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Skeletal muscle satellite cells: Mediators of muscle growth during development and implications for developmental disorders

Sudarshan Dayanidhi, PT, PhD[1,2] and **Richard L. Lieber, PhD**[1,2,3,*]

[1]Department of Orthopaedic Surgery, University of California, San Diego, CA, USA

[2]Department of Orthopaedic Department of Veterans Affairs Medical Center, San Diego, CA, USA

[3]Department of Bioengineering, University of California, San Diego, CA, USA

Abstract

Satellite cells (SCs) are the muscle stem cells responsible for longitudinal and cross-sectional postnatal growth, repair after injury and which provide new myonuclei when needed. Here we review their morphology, contribution to development, and their role in sarcomere and myonuclear addition. SCs, similar to other tissue stem cells, cycle through different states such as quiescence, activation, and self-renewal and thus we consider the signaling mechanisms involved in maintenance of these states. The role of the SC niche, their interactions with other cells such as fibroblasts and the extracellular matrix are all emerging as important factors that affect aging and disease. Interestingly, children with cerebral palsy appear to have a reduced SC number, which could play a role in their reduced muscular development and even in muscular contracture formation. Finally we review the current information on SC dysfunction in children with muscular dystrophy and emerging therapies that target promotion of myogenesis and reduction of fibrosis.

Keywords

Postnatal development; satellite cells; muscle stem cells; cerebral palsy; myonuclei

Introduction

Skeletal muscles are composed primarily of multinucleated myofibers with their basic contractile elements, sarcomeres, arranged in series to provide length and in parallel to provide cross-sectional area. Alexander Mauro[1] first named the satellite cell (SC) in frog skeletal muscle based on its peripheral location in the myofiber, sandwiched between the sarcolemma and basal lamina. In terms of location, SCs are similar in placement to skeletal muscle myonuclei, i.e. on the periphery of the myofiber but are outside the sarcolemma whereas myonuclei are just under the sarcolemma. In other words, SCs represent a distinct cell type from myofibers. While the postnatal increase in myonuclear number has been

*Corresponding Author University of California, San Diego, 9500 Gilman Drive, Mail Code 0863, La Jolla, CA 92093-0863, USA. Tel.: +1 858 822 1344; fax: +1 858 822 3807. rlieber@ucsd.edu. .

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known since the 1960s[2], the source of these nuclei during growth and repair has been thought to be SCs. This is because adult myonuclei are terminally differentiated, i.e. unable to divide, proliferate, or regenerate. Consequently there must be other myogenic tissue specific stem cells that can make skeletal muscle. Indeed, isotope tracing experiments strongly suggested that the source for postnatal increase in myonuclei comes from mitosis of mononucleated SCs[3,4].

By definition, an adult tissue stem cell has 2 properties—the ability to differentiate to create new tissue and the ability to self-renew[5]. However, it was not until the 2000s, after molecular markers such as the Pax7 transcription factor were identified[6], that it was convincingly shown that the SCs are indeed the primary muscle stem cells capable of self-renewal and differentiation[7-9]. In this review, we will focus on postnatal development of muscle, SCs, their functional and regulatory mechanisms and their dysfunction and therapeutic implications. A number of excellent recent reviews on specific topics related to satellite stem cell biology and their role in myogenesis have been published[10-17]. For a state-of-the-art review on the molecular biology of SCs, see Yin et al.[17]; for a historical perspective on the experiments that led to the discovery of the SC as well as recent developments, see Yablonka-Reuveni[16].

While SCs were initially identified based on their sublaminar anatomical location, specific cell surface membrane glycoproteins and intracellular markers have now been identified. The most common surface markers are NCAM (CD56), M-cadherin, and CD34 while Pax7 is nuclear (for a detailed list see Yin et al.[17]) and is considered the classic SC transcription factor[6]. Currently these markers have been used in human and animal studies to evaluate SCs by immunohistochemistry, fluorescence microscopy, fluorescence-activated cell sorting (FACS) and/or *in vitro* cell culture.

Satellite cell quiescence, activation, self-renewal and return to quiescence

The transition from SC to myofiber consists of specific steps that proceed from quiescence, to activation, proliferation, differentiation and finally, cell fusion (Fig. 1). During quiescence, SCs are located in their microenvironment and express Pax7. Upon activation, they enter the cell cycle to progress down the myogenic pathway by expressing myogenic regulatory factors (MRFs)[18], starting with Myf5, then proliferate (amplify cell number) and are considered to be “committed” to the myogenic lineage after they express MyoD, and form myoblasts. At this stage, myogenin is expressed, differentiated myoblasts fuse to create myotubes and express myosin heavy chain, the major muscle contractile protein. Myotubes fuse with existing myofibers in both growth and repair (reviewed in[13]). At the stages of proliferation, differentiation and fusion, cells no longer express purely SC markers but may also express myogenic markers. The signaling pathways mediating myoblast fusion are multifactorial and complex (for review, see Hindi et al.[19]).

While SCs participate in growth and repair, they must also meet the other functional requirement of being a tissue-stem cell, i.e. self-renewal, without which the SC pool would be exhausted over time. SCs, like other stem cells, can undergo either symmetric or asymmetric division (Fig. 2). Using lineage tracing it was demonstrated that 90% of SCs had

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expressed Myf5 at some point, indicating they had previously undergone commitment to the myogenic lineage and then returned to quiescence—in other words, they had self-renewed[20]. Importantly, since 10% of the SCs never expressed Myf5, this indicated that this subgroup's function was to self-renew rather than differentiate. It was also shown that cellular orientation during division critically determined SC fate. Specifically, if the SC division were planar (both daughter cells in the traditional position between basal lamina and sarcolemma, Figs. 2A, 2B) division would result in two identical cells (symmetrical division), which could either increase satellite cell number or create two activated cells that proceed down the myogenic path. However, if orientation were apicobasal, (one daughter cell touching the basal lamina and the other touching the sarcolemma, Fig. 2C) development was likely to split with one cell becoming a myoblast and the other creating a new SC (asymmetrical division)[20].

Postnatal muscle development

SC nuclear length is 8-12 μm across various species[21,22]. SC number reduces with age during the early postnatal period to reach a steady state value of 5-6% of the myonuclei[23] with greatest number soon after birth (~30% of the myonuclei[23],[24]). At the extreme end of life, there is a reported SC number decline[24-26]. While the functional consequences of SC number decline are unclear, it is becoming clear that the SC function changes profoundly with aging[27]. The intrinsic differentiation potential of the aged SCs can remain unaltered but they may decline in proliferation potential, which can be rescued with the use of systemic factors such as Fibroblast growth factor (FGF)[25] and exposure to young serum[28].

Sarcomere addition

Postnatal muscle development is characterized by both longitudinal and radial muscle fiber growth[29]. Longitudinal growth increases the range over which a muscle functions while radial growth increases muscle contractile force[30]. During postnatal development in mammalian muscles, the number of myofibers does not increase[2,31]. In a series of seminal murine studies[32-35], Williams and Goldspink measured skeletal muscle myofiber longitudinal and cross-sectional area increases during development. They reported increased myofiber cross-sectional area (Fig. 3A) by addition of myofibirils[29,35] which occurred by fusion of the myoblasts from SCs into existing myofibers. We have recently shown[29] that between postnatal day 1 and day 28 there was an almost twofold increase in myofibrillar packing, a sevenfold increase in myofiber cross-sectional area and a fourfold increase in muscle mass[29]. Longitudinal myofiber length increased fivefold primarily by addition of sarcomeres-in-series during the first 4-6 postnatal weeks [29,32,33]. It was suggested that this sarcomere addition occurred primarily at the ends of the growing myofibers. Importantly, this distal region has been shown to be associated with the greatest number and concentration of SCs in developing muscles in chicks which was the basis of the suggestion[22]. Additional experiments demonstrated that growing muscle, prevented from increasing in length by maintaining a shortened position for 4 weeks, did not increase serial sarcomere number to the same extent. However, if it was then allowed to recover[33] by removing the immobilization, subsequent stretch and growth resulted in rapid serial sarcomere number increase. These experiments demonstrate that the postnatal period is

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particularly plastic for adaptation and suggest that SCs may be involved in the process of serial sarcomere addition[33]

Myonuclear number and domain

In parallel with increased serial sarcomere number (i.e., increased fiber length) and myofiber area during the postnatal period there is also an increase in nuclear number[2,36] in growing myofibers. After the initial 6 postnatal weeks of increase in sarcomere number in mouse solei and biceps brachii, the myonuclear addition continues for another 10 weeks suggesting a role for myonuclear accretion for radial growth[33]. However the exact relationship between myonuclear addition, cross-sectional and longitudinal growth is not entirely clear[36]. White et al.[36] report a significant increase in both myofiber cross-sectional area and length in mouse EDL without accretion of any addition myonuclei beyond the first 21 postnatal days.

Myonuclear domain, i.e. the volume of cytoplasm per myonucleus might be a relevant parameter that relates myonuclear number to fiber length and size[37]. It has been suggested that myonuclear domain is maintained during atrophy by myonuclear loss[38-40] or during hypertrophy by myonuclear accretion[41] but this is not universally agreed upon[24,42]. The precise relationship between myonuclear domain and fiber atrophy and hypertrophy is thus not fully defined (see below).

Satellite cell function

As stated, postnatal muscle development is critically dependent on SCs and Pax7[43,44]. Pax7 null mice demonstrated a dramatic reduction in both myofiber size and in SC number during the postnatal period[44]. Using a transgenic mouse that allowed conditional inactivation of Pax7, Lepper et al. [43] showed that myoblasts from Pax7 lineage fuse into myofibers and are indispensible during the postnatal period.

In contrast, the “obligatory” role of SCs for adult hypertrophy and regrowth after atrophy is not clear[49-51]. A 90% reduction in SCs does not prevent fiber hypertrophy in a synergistic ablation mouse model, in which the gastrocnemius and soleus are surgically excised and compensatory hypertrophy of the plantaris is measured[52]. However, it is important to note that, in control animals, where SCs were *not* knocked down, there was robust SC activation and participation in hypertrophy, indicating that, if present, they certainly do appear to participate in the hypertrophic response. This hypertrophy was not different between SC depleted and control groups. Similarly, recovery from atrophy was not hampered by a 90% knockdown of SCs[53]. Interestingly, the most recent results[54] show that, while hypertrophy is possible initially, long-term hypertrophy is blunted and associated changes in the extracellular matrix and fibroblasts are observed, implying that hypertrophy in adult muscle is not completely independent of SCs.

Conditional SC inactivation during the postnatal period resulted in severely compromised muscle regeneration after injury[43]. A number of studies[45-48] have conclusively shown that Pax7 expressing SCs are critical for long-term muscle repair capability even in adult muscle. While Lepper et al. reported that Pax7-inactivated-SCs could still regenerate normally in the short term, suggesting an additional non-Pax7 dependence for SC function in adults, this

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interpretation was confounded by an incomplete understanding of the timelines of deletion[48]. Günther et al.[48] using a similar mouse model demonstrated that conditional inactivation of the Pax7 gene led to a delayed but significant loss of SCs and continued inactivation of Pax7 led to impaired muscle regeneration even in adults.

Signaling pathways for satellite cell activation, quiescence and self-renewal

Satellite cells have a large number of activation factors[55] including mechanical stretch, which are important in the postnatal period during bone mediated muscle growth (Fig. 3). Local signaling factors such as nitric oxide[56], growth factors such as fibroblast growth factor (FGF) and insulin-like growth factor (IGF)[57] play an important role in SC activation and muscle growth. Mechanical stretch is strong regulator of SC activation through hepatocyte growth factor (HGF) and nitric oxide[58]. SCs can be activated after only brief period of stretching of 2 hours[59] and this mechanical stretch can induce increased expression of the matrix metalloproteinases (MMPs) which are responsible for extracellular matrix remodeling[60]. MMPs play an important role in promoting migration of activated satellite cells permitting robust regeneration[61] (see section on satellite cell niche below).

Maintaining the balance amongst the states of quiescence, activation, proliferation, differentiation and self-renewal is critical for continued myogenic potential. Lack of maintenance of quiescence or self-renewal leads to depletion of the stem cell pool while prevention of activation leads to impaired regeneration. There are many signaling mechanisms involved in this dynamic balance. Notch is an extrinsic signaling pathway whose influence on cell function has been studied extensively. SCs in the quiescent state (Fig. 1) are maintained actively rather than it being in a default inactive state. Active notch signaling is required to maintain this state[62,63]. Transgenic mice, in which canonical notch signaling was conditionally ablated, demonstrated increased propensity for spontaneous differentiation and dramatic depletion of the satellite cell pool[62]. Interestingly, SCs with impaired notch signaling progressed immediately to differentiation without initially dividing and simply fused to existing myofibers[63]. During aging, muscle regenerative potential decreases, which can be improved via notch-mediated pathways[64]. Recently it was shown that the quiescent state might not actually be a single homogenous state, rather it is heterogeneous, and progresses from a mitotically quiescent G_0 phase to a G_{Alert} (pre-activation) phase, where it is primed for activation[65].

Wnt signaling plays an important role during SC activation, proliferation and helps determine stem cell fate66. Symmetric expansion likely occurs through wnt7a utilizing the planar cell polarity pathway, i.e. a non-canonical pathway not involving β-catenin[67]. This pathway might be critical for maintaining the SC pool, since muscles without wnt7a show decreased SC number after regeneration[21]. After activation, while Notch-1 signaling has been implicated in SC proliferation[68], to progress from proliferation to differentiation, a switch in signaling from notch to wnt is required[69]. Wnt and notch signaling interact to create sufficient proliferation prior to differentiation to maintain efficient repair and appropriate progression down the myogenic lineage. Furthermore, it has been shown that, in aging, increased canonical wnt signaling during SC proliferation can convert the SC myogenic lineage to a fibrogenic one resulting in aberrant fibrosis[70]. Importantly, this

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conversion can be suppressed with wnt inhibitors, suggesting a critical role of wnt signaling in altering SC fate.

An emerging research area is SC self-renewal and how activated SCs revert to quiescence to maintain the SC pool. Elevated activity of p38 mitogen-activated protein kinase (MAPK) in aging was shown to be involved in loss of self-renewal[71] while transient inhibition of this pathway expanded the stem cell population[72]. Sprouty1 (spry1), a tyrosine kinase inhibitor, is expressed during SC quiescence, downregulated during proliferation and re-expressed during return to quiescence[73]. Conditional ablation of spry1 in SCs led to a dramatic reduction in SC pool after activation due to injury. This indicates that spry1 is required for restoring the muscle stem cell pool after activation, i.e. for reversible quiescence and self-renewal[73]. Homeodomain transcription factor six1 has also been implicated to play a role in limiting SC self-renewal, as evidenced by the increased SC pool observed in Six1 knockout mice[74]. Recently it was shown that forkhead box O3 (foxo3), which is most widely known as the factor controlling the skeletal muscle atrophy pathway[75,76], also promotes quiescence during self-renewal[77]. Together, these results point to an intricate interaction among signaling pathways to control the state of muscle and its resident stem cells. A number of signaling pathways are required to maintain the dynamic balance between quiescence, activation, return to quiescence and self-renewal, all of which are necessary to maintain a healthy and functional SC pool (Table 1).

Satellite cell niche and interactions

Unlike the initial impression that a SC had a fairly simple extracellular localization, it is becoming clear that the SC “niche” (defined as the microenvironment where the quiescent SC resides) is complex, important and thus, highly regulated. The niche composition and structure is critical because extrinsic environmental cues are important determinants of SC functional state, i.e. maintenance of quiescence, activation, and return to quiescence. SCs have a complex interaction with their associated extracellular matrix (ECM). During quiescence, they interact with both the basal lamina and sarcolemma, but, once activated, actively remodel the local extracellular matrix via increased levels of matrix metalloproteinases (MMPs)[78]. This interaction apparently is partly responsible for SC quiescence since simple mechanical disruption of this contact results in immediate activation. During postnatal development[79,42] and in adulthood[80] proliferating myoblasts are fairly motile and can rather easily cross the ECM between fibers depending on where they are needed. Biomechanical and biochemical properties of the niche may influence SC response. *In vitro* methods have demonstrated that the elastic stiffness of the extracellular matrix might be important for functional differentiation[81] and for self-renewal of SCs[82].

Furthermore, tamoxifen-induced experimental ablation of 90% of the SCs [83] revealed that SCs have a regulatory effect on fibroblasts (identified as $Tcf4^{+}$) since their ablation and chemical injury to the muscles led to increased fibrosis along with poor regeneration. Similarly, experimental ablation of 42% of fibroblasts and chemical muscle injury impaired SC ability to proliferate, leading to premature SC differentiation and smaller regenerated myofibers[83]. Connective tissue fibroblasts have also been shown to regulate myogenesis and expression of myosin heavy chain (MyHC) isoform[84]. In another study evaluating the role

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of SCs on adult muscle hypertrophy and ECM remodeling[54] it was shown that after ~90% SC ablation and synergistic ablation of the gastrocnemius and soleus, while compensatory hypertrophy of the plantaris was possible, there was dysregulation of the connective tissue with an increased accumulation of the ECM and an expansion of the fibroblasts. Additionally, *in vitro* studies suggested that activated SCs exerted negative regulation of fibroblasts. Together, these studies show that ECM, fibroblasts and SCs interact to regulate their function and myogenesis. Interestingly, in other organ systems such as in the liver, similar feedback processes are at play wherein hepatic stellate cells interact intimately with other cells such as hepatocytes and endothelial cells, particularly after injury and inflammation, to ensure appropriate repair. Inappropriate interactions amongst these cells leads to fibrosis[85-88].

Apart from the ECM, quiescent SCs are present in close proximity with muscle microvasculature[89]. On activation, interaction with endothelial cells is facilitated, which is important for angiogenesis to coordinate myogenesis. Furthermore, change in factors associated with the niche can influence SC function. With aging, aberrant signaling within the niche can lead to increased loss of quiescence and SC depletion[90]. Our current understanding of the composition, cellular interactions and molecular control of the SC niche is quickly evolving.

Cerebral Palsy Palsy & Muscular Dystrophy

Our laboratory has a particular interest in cerebral palsy (CP), which is the most common developmental motor disorder affecting 2-4 children per 1000 every year[91]. After perinatal brain injury, these children present with significant clinical problems that are related to impaired longitudinal and cross-sectional muscle growth. A most obvious impairment is weakness, that is due in part, to decreased muscle fiber size[92] and decreased neural drive[93,94]. However, more complex musculoskeletal changes are also noted[95,96], specifically, the formation of contractures[97,98]. Paradoxically, these shortened muscles are accompanied by overstretched sarcomeres within the tissue[98]. Changes in contracture extracellular matrix[97], i.e. fibrotic changes and transcriptional profile[99,100] also highlight the deranged nature of the muscle tissue. Grossly, there may be changes in the fascicle length[95] and tendon length[101]. Overall it is clear that CP muscle has reduced capacity for longitudinal and cross-sectional growth during the postnatal period. It is our hypothesis that this inability to accommodate growth, because of SC loss and dysfunction leads to contractures (Fig. 3B).

In light of the discussion above where we presented evidence that SCs play a significant role in muscle growth, we speculated that contracture formation may, in part, be due to SC dysfunction. Using flow cytometry of muscle biopsies from children with CP[102], we showed that, indeed, compared to typically developing children, children with CP had a significantly reduced (~60%) SC population, expressed as a percentage of all mononuclear cells (Fig. 4A). However, as noted, children with CP have extracellular matrix abnormalities that may systematically bias flow cytometry results in that it may be more difficult to extract SCs from CP muscle. To test this idea, we used the more labor intensive *in situ* immunohistochemistry method to quantify SCs[103] using antibodies for SCs (anti-Pax7) the basal lamina (anti-Laminin) and a nuclear stain (DAPI). By systematically sampling large

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volumes of tissue, we quantified SC number *in situ* without significant tissue manipulation (Fig. 5). It turned out that SC number quantified from these sections, as number per 100 myofibers, similarly showed a 70% decrease compared to age-appropriate controls (Fig. 4B). Since total nuclear number was not different between groups, we speculate that SC reduction occurred later during development. Together, these two studies using different methods and different human subjects, demonstrate that it is highly likely that there are significant changes in the SC population in children with CP and suggest possible future avenues for therapeutic intervention using regenerative medicine.

Duchenne muscular dystrophy (DMD) is the most common form of muscular dystrophy that results from a genetic defect leading to a lack of the cytoskeletal muscle protein dystrophin[104]. Becker muscular dystrophy (BMD) is also associated with a defect in the dystrophin gene but is functionally milder. Clinically, children with DMD have progressive weakness starting at age 3-5 that leads to premature death by late adolescence/young adulthood[105,104]. The impairment in dystrophin and its associated proteins causes an interruption between the myofiber, its sarcolemma and extracellular matrix (ECM)[106] leading to altered mechanical stress, reduced stiffness, inflammation, and consequent muscle regeneration[107,108]. Transgenic mouse models for DMD (mdx, mdx/mTR, mdx/utrophin$^{-/-}$) have defined the phenotype of muscle dysfunction in DMD and have been used to evaluate the role of SCs in the progressive weakness associated with DMD[109]. Sacco et al.[110] showed that pathological muscle progression in DMD could be related to an inability of the SCs to maintain the capacity to repair following multiple damage-repair cycles, i.e. an early exhaustion of the stem cell pool. Consistent with the idea that dystrophic muscle experiences multiple cycles of regeneration, it has been shown that telomere shortening[110] occurs in DMD patients' muscles[111]. Most interestingly, somewhat similar to the extracellular matrix changes in CP, there are marked fibrotic changes observed in DMD patients' muscles and in transgenic mouse models[110,112,113]. Currently, novel therapies targeting muscle stem cell dysfunction are being evaluated as a means to improve muscle function in dystrophies[114-116]. Recently focal treatment in mdx mice with wnt7a results in structural improvements such as increased SC number and fiber hypertrophy[111]. In addition, as would be expected, antifibrotic therapies can improve muscle function by reducing fibrosis and improving muscle regeneration capacity[109].

Conclusions

In summary, we have reviewed the role that skeletal muscle stem cells, SCs play during postnatal development and repair. SCs, on activation participate in myogenic function and provide the biological basis for longitudinal and cross-sectional growth. Their activation and subsequent return to quiescence is controlled by complex molecular mechanisms that ensure participation in growth, regeneration and repair while maintaining the SC pool. The SC niche facilitates intimate interaction between SCs and other cell types and allows feedback control among cells to coordinate participation in myogenic function. Children with cerebral palsy have significant problems with longitudinal and cross-sectional muscle growth. Our recent work showed that SC dysfunction could explain that finding and provide new therapeutic directions to enhance muscle function. Children with muscular dystrophies also

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show similar features of SC depletion and fibrotic changes that may also lend themselves to novel therapeutic treatments.

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Abbreviations

BMD	Becker muscular dystrophy
CD	Cluster of differentiation
CP	Cerebral Palsy
DAPI	4′, 6-diamidino-2-phenylindole
DMD	Duchenne muscular dystrophy
ECM	Extracellular matrix
FACS	Fluorescence- activated cell sorting
FGF	Fibroblast growth factor
FOXO3	Forkhead box O3
HGF	Hepatocyte growth factor
IGF	Insulin-like growth factor
NCAM	Neural cell adhesion molecule
MAPK	Mitogen-activated protein kinase
MMP	Metalloproteinases
MRF	Myogenic regulatory factor
MYF5	Myogenic factor 5
MYHC	Myosin heavy chain
PAX7	Paired box 7
SC	Satellite cell
SPRY1	Sprouty1

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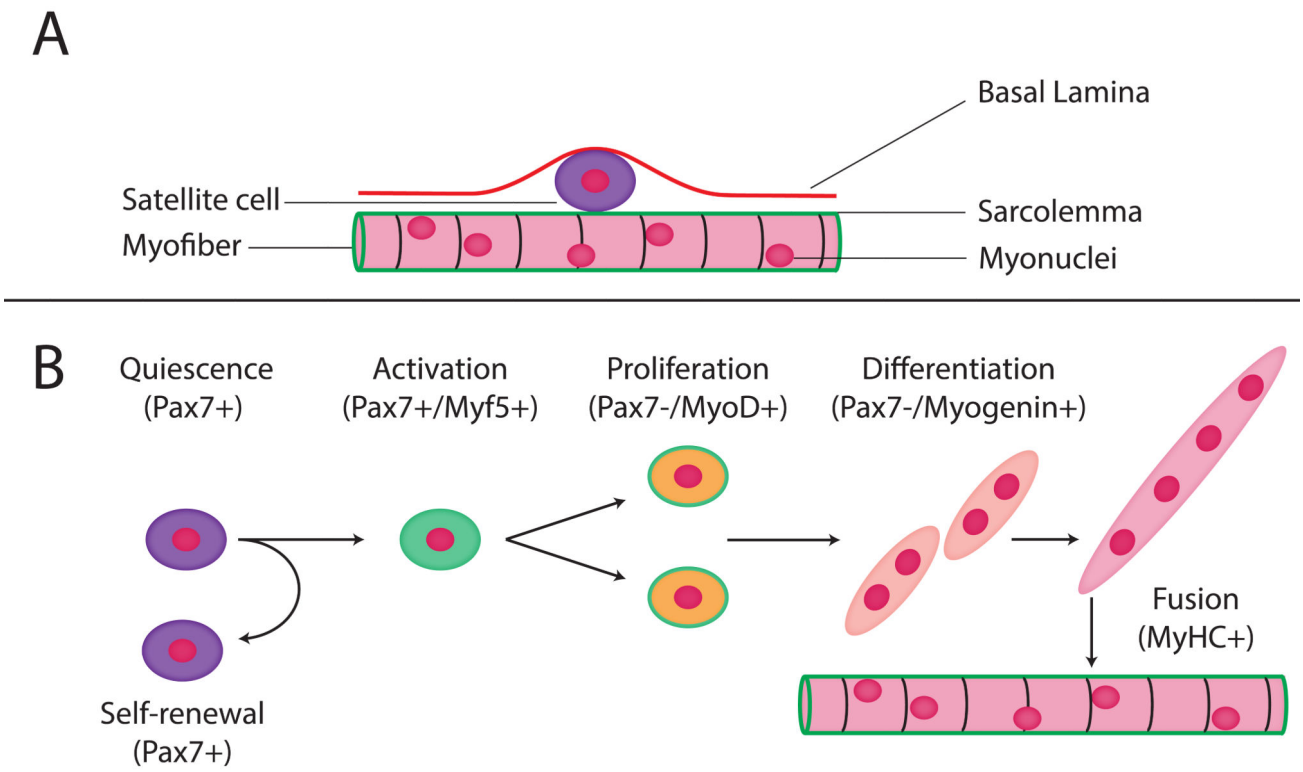

Figure 1.

Satellite cell (SC) location and function. A) The SC is anatomically located between the myofiber basal lamina and sarcolemma. B) The relationship between gene expression and SC activation, self-renewal, proliferation, differentiation and fusion with existing myofiber.

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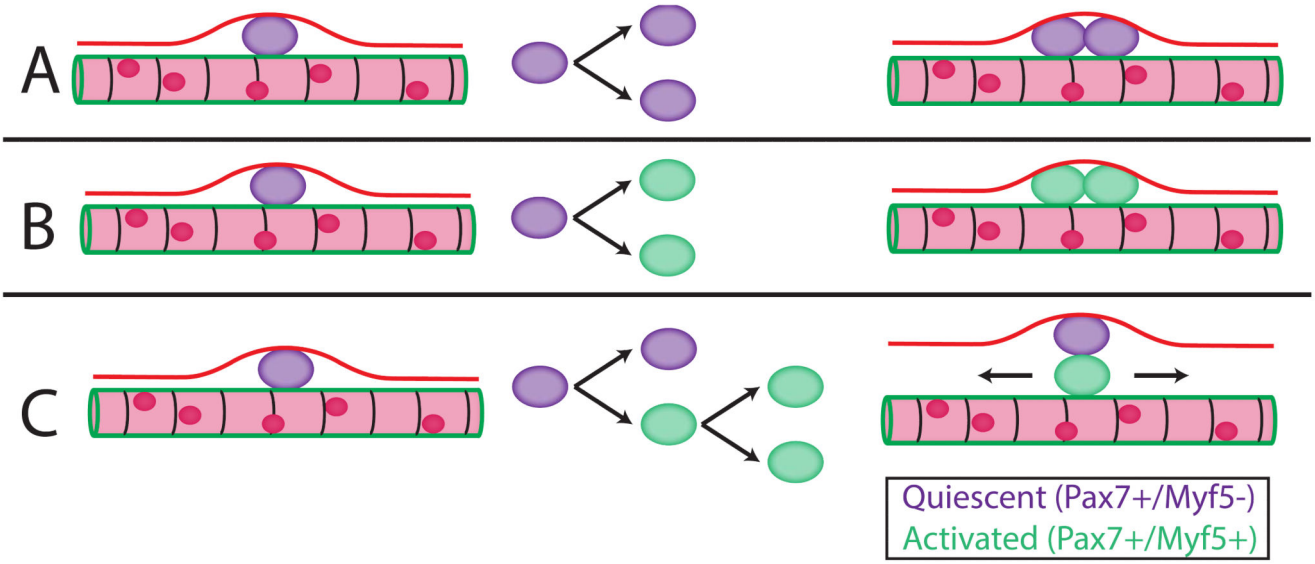

Figure 2.

Satellite cell division, quiescence, and activation. A) Quiescent SC symmetrically divides into two quiescent cells, B) Quiescent SC symmetrically divides into two activated cells C) Quiescent SC asymmetrically divides into one quiescent cell and one activated cell, which can then continue down the myogenic path. Pax7+/Myf5− indicates quiescence and Pax7+/Myf5+ indicates activation. Using lineage-tracing experiments, it was shown that 10% of SCs never express Myf5 indicating that this subset functions to maintain self-renewal. If the situation shown in B were the only process occurring, it would lead to depletion of the SC pool.

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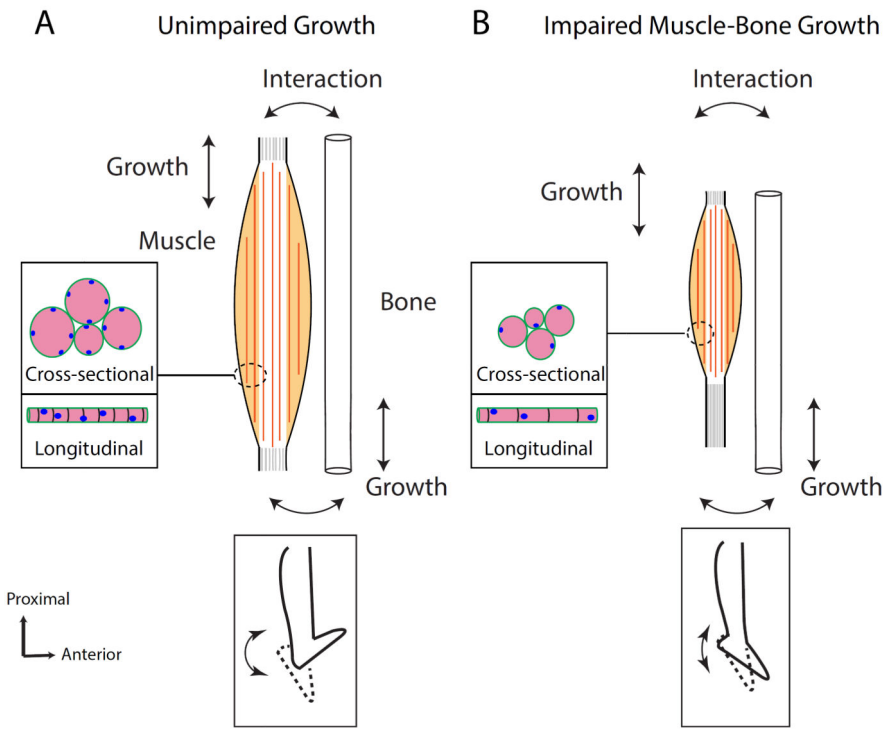

Figure 3.

Schematic of postnatal muscle growth. A) Unimpaired muscle growth resulting from bone growth. Myofiber length increase is associated with adding sarcomeres, myonuclei and girth by adding myofibrils (Inset, Cross-sectional or Longitudinal growth). This allows normal joint range of motion (Bottom Inset) B) In developmental disorders such as cerebral palsy (CP), longitudinal sarcomere growth may be impaired leading to overstretched sarcomeres as well as reduced cross-sectional growth of myofibers (Inset). In the case of children with CP this can lead to contracture development (Bottom Inset).

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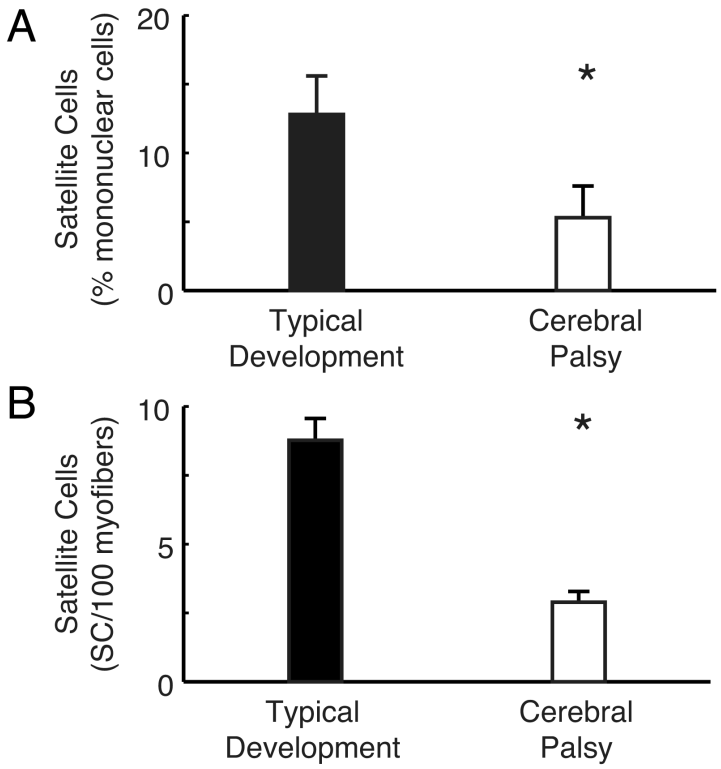

Figure 4.

Satellite cell populations in children with typical development (TD) and cerebral palsy (CP) measured using two different methods. (A) Satellite cell percentage measured by flow cytometry (B) Satellite cell percentage measured by immunohistochemistry. Both of these methods, using different human subjects, demonstrate a decreased number of SCs with in CP muscle contractures. Data are replotted from Smith et al.[102] (A) or Dayanidhi et al.[103] (B). Asterisks indicate significant difference, $p<0.05$.

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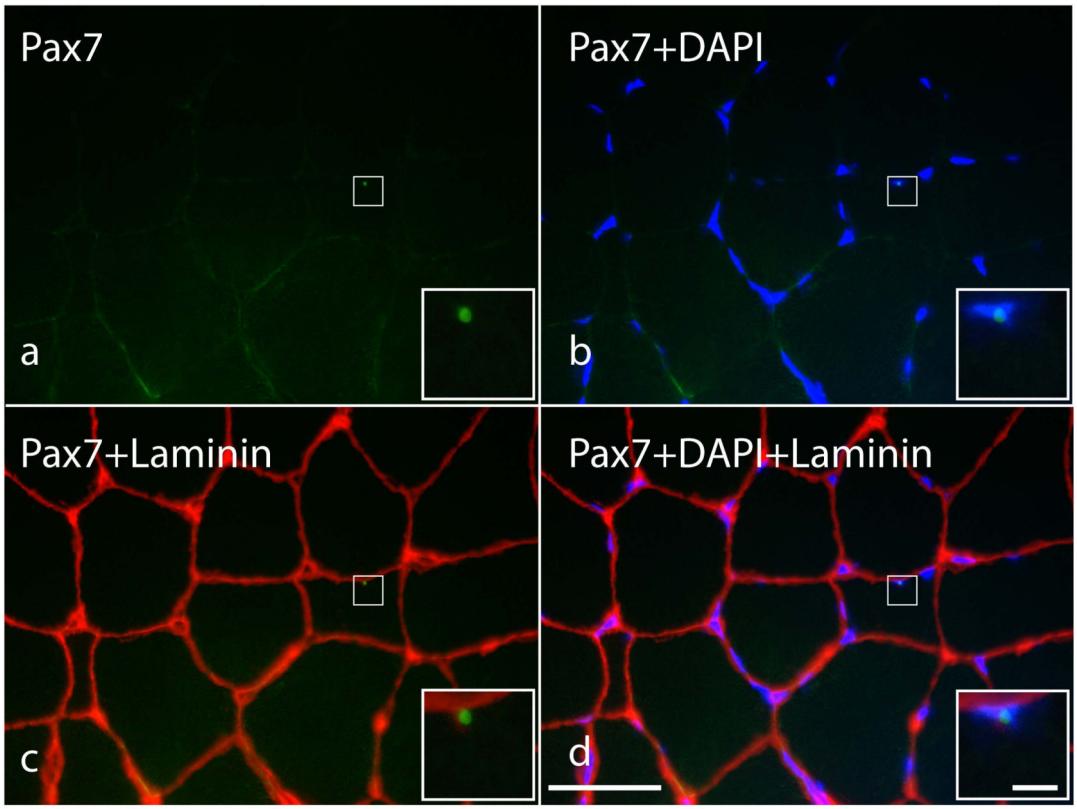

Figure 5.

High-resolution immunohistochemical identification of satellite cells in a representative gracilis cross-section from a child with cerebral palsy. Because satellite cells are indistinguishable from myonuclei based on morphology at the light microscope level, it is necessary to use immunohistochemistry for the basal lamina (laminin, red), a transcription factor (Pax7, green) and DNA stain (DAPI, blue) to unambiguously distinguish satellite cells from myonuclei and other mononuclear cells within muscle tissue. Satellite cells identified based on a positive label for Pax7 (a), co-localization with DAPI (b) and location outside of the basal lamina (c). The merged image is shown in d. Square box in a, b, c and d show the location of the satellite cell. Inset shows magnified view. Scale bar is 50μm except for inset which is 5 μm.

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Table 1

Various signaling pathways involved in the dynamic balance among maintaining quiescence, activation, proliferation, differentiation, return to quiescence and self-renewal. Numbers refer to respective references.

Signaling Pathway	SC function	References
Nitric oxide	Activation	56,58
Growth factors (IGF, FGF)	Activation	57
Notch	Maintenance of quiescence, proliferation, SC fate	62,63,64,67
Wnt	Differentiation, SC fate	66,68,69
MAPK	Self-renewal	70,71
Spry1	Quiescence, return to quiescence after Self-renewal	72
Six1	Self-renewal	73
Foxo3	Return to quiescence after self-renewal	76