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Authors

Tu, Michelle K
Levin, Jacqueline B
Hamilton, Andrew M
et al.

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Calcium signaling in skeletal muscle development, maintenance and regeneration

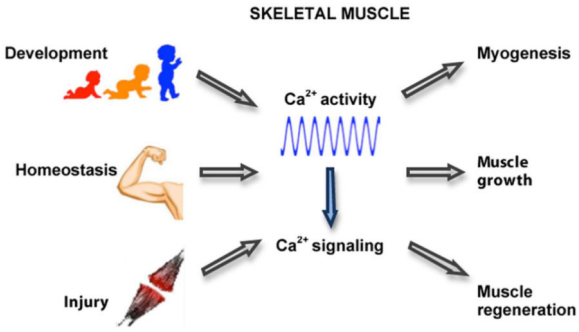
Michelle K. Tu, **Jacqueline B. Levin**, **Andrew M. Hamilton**, and **Laura N. Borodinsky**

Department of Physiology and Membrane Biology and Shriners Hospital for Children Northern California, University of California Davis, Sacramento CA 95817.

Abstract

Skeletal muscle-specific stem cells are pivotal for tissue development and regeneration. Muscle plasticity, inherent in these processes, is also essential for daily life activities. Great advances and efforts have been made in understanding the function of the skeletal muscle-dedicated stem cells, called muscle satellite cells, and the specific signaling mechanisms that activate them for recruitment in the repair of the injured muscle. Elucidating these signaling mechanisms may contribute to devising therapies for muscular injury or disease. Here we review the studies that have contributed to our understanding of how calcium signaling regulates skeletal muscle development, homeostasis and regeneration, with a focus on the calcium dynamics and calcium-dependent effectors that participate in these processes.

Graphical Abstract



Keywords

skeletal muscle; muscle satellite cells; muscle regeneration; muscle hypertrophy; calcium signaling; calcineurin; ryanodine receptors; muscle wasting

Corresponding author: Laura N. Borodinsky, Department of Physiology & Membrane Biology and Shriners Hospital for Children Northern California, University of California Davis School of Medicine, 2425 Stockton Blvd, Sacramento, CA 95817. Phone: 916-453-2285, Fax: 916-453-2288, lnborodinsky@ucdavis.edu.

Conflict of interest

None

1. Introduction

Throughout tissue morphogenesis and homeostasis, stem cells are recruited to generate the necessary tissue mass, to enable plastic changes in tissue size when challenged by changing stimuli, and to replenish damaged or degenerated tissue. Ca^{2+} is a ubiquitous intracellular signal that regulates a myriad of cellular processes. Skeletal muscle formation and plasticity presents an excellent model system for the study of the role of Ca^{2+} signaling due to the fact that Ca^{2+} dynamics are essential for muscle function. While the tight coupling of muscle excitation and contraction by Ca^{2+} dynamics has been well established, comparatively little is known about the role of Ca^{2+} dynamics in muscle formation, growth and regeneration. Because all these physiological contexts recruit stem cells, the investigation of muscle stem cell Ca^{2+} physiology becomes crucial for the elucidation of Ca^{2+} signaling-dependent regulation of skeletal muscle dynamics.

Myogenesis occurs during embryonic development through the proliferation and differentiation of dedicated progenitors in the somites. These cells initially express the transcription factors Pax3 and Pax7, but lose this expression during progressive specialization through the expression of a family of myogenic regulatory factors (MRFs), which include Myf5, MyoD, myogenin and MRF4 [1, 2]. Skeletal muscle formation continues with the differentiation of these specialized progenitors to form muscle fibers. A subset of the myogenic progenitors does not proceed through this specialization, retains Pax3/Pax7 expression and remains quiescent in the maturing and adult skeletal muscle. These muscle-specific stem cells are called muscle satellite cells [2, 3].

The participation of muscle satellite cells in skeletal muscle homeostasis has been a matter of debate, although robust evidence supports the role of satellite cells in muscle regeneration [4]. Inhibition of the muscle growth inhibitors myostatin and activin A by knocking out their receptor Acvr2 from myofibers in mice deficient in muscle satellite cells induces muscle hypertrophy, without satellite cell proliferation or an increase in nuclei number in myofibers [5]. This suggests that satellite cells may not play an essential role in muscle hypertrophy. In contrast, depletion of Pax7-expressing cells from the adult injured muscle blocks muscle regeneration [6–9], indicating the indispensable function of muscle satellite cells for muscle regeneration. The different roles of skeletal muscle stem cells in muscle development, growth and regeneration may originate from distinct physiological profiles of muscle stem cells in the different contexts. Identifying conserved and distinct mechanisms among myogenesis, muscle homeostasis and regeneration may be relevant to devising effective therapies for the injured and dystrophic skeletal muscle.

Here we review the role of Ca^{2+}-mediated activity in myogenesis, skeletal muscle plasticity and regeneration.

2. Calcium signaling in skeletal muscle development

Skeletal muscle development progresses through several stages by which muscle progenitor cells become mature muscle fibers. Although different species proceed through distinct cellular events, they all share a common program consisting of the proliferation of

mesodermal stem cells, then the progressive specialization into skeletal muscle progenitors, followed by the differentiation of muscle cells and further specification into different muscle cell types (Figure 1). This sequence of events finishes with the spatial arrangement of cells to form the functional musculature [2, 10–12]. Finally muscle cells undergo two rounds of fusion, first into multinucleated nascent myotubes and second into myofibers [13–16].

The role of Ca^{2+} signaling has been considered in each of these developmental steps and clear evidence of the necessity for different aspects of Ca^{2+} signaling has emerged in a broad spectrum of species, including the invertebrates *Caenorhabditis elegans* and *Drosophila melanogaster*, the lower vertebrates *Xenopus laevis* and zebrafish and in mammals such as mice and humans. The identified molecular mechanisms underlying Ca^{2+} participation in muscle development are responsible for either shaping Ca^{2+} dynamics or for transducing Ca^{2+} signals into a cellular response. Ca^{2+} stores are pivotal for eliciting a precise spatiotemporal pattern of Ca^{2+} signal in developing muscle cells. Expression of inositol-triphosphate receptors (IP3R) and ryanodine receptors (RyR) is developmentally regulated in mouse [17] and frog embryos [18], suggesting critical roles at different stages of muscle morphogenesis. Indeed, inhibiting Ca^{2+} transients in *Xenopus laevis* embryos disrupts skeletal muscle development by interfering with myofibril organization and sarcomere assembly [19]. In addition, inhibiting the Ca^{2+}/Calmodulin (CaM)-dependent myosin light chain kinase by interfering pharmacologically with its kinase activity or by incubating with a peptide pseudosubstrate impairs myosin thick filament assembly [20], implying a potential mechanism for RyR-Ca^{2+}-driven muscle development. RyR1 homozygous mutant mice in which RyR-mediated Ca^{2+} release is abolished die perinatally and also exhibit a severely disrupted musculature with small myotubes and disarranged myofibrils [21]. Altogether, these findings demonstrate a universal requirement for RyR-mediated Ca^{2+} dynamics in skeletal myogenesis. In addition, human myoblast differentiation *in vitro* is regulated by intracellular Ca^{2+} increases induced by changes in membrane potential [22–24]. *Xenopus* embryonic myocytes exhibit two types of Ca^{2+} transients, both RyRdependent, but of different durations [25]. The long-duration transients that last on average 80 seconds are present during a restricted developmental window prior to formation of myofibrils, while short 2-second-long transients persist during sarcomere assembly. Interestingly, artificial extension of long transient production inhibits sarcomere assembly [25], suggesting that the spatiotemporal code contained in the Ca^{2+} dynamics of differentiating muscle cells is critical for muscle development.

Directly linked to the pattern of Ca^{2+} dynamics in developing muscle cells is the store-operated calcium entry (SOCE) orchestrated by the sensor of internal Ca^{2+} stores, stromal interaction molecule 1 (STIM1), and the SOCE channels Orai1 and Transient Receptor Potential Canonical (TRPC) channels. STIM1 expression is developmentally regulated, peaking postnatally in the developing muscle in mice [26]. Mice lacking functional STIM1 die perinatally from a skeletal myopathy [27], indicating that STIM1-dependent Ca^{2+} signaling is necessary for myogenesis. Moreover, sarcolipin, an inhibitor of the sarcomere reticulum Ca^{2+} pump that opposes STIM1 action, is highly expressed in the embryonic muscle and is markedly increased in the muscle of loss-of-function mutant STIM1 mice suggesting that sarcolipin and STIM1 govern SOCE during myogenesis [26]. Expression of TRPC1 is also developmentally regulated increasing at the beginning of differentiation, and

is necessary for myoblast migration and fusion into myotubes [28]. Moreover, in myoblasts TRPC1 constitutes an essential stretch-activated channel modulated by sphingosine 1-phosphate, a bioactive lipid involved in satellite cell biology and myogenesis [29]. These studies serve to highlight the importance of controlling Ca^{2+} dynamics to proper muscle development.

A number of signaling elements immediately downstream of Ca^{2+} signal are demonstrably vital to normal muscle development. The candidate effectors that account for the importance of Ca^{2+} signaling in myogenesis comprise the CaM-dependent kinases and phosphatases, mitogen-activated protein kinases (MAPKs) and Ca^{2+}-sensitive transcription factors including the nuclear factor of activated T cells (NFATc). Ca^{2+}- calmodulin-dependent protein kinase (CaMK) signaling prevents formation of histone deacetylase-myocyte enhancer factor 2 (HDAC-MEF2) complexes [30, 31], thereby releasing MEF2 myogenic transcriptional activity [30, 32, 33], which otherwise is repressed by HDAC4 and 5 nuclear export [34].

The role of the CaM-dependent phosphatase, calcineurin, in mouse myogenesis starts with its function in early skeletal muscle cell differentiation [35, 36] by regulating expression of transcription factors MEF2, MyoD and myogenin [35–37]. In *Drosophila*, the role of calcineurin in muscle development is also apparent; mutants for the regulatory subunit of calcineurin exhibit severe defects in flight muscle organization [38]. Additionally, calcineurin is involved in further muscle cell specialization, promoting differentiation of slow fibers *in vitro* and *in vivo* by recruiting the transcription factor NFATc [39–43]. Calcineurin dephosphorylates NFATc, promoting its translocation to the nucleus for the upregulation of target genes [37, 44, 45]. Knockout mice for different NFATc isoforms revealed that these variants contribute to distinct aspects of muscle development and function. NFATc3 knockout mice present with reduced muscle mass and number of fibers but appropriate organization of the existing fibers, demonstrating a role for NFATc3 in early stages of primary myogenesis [46]. In contrast, mice lacking NFATc2 present a normal number of formed fibers but are deficient in myoblast fusion resulting in significantly fewer nuclei per fiber [47, 48], demonstrating a dual role for NFATc in both formation and organization of musculature.

In addition to the classic CaM-dependent pathways, other signaling cascades may contribute to the transduction of Ca^{2+} dynamics-driven skeletal muscle development. Signaling through several elements of the MAPK pathway regulates different steps of myogenesis [49–51]. Erk2 promotes muscle progenitor proliferation by upregulating cyclin D1 expression [49]. Subsequently, MAPK p38 activity is induced during differentiation of L8 myoblasts. Inhibiting p38 impairs myogenesis shown by reduced expression of MyoD in *Xenopus* embryos and of MEF2 factors in L8 cells [50, 51]. Because MAPKs interact with Ca^{2+} signaling [52] in the developing spinal cord [53] and, importantly, in the skeletal muscle [54], they may jointly coordinate regulation of skeletal muscle development (Figure 2).

3. Calcium signaling in skeletal muscle growth and maintenance

Once the skeletal muscle is formed during development, its size, performance and overall physiology remain plastic and the tissue responds to the changing surroundings (Figure 1). Skeletal muscle growth is based on further formation of large multinucleated muscle cells. After birth the tissue is subjected to an intense period of growth and differentiation coordinated by multiple signaling pathways. Some aspects of the cellular and molecular mechanisms responsible for the regulation of skeletal muscle growth are known and widely accepted but others remain unknown or controversial. Many of the myogenic factors that operate during embryonic development are also recruited for the growth of mature or maturing skeletal muscle, but myogenesis and plasticity are distinguished by different intrinsic and extrinsic environments and distinct competencies of cells. Here we will discuss signaling factors that are important in skeletal muscle growth and maintenance and the role of Ca^{2+} in their regulation.

The Insulin-like Growth Factor 1 (IGF-1) recruits the phosphoinositide 3-kinase-mammalian target of rapamycin (PI3-K/Akt/mTOR) signaling axis to implement muscle hypertrophy [55–57]. Whether the IGF-1-triggered pathway also recruits Ca^{2+} signaling to promote skeletal muscle growth, and in particular the calcineurin/NFAT signaling axis, has been a matter of debate. Some studies show that overexpressing calcineurin is sufficient to induce hypertrophy of soleus muscle fibers [58] and transgenic mice expressing either a null mutation for calcineurinAβ or muscle-specific overexpression of the calcineurin inhibitor MCIP1 exhibit reduced fiber size [59, 60], demonstrating a role for calcineurin in hypertrophy. In contrast, mice with either global or muscle-specific calcineurin depletion subjected to muscle hypertrophic growth by mechanical overload or IGF-1 stimulation do not show defects in muscle growth [61]. Nevertheless, these mice did show impairment in overload-mediated fiber-type switching [61]. These studies suggest that calcineurin is important for muscle growth and remodeling, however different animal models may lead to different levels of perturbation of calcineurin action and diverse compensatory mechanisms associated with the experimental approach. Importantly, insulin and IGF-1 induce Ca^{2+} dynamics through both Ca^{2+} influx and release from IP3R and RyR-operated stores [62–64]. Moreover, another hormone-like signaling molecule, prostaglandin F2α, increases intracellular Ca^{2+} concentration, activating NFATc2 and inducing muscle cell growth and nuclear accretion [65]. These studies suggest that molecularly diverse stimuli may converge at recruiting Ca^{2+} signaling to implement muscle growth (Figure 2).

Another experimental paradigm for studying muscle plasticity is the imposition of cyclic stretch in cultured muscle satellite cells. This activates Ca^{2+} influx through the mechanosensitive cation channel and the long-lasting-type voltage-gated Ca^{2+} channel [29, 66, 67]. Inhibiting these channels prevents muscle satellite cell activation and proliferation triggered by the mechanical stimulus [67], suggesting that Ca^{2+} dynamics are necessary for the mechanosensing response of muscle satellite cells. Stretch also activates the ras-MEK-extracellular signal-regulated kinase (ERK) signaling pathway through the recruitment of phospholipase A2, which may interact with the stretch mechanoreceptors [68]. The integration of signaling pathways is given by the stimulus-driven, Ca^{2+}-dependent phosphorylation of ERK and CREB, which results in the upregulation of early genes c-*fos*,

c-*jun*, and *egr*-1 [69]. In turn, a timely targeted gene expression is required for long-term changes in muscle strength during physical training. Exercise also induces switching from fast-twitch to slow-twitch fibers, which is mediated by PKD [70]. This kinase phosphorylates class IIa HDACs, releasing their inhibition of MEF2, leading to transcriptional activation of myosin heavy chain genes that enables muscle fiber type transformation [71]. Moreover, disrupting expression of myostatin in mice results in a switch in muscle fiber type from slow to fast, in addition to muscle growth by recruiting the non-canonical, Ca^{2+}-dependent Wnt pathway [72]. This may be triggered by a change in Ca^{2+} dynamics as a consequence of the reduction in sarcoplasmic Ca^{2+} release [73].

The precise dynamics of intracellular Ca^{2+} levels in muscle cells are crucial for specifying the stimuli-driven changes in muscle growth and performance through the coordination of Ca^{2+} influx and release from stores. Orai1 promotes growth and limits fatigue in adult skeletal muscle, while dominant negative Orai1 mice show increased susceptibility to fatigue [74]. Additionally, the burst of muscle growth and differentiation that occurs after birth in mice is dependent on the Ca^{2+} signaling regulated by STIM1 [75]. Excitation-contraction coupling is normal in mice lacking STIM1 from the skeletal muscle. However, muscle fibers of neonatal mSTIM1$^{-/-}$ mice fail to elicit Ca^{2+} transients evoked by tonic neurostimulation, resulting in inhibition of calcineurin, MAPKs, ERK1/2, and AKT signaling pathways. This suggests that the interaction between STIM1 and SOCE is necessary for neonatal muscle growth and differentiation [75]. An additional pathway that may participate in Ca^{2+}-induced muscle plasticity is CaMKK which, when constitutively activated, promotes muscle growth by recruiting mTORC1 signaling and promotion of protein synthesis [76].

Another relevant aspect of muscle homeostasis is the limitation to growth and performance experienced during aging. Aging is accompanied by active muscle wasting through mechanisms that are not fully understood, but correlate with age-dependent changes in Ca^{2+} dynamics. Evidence for a relationship between Ca^{2+} signaling and aging muscle comes from studies on Ca^{2+} sparks, which consist on focalized Ca^{2+} release from the sarcoplasmic reticulum. In the young muscle Ca^{2+} sparks are not apparent at rest but are activated upon membrane deformation due to mechanical stimulation or osmotic stress [77, 78]. In contrast, in the aged skeletal muscle, the Ca^{2+} spark response is altered and there seems to be a segregated intracellular Ca^{2+} reserve that cannot be recruited by voltage-induced Ca^{2+} release, uncoupling Ca^{2+} dynamics from the excitation-contraction process [79]. This alteration in Ca^{2+} dynamics precedes muscle wasting and correlates with downregulation of mitsugumin-29 expression, a synaptophysin-related membrane protein important for muscle structure and function and Ca^{2+} homeostasis [79]. SOCE is also affected in the muscle of aged mice, presumably due to downregulation of mitsugumin-29 expression [80]. This protein interacts with TRPC3 [81, 82] and RyR1 and regulates apoptosis [83], providing a potential link between Ca^{2+} signaling and control of muscle homeostasis.

Muscle wasting is not exclusive to aging, but is shared by many physiological and pathological conditions. In metastatic cancer concurring with bone destruction, secreted transforming growth factor-β (TGF-β) induces excessive oxidation of RyR1, resulting in leaky channels that interfere with Ca^{2+} signaling and muscle contraction. Preventing RyR leakage improves muscle function, suggesting that muscle weakness induced by

pathological TGF-β signaling is due to decreased Ca^{2+}-induced muscle force production [84]. Ca^{2+} sparks induced by membrane deformation and exercise in the young healthy muscle, which are decoupled in the aged muscle as mentioned above, are also deregulated and sustained irreversibly in the dystrophic muscle [78]. In a mouse model of muscular dystrophy, increased sarcolemma localization of a TRP channel, the growth factor-regulated channel, which results in Ca^{2+} overload in response to stretch, leads to muscle cell degeneration [85].

Skeletal muscle homeostasis relies on spatiotemporally regulated Ca^{2+} signaling in the different cell types involved in muscle plasticity. Aging and disease disables muscle homeostasis due to loss of the regulatory mechanisms dependent on appropriate Ca^{2+} dynamics.

4. Calcium signaling in muscle regeneration

Tissue regeneration involves a tightly orchestrated sequence of cellular events consisting of cell proliferation, migration, and differentiation, culminating in integration of cells into functional regenerating tissues. These cellular events are similar to the processes that occur during development (Figure 1) raising the question of whether the Ca^{2+} signaling-mediated mechanisms of muscle development are apparent in muscle regeneration.

In our recent study we found that spontaneous Ca^{2+} transients manifest in the early stages of muscle regeneration and that perturbing Ca^{2+} release from internal stores impairs the regenerative process. We discovered that muscle cells from the regenerating *Xenopus laevis* tail exhibit spontaneous Ca^{2+} transients during the first hours post injury [86].

Incubation of regenerating tadpoles with ryanodine, which abolishes Ca^{2+} transients in regenerating muscle cells, leads to a reduction in the number of muscle progenitor cells and activated muscle satellite cells in the regenerating tissue [86]. Muscle satellite cells are the major cell type that contributes to muscle repair and regeneration. When muscle is injured, activated muscle satellite cells proliferate and differentiate into skeletal muscle cells, giving rise to new tissue [87, 88]. Our findings suggest that perturbing Ca^{2+} release from RyR-operated stores interferes with the early phases of muscle regeneration, and that this Ca^{2+} activity is necessary for activation and proliferation of muscle satellite cells (Figure 2). In addition to RyR, release of Ca^{2+} from intracellular stores can be mediated by IP3R. Recently, investigators have determined that Ca^{2+} release mediated by IP3R type 1 is essential during the early steps of human myoblast differentiation [89], however our study found that Ca^{2+} transients in injured muscle were not IP3R-mediated and that IP3R function was not necessary for muscle regeneration [86], suggesting that muscle regeneration is mechanistically distinct from muscle development.

Unlike the dispensability of IP3R activation for muscle replenishment in injured tadpoles, regeneration of other tissues depends on IP3R-mediated signaling. For example, inhibition of IP3R expression in hepatocytes leads to a reduction in hepatocyte proliferation and delayed liver regeneration [90], showing its necessity for the early phases of repair. Another tissue in which Ca^{2+} activity is vital for development and regeneration is the skin.

Proliferating keratinocytes of the epidermis facilitate adult skin homeostasis and participate in the wound healing process following injury [91–93]. Ca^{2+} is a key regulator in both keratinocyte differentiation and proliferation. At low intracellular Ca^{2+} levels, keratinocytes retain proliferative activity. At higher Ca^{2+} concentrations, proliferative activity is suppressed and keratinocytes express differentiation markers [94]. Ca^{2+} is also necessary in driving migration of basal keratinocytes. Loss of Orai1 results in inhibited directional migration of keratinocytes [95]. Moreover, expression of RyRs in human keratinocytes has been linked to keratinocyte differentiation and epidermal barrier homeostasis [96]. Application of a RyR agonist or antagonist delays or enhances skin barrier recovery respectively [96]. Further studies will help determine whether the importance of Ca^{2+} activity in regeneration is universal and will identify the particular Ca^{2+} dynamics that facilitate regeneration in different tissues. Other sources of Ca^{2+} response in activated muscle satellite cells during regeneration are the TRPCs. In cultured mouse muscle fibers hosting satellite cells the addition of fibroblast growth factor-2 induces an increase in intracellular Ca^{2+} levels in activated muscle satellite cells through TRPCs [97]. Full elucidation of the molecular mechanisms regulating Ca^{2+} dynamics in the activation of muscle satellite cells upon injury requires further investigation.

The downstream candidates recruited by Ca^{2+} activity during muscle regeneration are numerous (Figure 2), given the crosstalk nature of Ca^{2+} signaling. A central effector of Ca^{2+} dynamics, calcineurin, is expressed in activated and proliferating muscle satellite cells four days after injury in rodent leg muscles, while it is absent in quiescent counterparts [98]. Moreover, inhibiting calcineurin by injecting injured mice with cyclosporine impairs regeneration and leads to muscle fiber atrophy [98], suggesting a role for calcineurin in skeletal muscle repair. In addition, enhancing calcineurin activity by expressing a constitutively active form in a model of muscle injury in mice enhances structural and functional muscle regeneration, presumably through upregulation of the expression of myogenic genes like MEF-2 and myogenin [99]. In turn, calcineurin activity is tightly regulated by several modulatory proteins [100, 101] including myosporin, a scaffolding protein localized to the *Z*-disc/costamere region of striated muscle that inhibits calcineurin activity, prevents the slow fiber type switch normally associated with calcineurin action, and impairs regeneration of the injured muscle [102].

Another class of Ca^{2+}-dependent phosphatases, calpains, also contributes to the control of muscle satellite cell activation [103]. Muscle satellite cells express m-calpain in a cell cycle-dependent manner, with m-calpain primarily localized to the cytoplasm in non-proliferating satellite cells. Upon injury, however, m-calpain localizes in the satellite cell nucleus. When m-calpain is inhibited, satellite cells show defects in cell cycle control. These defects lead to prevention of Myo-D accumulation in the nucleus and enhancement of Myf5 expression, subsequently impairing satellite cell function and the early stages of muscle regeneration [103].

Ca^{2+} signaling participation in skeletal muscle regeneration has become increasingly clear. However, further investigation is necessary to identify the Ca^{2+} dynamics specific to each type of cell participating in the repair and regeneration of the skeletal muscle. We also anticipate that elucidating the intra and intercellular signaling within the regenerating muscle

and with adjacent and supporting tissues will prove important. The progressive loss of the muscle regenerative capacity with age indicates that some signaling mechanisms present in development are no longer available in the aging muscle. Indeed, the satellite cells of aged, injured muscle exhibit insufficient upregulation of the Notch ligand Delta, which is necessary for proliferative expansion of myogenic progenitors and muscle regeneration [104]. Interestingly, the crosstalk between Notch and Wnt signaling pathways is necessary for a temporal balance between myogenic progenitor proliferation and differentiation in adult myogenesis [105], while activation of the canonical Wnt signaling pathway in aged progenitors favors differentiation towards the fibrogenic instead of myogenic lineage, leading to tissue fibrosis and poor muscle regeneration [106]. A pivotal role for Ca^{2+} signaling is expected considering that it modulates both the Notch [107] and Wnt [108, 109] signaling pathways.

5. Concluding remarks

In this review we have discussed evidence that Ca^{2+} is an important component of the signaling promoting muscle formation, muscle homeostasis, and regeneration. In particular, Ca^{2+} changes may direct muscle satellite cells to maintain their quiescent state, proliferate, or differentiate into functional muscle. A full understanding of muscle satellite cell physiology is crucial to devising appropriate therapies to promote muscle regeneration and prevent muscle wasting in aging and disease. The spatiotemporal changes in Ca^{2+} dynamics and their signaling partners in muscle satellite cells of both young and aged tissue in response to external demands await further investigation.

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Highlights

- Calcium regulates myoblast proliferation and differentiation during development
- Injury-induced calcium signaling recruits satellite cells for muscle regeneration
- Calcineurin, CaMKII, MAPK, CREB and NFATc transduce the calcium signal in muscle

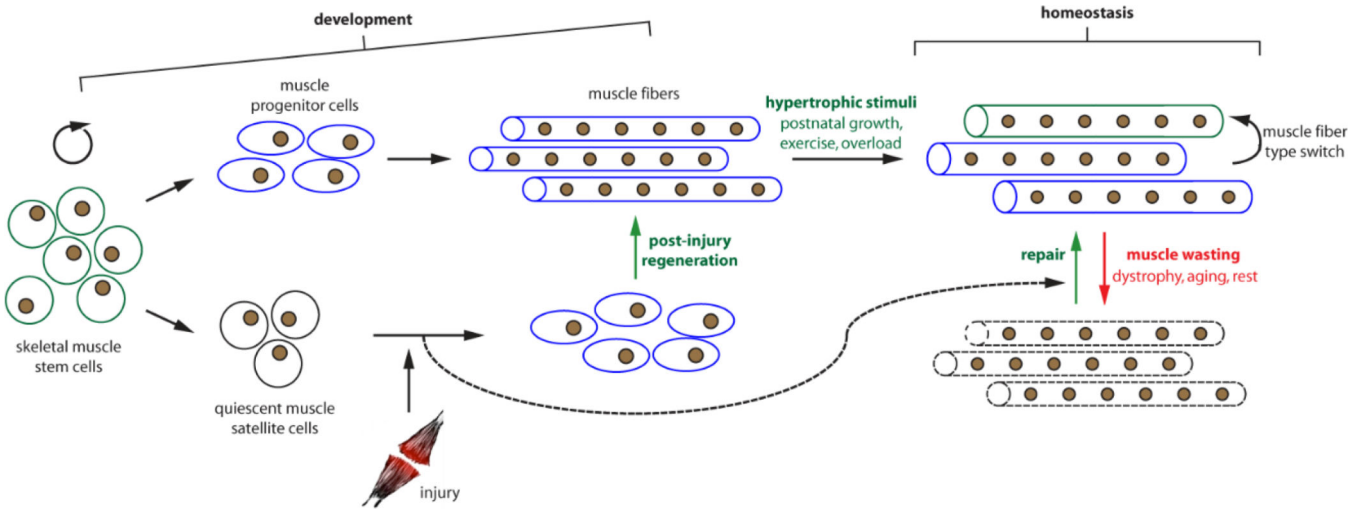

Figure 1.

Cellular mechanisms of skeletal muscle development, homeostasis and regeneration. During embryonic development mesodermal muscle stem cells expressing Pax3/Pax7 transcription factors proliferate and specialize into myogenic progenitors through the expression of the myogenic regulatory factors including Myf5, MyoD and myogenin. Progressive differentiation is followed by sarcomere assembly, spatial arrangement of muscle cells, and their fusion into multinucleated muscle fibers. Muscle growth requires protein synthesis and enlargement of individual fibers, and is triggered during postnatal development and upon exercise or muscle overload. Trophic stimuli can also elicit a switch in muscle fiber type. In contrast, muscle wasting is characteristic of muscle dystrophy and aging. Skeletal muscle regeneration requires activation of muscle satellite cells that recapitulate the myogenic program, repairing and replenishing the injured tissue.

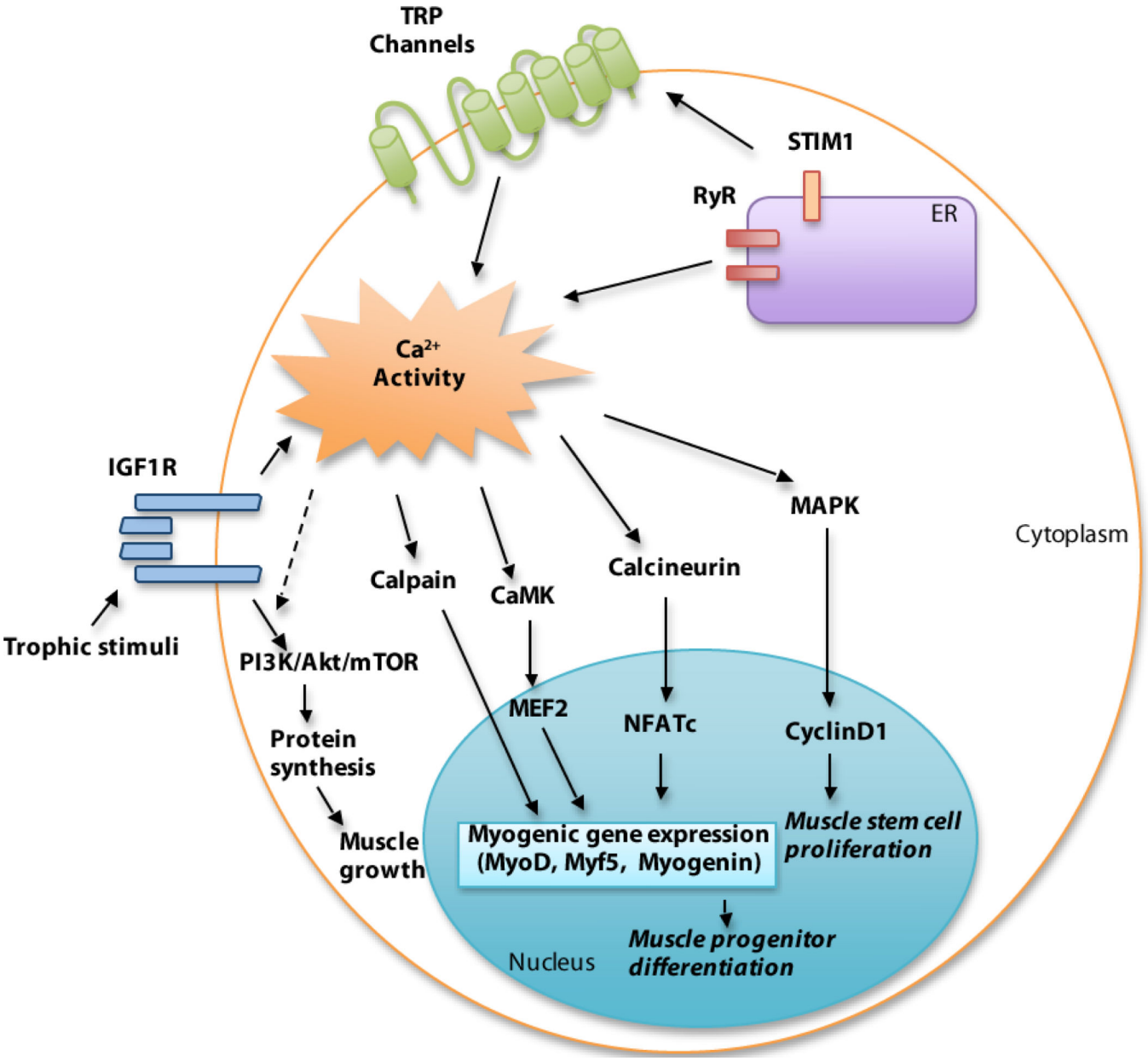

Figure 2.

Ca^{2+} signaling in skeletal muscle plasticity. Ca^{2+} activity in muscle cells at different maturational states leads to recruitment of Ca^{2+}-dependent kinases and phosphatases triggering diverse cellular responses required for myogenesis, muscle homeostasis and regeneration.