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Review

Calcium signaling in skeletal muscle development, maintenance and regeneration

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

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

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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.

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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 orig-

* Corresponding author at: 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, United States. Fax: +1 916 453 2288.
E-mail address: lnborodinsky@ucdavis.edu (L.N. Borodinsky).

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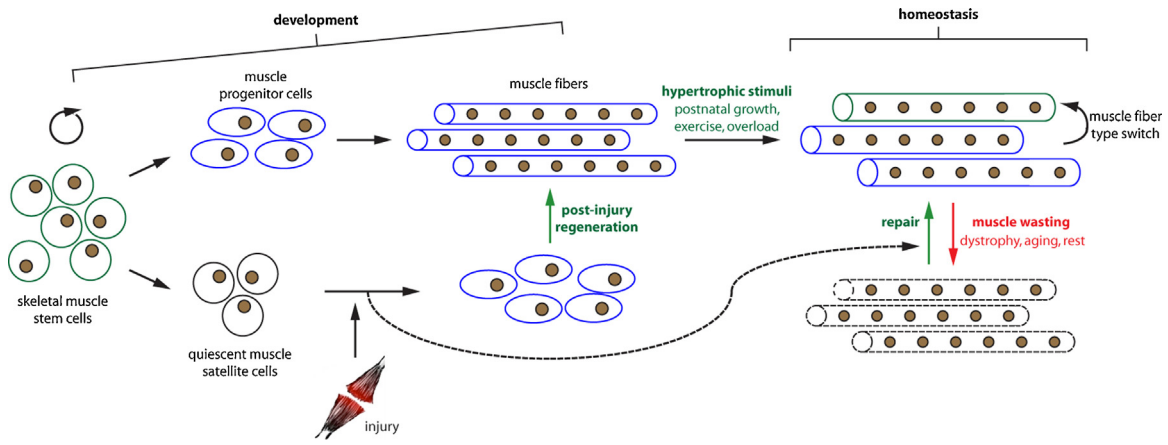

Fig. 1. Cellular mechanisms of skeletal muscle development, homeostasis and regeneration. During embryonic development mesodermal muscle stem cells expressing Pax3/Pax7 transcription factors proliferate and specialize into myogenic progenitors through the expression of the myogenic regulatory factors 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.

inate 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 (Fig. 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 RyR-dependent, 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 Ca^{2+}-calmodulin-dependent kinases and phosphatases, mitogen-activated protein kinases (MAPKs) and Ca^{2+}-sensitive transcription factors including

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