hyperthermia (MH), a pharmacogenetic skeletal muscle disorder, it can lead to life-threatening skeletal muscle contracture: An increase in body temperature due to the uncontrolled elevation of cytosolic Ca^{2+} levels is mediated by uncontrolled activation of RyR1, which ultimately causes sudden death (103, 104). A sustained skeletal SOCE also contributes to the maintained and uncontrolled elevation of cytosolic Ca^{2+} levels in patients with MH (105). In addition, MH-like symptoms have been observed in the knock-out mice of either CSQ1 or CSQ2 or the knock-in mice of RyR1 mutation, wherein the increase in body temperature is related to an increase in skeletal SOCE (67, 106-108). It is possible that skeletal SOCE could also be involved in the progression of central core disease (CCD involves progressive muscle weakness), because patients with CCD are also at high risk for the development of MH (109).

Duchenne muscular dystrophy (DMD) is a lethal form of skeletal muscular dystrophy that is characterized by progressive wasting of the skeletal muscle (110). The enhancement of skeletal SOCE in the skeletal muscle fibers of *mdx* mice (a mouse model of DMD) is accompanied by significant increases in STIM1 and Orai1 expression (111-113). Surprisingly, undifferentiated myoblasts from *mdx* mice have also shown enhanced SOCE, with a significant increase in STIM1 expression (114). Skeletal muscle fibers from transgenic mice with muscle-specific STIM1 show characteristics of DMD such as a significant increase in skeletal SOCE (96). Therefore, abnormalities in STIM1 expression and skeletal SOCE are causes of DMD pathogenesis.

The involvement of STIM1 and/or SOCE in skeletal muscle diseases, by way of proteins such as TRPC3 and MG53, have also been reported in the literature (115-121). In addition, other possible factors that could contribute to skeletal muscle diseases have also been examined in several articles (54, 122-124). As shown in other studies, Orai1 is also significantly related to skeletal muscle diseases as well as physiological functions (125-128).

CONCLUDING REMARKS

Extracellular Ca^{2+} entry into skeletal muscle via SOCE, particularly STIM-mediated SOCE, is the focus of this mini-review. STIMs and/or STIM-mediated skeletal SOCE participate in various skeletal muscle functions, ranging from short to long-term functions, and from physiological to pathophysiological phenomena, such as contraction and relaxation, growth, terminal differentiation, cellular remodeling, fatigue, aging, and diseases. Thus, it seems that STIMs always verify what the skeletal muscle is doing and tunes the various functions of skeletal muscle with the greatest of care.

The involvement of STIMs in both healthy and diseased states of skeletal muscles implies that these proteins may have dual roles. Unfortunately, despite all the evidence and the importance of the involvement of STIMs in various skeletal muscle functions, the extent of the extracellular Ca^{2+} contribution via STIM-mediating skeletal SOCE versus the intracellular Ca^{2+} contribution to skeletal muscle functioning has not been well addressed. Studies on the relative extent of extracellular Ca^{2+} contributions via STIMs to skeletal muscle functions could provide answers as to how the dual roles of these protein functions in the body could be utilized.

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CONFLICTS OF INTEREST

The authors have no conflicting interests.

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