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Current Opinion in Cell Biology

Muscle stem cells

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Despite being mainly composed of highly differentiated contractile fibers, the adult skeletal muscle possesses the remarkable ability to regenerate, following injury. The cells that are responsible for this capacity are the satellite cells, a small population of adult stem cells positioned under the basal lamina of muscle fibers and that can give rise to both differentiated myogenic cells while maintaining a stem cell pool by a self-renewal mechanism. We will discuss here recent publications on the developmental origin of muscle stem cells, on the signaling pathways that affect their proliferation and differentiation, with reference to works on skeletal muscle formation in the embryo as well as the adult, using the mouse and chick as reference models.

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Current Opinion in Cell Biology 2009, **21**:748–753

This review comes from a themed issue on
Cell differentiation
Edited by Carmen Birchmeier

0955-0674/$ – see front matter

DOI 10.1016/j.ceb.2009.10.002

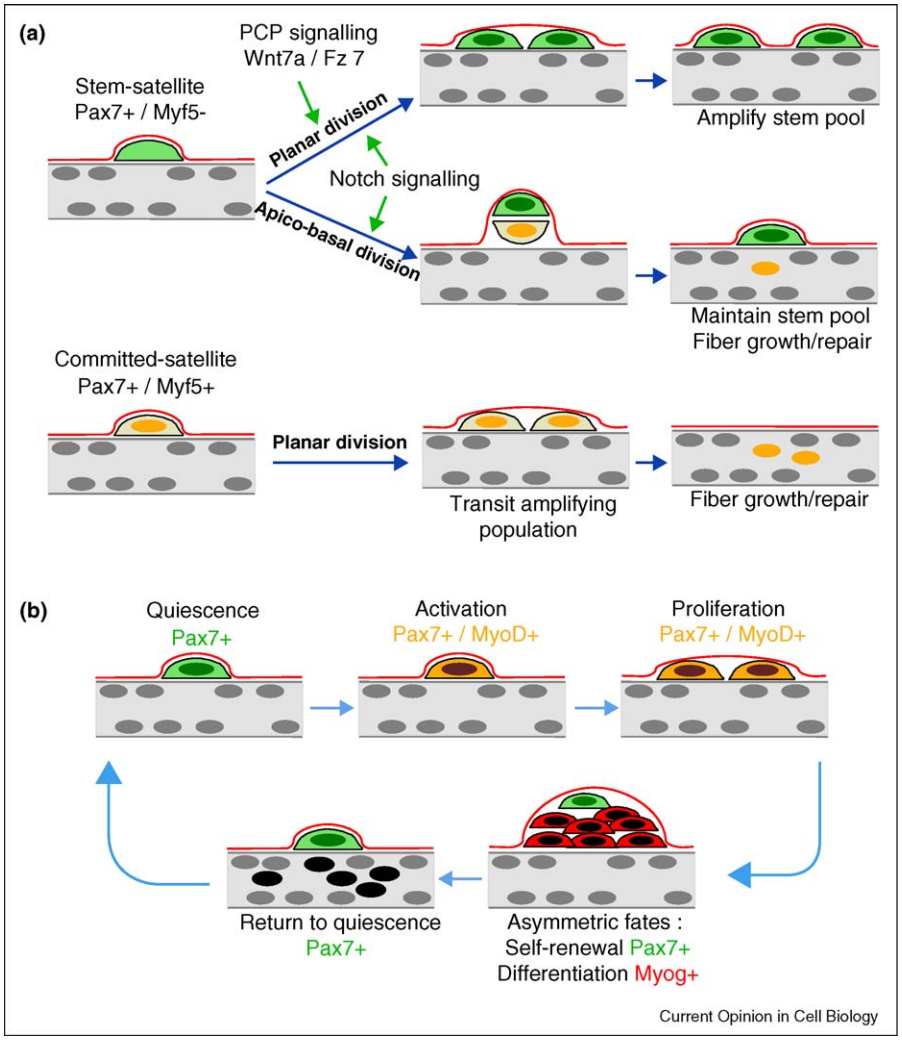
Embryonic origin of trunk, limb and head satellite cells

Skeletal muscles of the body (trunk and limbs) derive from segmental mesodermal structures, the somites that bud off from the anterior end of the pre-somitic mesoderm on each side of the neural tube [1]. Growing evidence indicates that satellite cells in the adult derive from a population of muscle progenitors that arise early during embryogenesis. There are significant differences in the morphogenetic processes that lead to the generation of muscle progenitors in the trunk, head and limb that will be summarized and discussed below. The description that follows derives from experiments performed in chick and mouse embryos. Differences between the two organisms are emphasized.

Trunk muscles are formed in two distinct stages: during the first day and a half of somite differentiation, trunk muscles form solely from a contribution of post-mitotic, mononucleated myocytes originating from the four epithelial borders of the dermomyotome, thereby generating a primitive muscle, the primary myotome. During the second stage of muscle growth, the central portion of the dermomyotome, located dorsal to the primary myotome, undergoes an epithelial-to-mesenchymal transition (EMT). In mice, the EMT is initiated in the interlimb region around E10.5 of development. In chick, it is observed at 3.5 days of development in the same region. The EMT follows the antero-posterior gradient of somite differentiation, such that as development proceeds, dermomyotomes from progressively more caudal somites undergo an EMT. Cells within the medial dermomyotome generate dermis and muscle, while cells in the lateral dermomyotome generate muscle and endothelia [2•,3,4•,5••]. Asymmetric cell division has been proposed to be the mechanism regulating muscle vs. dermis cell fate decision within the dermomyotome [6]. The EMT of the dermomyotome triggers the invasion of the primary myotome by a population of muscle progenitors [7••,8,9••,10]. Muscle progenitors that translocate into the primary myotome are characterized by the co-expression of the transcription factors Pax3 and Pax7. Once in the myotome, they either proliferate to maintain the pool of progenitors or undergo terminal myogenic differentiation. The latter process requires the sequential activation of the myogenic regulatory factors (MRFs: Myf5, MyoD, Myogenin, and MRF4; for review, see [11]. Immunohistochemistry analyses of cell proliferation done in the chick embryo have shown that Pax7+/Myf5− and Pax7+/Myf5+ cells constitute the vast majority of all proliferative cells within the trunk muscles, suggesting that they constitute a *bona fide* population of muscle progenitor cells. The initiation of MyoD expression is concomitant with an exit from cell cycle of progenitors and their engagement in a terminal differentiation process [12].

Similar studies performed in the mouse with a LacZ reporter gene targeted into the Myf5 locus and immunostained for beta galactosidase, the protein product of LacZ and Pax7 indicate that only the Pax7+/Myf5LacZ− population is proliferative, while Pax7+/Myf5LacZ+ do not significantly proliferate. While it is conceivable that this represents a true difference between chick and mouse, it is also possible that the long maturation of LacZ (i.e. the time taken to produce an active tetrameric enzyme) together with its considerable stability may bias such analyses.

Figure 1



Two current models explaining the self-renewal and differentiation of satellite cells in muscles. **A**. In a first model, Pax7+/Myf5− satellite 'stem' cells co-exist with Pax7+/Myf5+ 'committed' satellite cells. Pax7-only cells undergo symmetric or baso-apical cell division to amplify or maintain, respectively, the stem cell pool. Wnt7a and Frizzled7 (Fz7), through the Wnt Planar Cell Polarity (PCP) pathway, stimulate the symmetric division of satellite cells, thus promoting the expansion of the satellite stem cells pool. Notch signalling favors the self-renewal of satellite stem cells. Committed Pax7+/Myf5+ satellite cells, probably through planar cell division, preferentially undergo terminal differentiation. **B**. In a second model, when muscles are injured, quiescent (Pax7+) satellite cells go through an activated, proliferative (Pax7+/MyoD+) stage. From this transitory proliferating population, most cells undergo terminal differentiation while a few return to a Pax7+/Myf5− stage to renew the quiescent satellite cell pool.

Limb muscles originate from progenitor cells that delaminate from the ventrolateral border of the dermomyotome and migrate as single cells into the limb mesenchyme [1]. Lineage studies in the chick using both retroviruses and the quail–chick chimera technique, as well as genetic lineage studies in the mouse have shown that progenitor cells that delaminate from the dermomyotome derive from the Pax3+ lineage, but are multipotent, as they generate a portion of the limb vascular and lymphatic endothelia in addition to limb muscles [5••,13,14•,15]. In the chick, migrating progenitors co-express Pax7 and Pax3 [16] whereas in the mouse, Pax7 expression is initiated one day after that of Pax3, being observed at E11.5 day of development in the anterior limb [17]. Interestingly, the initiation of Pax7 expression in the murine limb progenitors restricts their potential to the muscle lineage [5••]. Future studies will need to address when the skeletal muscle and vascular lineages divert from each other, and how cell fate decisions are regulated.

Head muscle progenitors have multiple origins. The occipital somites deliver muscle progenitor cells into the tongue, as well as the posterior branchial arches that make posterior neck muscles. The cranial paraxial mesoderm

(CPM) gives rise to the bulk of head muscles, that is, most of the extraocular muscles (EOM) that move and rotate the eye in a coordinated manner and branchiomeric muscles (BM) that control jaw movement, facial expression, as well as pharyngeal and laryngeal function. Finally, the prechordal mesoderm (PM) contributes to some extraocular muscles [18]. Similarly to limb progenitors, Pax3+ tongue progenitors delaminate from the ventrolateral border of occipital somites and migrate as single cells into the branchial arches, whereas, in chick and mouse, EOM and BM muscle progenitors do not express Pax3.

Satellite cells in the adult make up 2–7% of the nuclei associated with a particular fiber. Their embryological origin was first addressed in a chick–quail chimera study. Satellite cells of quail origin were found in the wing muscles of chimeras when chick pre-somitic mesoderm was replaced by that of a quail, supporting a somitic origin for satellite cells [19]. Further studies in the chick and in the mouse have refined this initial finding by demonstrating that virtually all satellite cells from the trunk and limbs derive from the central and lateral dermomyotome, respectively, while those in the head derive from the head mesoderm [5••,8,9••,7••,20••]. Since early endothelial progenitors (i.e. hemangioblasts) that are known to efficiently differentiate into muscle tissues if exposed to a proper environment [21], also derive from somites and head mesoderm (see above), it was important to address whether satellite cells do not transit through an endothelial stage. Genetic labeling of the endothelial lineage from its earliest precursors, including the hemangioblasts [22] with a VE-cadherin^{Cre} mouse line crossed with a *Rosa YFP* mouse line showed that no satellite cell, neither in the head, nor in the trunk, were YFP labeled, thereby ruling out any significant endothelial contribution to the satellite cell pool [20••]. In the same study, it was shown that satellite cells maintain a close proximity with the muscles from which they derive, indicating a local, rather than a distant source, for satellite cells. In fact, compelling evidences indicate that satellite cells derive from Pax7+ muscle progenitors cells present in the muscle masses during embryonic and/or fetal life [5••,8,9••].

Although satellite cells remain recognized as the primary cells responsible for the regeneration of postnatal skeletal muscle, research over the past few years has shown that several other cell types, including Muscle Derived Stem Cells, side-population cells, macrophages, and mesoangioblasts, can participate to muscle regeneration in experimental conditions. The origin of these stem cell populations and their relationship to satellite cells remain largely unknown, as well as their relevance to muscle regeneration in physiopathological conditions. Despite this, intense research efforts are undertaken in many laboratories to improve the participation of these cell types to the regeneration of skeletal muscle fibers [23].

Satellite cells heterogeneity

Pax3 and Pax7 are specific markers of the adult satellite cell lineage. Both proteins probably act through the recruitment of a histone methyltransferase complex [24] in promoting expansion of the activated pool [25], while repressing premature differentiation of satellite cells by inducing proteins able to keep myogenesis at bay, such as the myogenic factor inhibitors Id2 or Id3 [26]. Whereas all satellite cells express and require Pax7, which acts as a survival factor of the adult lineage [27,28,29,30••], only a subset of the satellite cells express Pax3 [28]. Satellite cell heterogenity within muscles is further supported by the observation that, in a same muscle, 13% of satellite cells are LacZ-negative in the Myf5$^{nLacZ/+}$ mouse line, while the rest is LacZ-positive [31••]. Moreover, the same authors performed a cross between a Myf5-Cre knockin mouse line and a *Rosa26*$^{lox\text{-}stop\text{-}loxP\text{-}YFP/+}$ line. In the resulting mouse line, the YFP reporter is only expressed in cells that have seen the activity of the Cre recombinase [31••] (Figure 1). They observed that about 10% of satellite cells express Pax7, but not YFP, indicating that they have never expressed functional level of the Cre recombinase. Remarkably, the differential expression of the YFP reporter is associated with different capacities to regenerate injured muscles: Pax7+/YFP satellite cells display a stronger (threefold) regenerative potential than Pax7+/YFP+ when transplanted in regenerating muscles and they were shown to give rise to both Pax7+/YFP− and Pax7+/YFP+ satellite cells through a basal–apical asymmetric cell division [31••]. These data suggest different stemness properties within the satellite cell compartment, with a small proportion of undifferentiated 'true' stem cells that never expressed Myf5 and a large population of committed progenitors that have expressed Myf5. This view may be somewhat challenged by a recent work from the Goldhamer's lab [32] that shows, using a direct Cre knockin into the MyoD locus (*MyoD*$^{Cre/+}$) that nearly all satellite cells (98–100%, depending on the muscle) have expressed MyoD, even at very early stage of the satellite cell lineage. This is supported by a model for satellite cells self-renewal [33] that proposes that all satellite cells express MyoD when activated, before returning to a MRF-negative, quiescent state when muscle are repaired (Figure 1). Nonetheless, asymmetric division of satellite cells to generate a stem cell and a cell that undergoes myogenic differentiation is supported by the identification of label (i.e. BrdU) retaining cells (LRC) within the satellite cell pool, both *in vivo* and *in vitro* [34•,35].

Finally, recent studies show the surprising diversity in the developmental programs of satellite cells from distinct muscle groups [20••,36••]. By using RT-PCR on satellite cells from different muscle groups of the head and the body, these authors show that cells from each muscle group display specific molecular signatures characteristic of the particular muscles from which they were isolated. However, these signatures are influenced by the local

environment and are lost when the satellite cells are transplanted to ectopic locations, or placed in culture *in vitro*.

Regulation of muscle progenitor and satellite cells differentiation and self-renewal

A balance between proliferation and differentiation of muscle progenitor cells ensures the constant and harmonious growth of all skeletal muscles. How this balance is regulated during embryogenesis and in the adult is only partially understood.

During embryogenesis, it was recently shown that mutant mouse carrying mutations for Delta1 or RBP-J, two members of the Notch signaling pathway, display a premature increase in muscle differentiation that results in a rapid and complete exhaustion of the muscle progenitor cell population, eventually leading to a severe muscle hypotrophy [37,38]. Conversely, the overexpression of Delta1 maintains chick muscle progenitors in an early undifferentiated, proliferative state [39]. These data show that the Notch signaling pathway plays an essential role in maintaining the muscle progenitor pool by preventing the premature activation of the myogenic differentiation.

A second key regulator of muscle growth is myostatin. In the adult, myostatin, a secreted factor of the TGF superfamily, is a negative regulator of muscle size, since mutations that impair myostatin function in mice, cattle, and sheep result in a dramatic increase in muscle mass [40]. This effect is mediated through a regulation of muscle fiber sizes, rather than by an action on satellite cells that do not express the myostatin receptors [41]. By contrast, during embryogenesis, myostatin acts on the balance between proliferation and differentiation of muscle progenitors. Its overexpression increases the proportion of differentiated muscle cells at the expense of the muscle progenitor pool, while the inhibition of myostatin signalling results in an expansion of the progenitor population, paralleled by a decrease in the proportion of differentiated muscle cells [12].

FGF signalling may also play a role in muscle progenitor differentiation, since blocking its signalling with DN FGF receptors or by overexpressing Sprouty leads to a significant decrease in muscle progenitor differentiation [42,43].

These data suggest that the differentiation of muscle progenitors during embryogenesis is under the positive control of myostatin and FGF signalling, while it is under the negative control of Notch signalling.

Satellite cells in the adult express Notch 1, 2 and 3 receptors, as well as the ligands Dll1 and Jagged1 [44], and the sustained Notch activity prevents their differentiation [45]. Targeted mutation of the Stra13 transcriptional repressor leads stimulation of the Notch pathway, with impaired muscle regeneration and satellite cell differentiation [46].

Recently, it has been shown that another evolutionary conserved pathway, the Wnt signaling pathway might also play a role in this process. Wnt3a, through β-catenin-dependent Wnt signalling, was shown to promote differentiation by blocking the Notch signaling during the late phases of muscle regeneration [47]. Contradictory results have been obtained *in vitro*, where the activation of the β-catenin-dependent Wnt signalling was shown to activate satellite cell renewal [48]. Direct interaction of β-catenin with MyoD has also recently been shown, suggesting Lef/Tcf-independent regulation of myogenesis by the Wnt canonical pathway [49]. Interestingly, non-canonical Wnt signalling displays an unexpected role in satellite cell renewal. Wnt7a, as well as its receptor, Fzd7, both upregulated during regeneration, were recently shown to stimulate, through the planar cell polarity pathway, the symmetric expansion of the satellite stem cells pool during muscle regeneration [50••].

Conclusion

New studies published in the recent years have considerably improved our knowledge of the cellular and molecular events that coordinate the emergence, the proliferation and the differentiation of skeletal muscle stem cells. In recent years, elegant studies using the Cre/LoxP system in mice have shed a new light on the fine regulation of the molecular and cellular events regulating myogenesis. However, owing to technical limitations of such technology (notably a lack of accurate controls for the efficiency and the specificity of these tools), relative caution should be taken for the interpretation of those results. Systemic approaches to key questions in the field are under way in a number of laboratories and it is likely that they will pave the way to a global understanding of the regulatory networks that maintain muscle stem cells in an undifferentiated state or on the contrary allow their engagement into the myogenic differentiation pathway. Understanding what defines stemcellness may have a profound impact on our understanding of skeletal muscle growth and regeneration in normal or pathological conditions.

Acknowledgements

Our research is funded by grants from (CM) the Actions Concertées Incitatives (ACI), the Agence Nationale de la Recherche (ANR), the Association Française contre les Myopathies (AFM) and by the EU 6th Framework Program Network of Excellence MYORES; and from (FR) the INSERM Avenir program, the AFM, the Myology Institute (AIM), MYORES, the Institut National du Cancer (INCa) and the ANR.

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