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Review

The role of store-operated calcium influx in skeletal muscle signaling

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ABSTRACT

In cardiac and skeletal muscle Ca^{2+} release from intracellular stores triggers actomyosin cross-bridge formation and the generation of contractile force. In the face of large fluctuations of intracellular calcium ($[Ca^{2+}]_i$) that occur with contractile activity, myocytes are able to sense and respond to changes in workload and patterns of activation through calcium signaling pathways which modulate gene expression and cellular metabolism. Store-operated calcium influx has emerged as a mechanism by which calcium signaling pathways are activated in order to respond to the changing demands of the myocyte. Abnormalities of store-operated calcium influx may contribute to maladaptive muscle remodeling in multiple disease states. The importance of store-operated calcium influx in muscle is confirmed in mice lacking STIM1 which die perinatally and in patients with mutations on STIM1 or Orai1 who exhibit a myopathy exhibited by hypotonia. In this review, we consider the role of store-operated Ca^{2+} entry into skeletal muscle as a critical mediator of Ca^{2+} dependent gene expression and how alterations in Ca^{2+} influx may influence muscle development and disease.

1. Introduction

Calcium signaling plays a fundamental role in many cellular processes including growth and differentiation, metabolism, and regulation of gene expression. Nowhere is this more clear than in skeletal muscle where Ca^{2+} release is required for muscle contraction through excitation contraction coupling (ECC). But changes in cytosolic Ca^{2+} in muscle can also be converted into biochemical changes through activation of signal transduction cascades that are require Ca^{2+}/calmodulin for activation. Examples of these cascades include signaling through calmodulin kinases (CamK) or the Ca^{2+}/calmodulin-activated serine-threonine phosphatase, calcineurin, where changes in Ca^{2+} can influence the phosphorylation state of key target proteins [1,2]. It is through these signaling cascades that Ca^{2+} can influence skeletal muscle development and differentiation. Here, we consider the role of Ca^{2+} entry into skeletal muscle as a critical mediator of Ca^{2+}-dependent gene expression and how alterations in store-operated Ca^{2+} entry may influence muscle development and remodeling. Finally we discuss the role of abnormal store-operated calcium influx in the pathogenesis of myopathies: both in mouse models and in patients with combined immunodeficiency due to mutations in STIM1 or Orai1 (Figs. 1 and 2).

2. Calcium signaling in myotube development

During muscle development and muscle regeneration, myoblasts proliferate and then undergo a highly ordered process of myogenic commitment in which they leave the cell cycle and express muscle specific proteins [3]. Myoblasts then migrate and align with each other, and ultimately undergo fusion with one another to form primary myotubes. Myoblasts then fuse with the primary myotubes generated in this manner to form secondary myotubes. A multitude of elements are critical for the process of myoblast fusion including membrane-associated proteins, signaling complexes, and extracellular/secreted molecules [4]. Calcium plays a critical role in multiple steps involved in myotube formation. Calcium activates intracellular cysteine proteases, calpains, which are required for cytoskeletal re-organization during migration and cell fusion [5]. Increased intracellular calcium also activates calcineurin, a serine-threonine phosphatase, involved in the downstream activation of MEF-2 and the NFAT family of transcription factors which have been shown to regulate myotube development [6–9]. Ca^{2+}-calmodulin can also influence muscle specific gene expression through the activation of the CamKII pathway [10]. Here, CamKII can influence MEF2 signaling by altering the actions of class II histone deacetylases (HDAC) [11].

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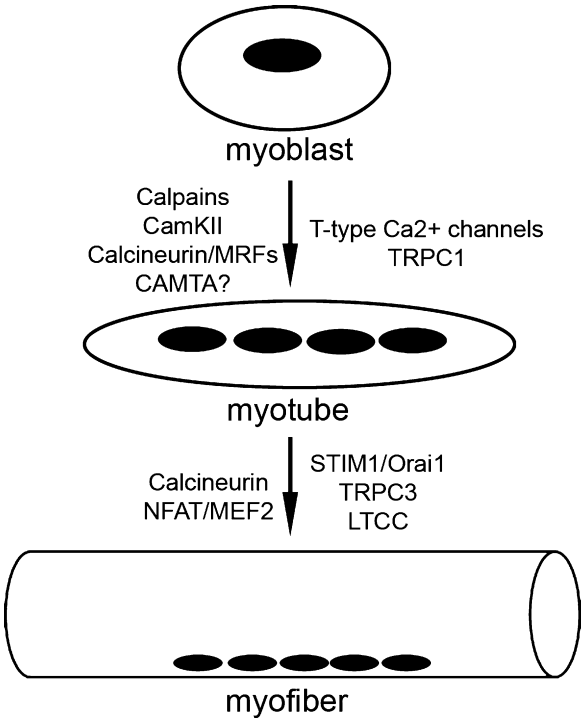

Fig. 1. Calcium signaling proteins involved in the differentiation of myoblasts into myotubes and in the subsequent differentiation of myotubes into myofibers. Signaling proteins and transcription factors are listed to the left of the arrows. Ion channels and their regulatory proteins are listed on the right.

In addition CamKII can stimulate the expression of peroxisome proliferator-activated receptor gamma coactivator 1 (PGC-1), a master regulator of mitochondrial biogenesis [2]. Finally, calmodulin can also influence the actions of a transcriptional coactivator called calmodulin binding transcriptional activator (CAMTA). CAMTAs are known to activate cardiac transcription through a mechanism that involves class II HDACs [12]. Interestingly, dCAMTAs have been implicated in phototransduction of the drosophila eye [13]. Here, mutants of CAMTA signaling reveal a defect in the deactivation of rhodopsin. Given the critical importance of TRP channels in phototransduction, it is likely that Ca^{2+}/calmodulin from TRP channels are required to activate CAMTA dependent transcription. Interestingly, several recent studies have demonstrated the importance of TRPC channels to striated muscle development, degeneration and performance [14–16]. It will be important to determine if CAMTAs have a role in the TRPC response of Ca^{2+} dependent gene expression in skeletal muscle. Furthermore a deeper knowledge of the specific pathways by which Ca^{2+} signaling influences gene expression in muscle will be important in our understanding of how these events occur during muscle development and are altered during the adaptation response to exercise or in the pathogenesis of myopathies (Table 1).

Transient receptor potential (TRP) channels have previously been shown to function in axonal pathfinding during neuronal development [17]. TRP channel activation by local growth factor concentrations allows for extension or retraction of axonal processes [18]. Recent studies have also implicated transient receptor potential channels in myotube development. We previously showed that overexpression of TRPC3 in C2C12 myotubes resulted in increased NFAT transactivation: a process involving activation of calcineurin by Ca^{2+} influx, dephosphorylation of NFAT by calcineurin, translocation of NFAT to the nucleus, and DNA binding by NFAT resulting in altered gene expression [15]. Similarly the scaffolding protein Homer, which has been shown to bind to multiple members of the TRP channel family, is expressed as part of the myogenic differentiation program and promotes myotube differentiation through modulation of calcium-dependent gene expression [19]. Homer enhanced calcium signaling via the calcineurin/NFAT pathway resulting in greater activation of a muscle-specific transcriptional program [20].

Evidence also suggests that TRPC1 may be a route for calcium influx required for calpain activation during myoblast migration and fusion. Migration of C2C12 myoblasts was inhibited by GsMTx-4 peptide, an inhibitor of mechanosensitive channels, and Z-Leu-Leu, an inhibitor of calpains. Knockdown of TRPC1 in C2C12 myoblasts resulted in decreased calpain activity, reduced cell migration, and a reduction in myotube fusion [21]. Growth factor stimulation resulted in increased calcium influx, calpain activity, and accelerated migration which was blocked by TRPC1 knockdown [21]. TRPC1 has also been shown to play a role in mechanotransduction during myotube development. TRPC1 knockdown inhibited stretch-activated calcium influx in C2C12 myoblasts in response to atomic force microscopic pulling and blocked stretch-activated current assessed by the whole-cell patch clamp technique [22]. TRPC1 activity was negatively regulated by cholesterol depletion, suggesting that TRPC1 was functionally assembled in lipid rafts, but enhanced by sphingosine-1-phosphate suggesting a role for stress fibers and the cytoskeleton in TRPC1 recruitment [22].

3. Store-operated calcium influx in skeletal muscle

It has long been assumed that Ca^{2+} entry into skeletal muscle fibers contributes little to calcium signaling. However recent evidence has challenged this notion. Three forms of Ca^{2+} entry have been characterized in skeletal myotubes and fibers: excitation coupled calcium entry (ECCE), stretch activated Ca^{2+} entry (SACE), and store operated calcium entry (SOCE) [23,24]. ECCE is activated in myotubes following prolonged membrane depolarization or pulse trains and is independent of the calcium stores. ECCE requires functioning L-type calcium channels (LTCC) and RYR1 channels. Although the molecular identity of the pore required for ECCE remains undefined, the skeletal L-type current mediated by DHPR has been shown to be a major (and perhaps sole) contributor to ECCE [25–27]. Supporting this concept is recent data showing that expression of the cardiac alpha(1C) subunit in myotubes lacking either DHPR or RYR1 does result in Ca^{2+} entry similar to that ascribed to ECCE [28]. Unlike SOCE, ECCE is unaffected by silencing of STIM1 or expression of a dominant negative Orai1 [29]. ECCE is altered in malignant hyperthermia (MH) and may contribute to the disordered calcium signaling found in muscle fibers of MH patients [30]. Stretch activated Ca^{2+} entry (SACE) has been described in skeletal muscle and is believed to underlie the abnormal Ca^{2+} entry in disease states such as muscular dystrophy [31–33].

SOCE, on the other hand, requires depletion of the internal stores and has been best characterized in non-excitable cells [34,35]. SOCE in skeletal muscle was described previously in myotubes [36], but it was not until the discovery of two important molecules, stromal interaction molecule 1 (STIM1) and Orai1 in non-excitable cells, that the full importance of SOCE was recognized in muscle [37]. SOCE is likely to be important for refilling calcium stores necessary for normal metabolism and prevention of muscle weakness as well as contributing a signaling pool of calcium needed to modulate muscle specific gene expression. Key questions regarding Ca^{2+} entry in skeletal muscle include the identity of the molecular components of these pathways, the interrelationship of ECCE, SOCE and EC coupling, and finally, the relevance of these pathways to muscle performance and disease. It is important to point out that considerable overlap may exist between these different forms of Ca^{2+} entry. For example, recent stud-