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Review

Satellite Cell Heterogeneity in Skeletal Muscle Homeostasis

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The cellular turnover required for skeletal muscle maintenance and repair is mediated by resident stem cells, also termed satellite cells. Satellite cells normally reside in a quiescent state, intermittently entering the cell cycle to fuse with neighboring myofibers and replenish the stem cell pool. However, the mechanisms by which satellite cells maintain the precise balance between self-renewal and differentiation necessary for long-term homeostasis remain unclear. Recent work has supported a previously unappreciated heterogeneity in the satellite cell compartment that may underlie the observed variability in cell fate and function. In this review, we examine the work supporting this notion as well as the potential governing principles, developmental origins, and principal determinants of satellite cell heterogeneity.

Heterogeneity in the Satellite Cell Compartment

Satellite cells were originally identified via electron microscopy in 1961 by Alexander Mauro, located underneath the basal lamina and adjacent to the plasma membrane of the skeletal muscle myofiber [1]. Remarkably, Mauro correctly predicted the origin and function of satellite cells as remnants of embryonic development, prepared to recapitulate this process following muscle injury. Grafting experiments demonstrated that endogenous myogenic cells directly participate in myofiber repair [2], but direct evidence identifying satellite cells as the resident stem cell population remained elusive for several years.

The transcriptional program supporting stem cell function in undifferentiated myogenic cells is dependent upon the paired-box transcription factors *Pax3* and *Pax7*. *Pax3* is first expressed in the presomitic mesoderm during development and is required for limb muscle formation, cell survival, and migration [3]. *Pax7* was shown to be required for postnatal muscle growth and population of the satellite cell pool [4]. Ablation of both *Pax3* and *Pax7* allowed satellite cells to adopt alternative cell fates, confirming their crucial role in maintaining myogenic identity [4,5]. The basic helix–loop–helix (bHLH) factors *Myod1*, *Myf5*, *Myf6* (also known as *MRF4*) and myogenin, known collectively as the myogenic regulatory factors (MRFs), then act sequentially to advance satellite cells towards myogenic differentiation and fusion to form multinucleated myofibers [6]. The upregulation of *Myf5*, followed by *Myod1*, are required for myogenic determination [7,8]. Myogenin works downstream to trigger advancement to the myocyte stage and subsequent terminal differentiation [9]. Reciprocal inhibition exists between *Pax7* and the MRFs *Myod1 and Myog* [10], but neither *Pax3* or *Pax7* interfere with *Myf5* expression [11]. Together, these findings led to the classification of three distinct states as satellite cells differentiate: (i) $Pax7^+$ cells that maintain the stem cell pool, (ii) $Myod1^+$ myogenic progenitors that have entered the myogenic program, and (iii) $Myogenin^+$ myocytes primed for fusion with existing or newly formed myofibers (Figure 1A).

A major hurdle towards assaying the functional potential of satellite cells was overcome by the identification of specific cell surface markers, allowing researchers to employ fluorescence-activated cell sorting (FACS) strategies for their prospective isolation [12]. Intramuscular

Trends

Satellite cells are a functionally heterogeneous pool of skeletal muscle stem cells, differentially able to generate hierarchically composed pools of stem and progenitor cells during tissue regeneration.

Accumulating evidence supports the dominant role of microenvironmental signaling and stochastic acquisition of satellite cell fate in coordinating satellite cell fate and heterogeneity.

Reversible and competitive plasticity between functional states of self-renewal and early differentiation may underlie overall fitness and the preservation of population diversity during tissue repair.

Developmental myogenesis offers a physiological context to study the evolution of heterogeneity during satellite cell specification as it is critically regulated by local niche entry and the induction of quiescence.

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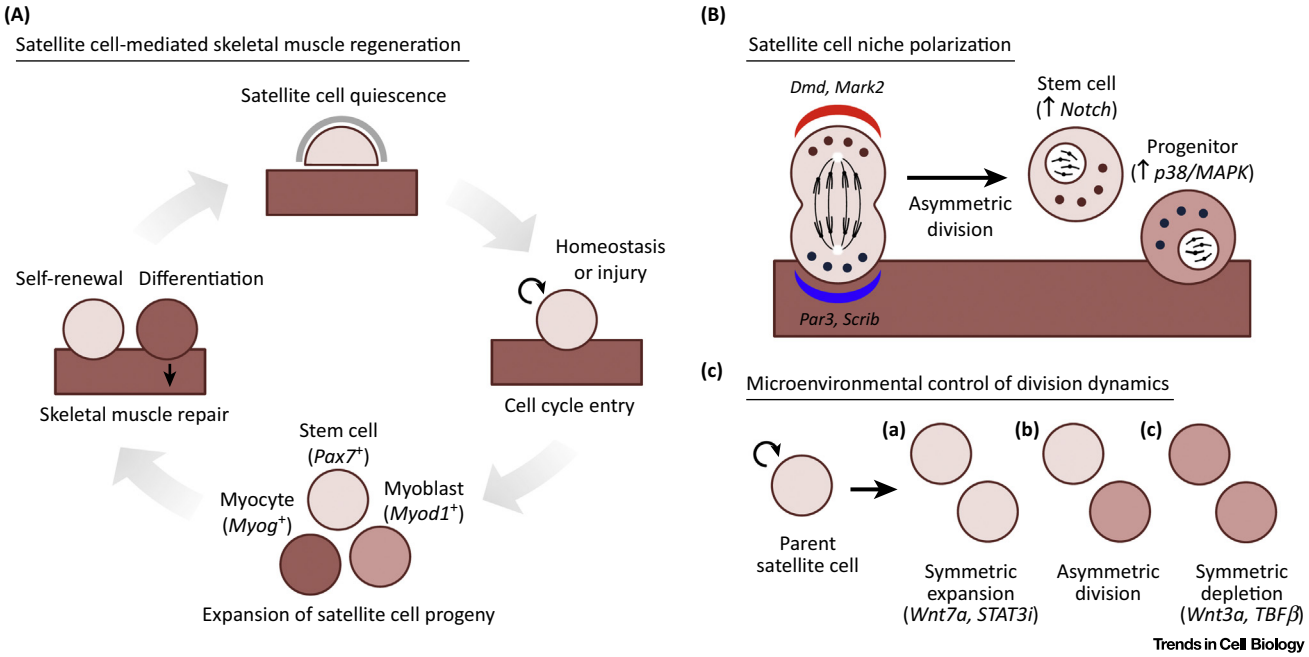

Figure 1. Modes of Satellite Cell Self-Renewal. (A) Stages of satellite cell-mediated skeletal muscle regeneration. (B) Regulation of daughter cell fate achieved by polarization in the satellite cell niche. (C) Symmetric and asymmetric division events in satellite cells controlled by soluble factors in the microenvironment.

transplantation of sorted satellite cells revealed their robust capacity for muscle repair and ability to colonize the satellite cell niche. Real-time assessment of satellite cells enabled the dynamic quantification of their expansion and responsiveness to regenerative stimuli [13]. Recombination-based labeling strategies to monitor endogenous satellite cell behavior substantiated these stem cell properties [14–16]. Finally, proper muscle regeneration failed following the genetic ablation of satellite cells [17–19], resolving their identity as a genuine somatic stem cell population indispensable for skeletal muscle repair.

Attempts to more rigorously assess satellite cell behavior uncovered a significant cellular heterogeneity. Clonal analyses revealed variability in gene expression and proliferation dynamics, including time to first division and rate of division [20–22]. These findings were confirmed on myofiber-associated satellite cells, supporting these traits as an inherent property rather than artifact of the isolation procedure [22–24]. Variance in regenerative properties was first evaluated by single myofiber grafting, where donor cell contribution was not proportional to the initial number of associated satellite cells per myofiber [25]. Single cell transplantation experiments later provided conclusive evidence of stem cell behavior at the clonal level, but only in a subset of satellite cells [13]. Functional repopulation assays verified the capacity of satellite cells for long-term self-renewal over serial rounds of regeneration but also observed disparity with regard to repopulation efficiency [26,27]. Altogether, these results support an appreciably complex level of heterogeneity in the satellite cell pool that warrants further investigation.

In this review, we discuss the principles and developmental origins underlying satellite cell heterogeneity. Although several studies have described behavioral diversity on the basis of myofiber type association [28,29] or embryological origin, including those derived from craniofacial and extraocular muscles [30,31], we focus on satellite cells of somitic origin that reside in the limb. A discussion of cellular behavior at the population level summarizes our understanding of the potential basic tenets of satellite cell heterogeneity. Finally, we examine the origin of pool