

REVIEW

Muscle stem cells in development, regeneration, and disease

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Somatic stem cell populations participate in the development and regeneration of their host tissues. Skeletal muscle is capable of complete regeneration due to stem cells that reside in skeletal muscle and nonmuscle stem cell populations. However, in severe myopathic diseases such as Duchenne Muscular Dystrophy, this regenerative capacity is exhausted. In the present review, studies will be examined that focus on the origin, gene expression, and coordinated regulation of stem cell populations to highlight the regenerative capacity of skeletal muscle and emphasize the challenges for this field. Intense interest has focused on cell-based therapies for chronic, debilitating myopathic diseases. Future studies that enhance our understanding of stem cell biology and repair mechanisms will provide a platform for therapeutic applications directed toward these chronic, life-threatening diseases.

Somatic or adult stem cell populations reside in tissues and participate in the maintenance and regeneration of their host tissues. Skeletal muscle is a dynamic tissue that is capable of responding to physiological stimuli (i.e., intense exercise training) or a severe injury by mounting a well orchestrated regenerative response that restores the cytoarchitecture within a 2-wk period (for reviews, see Hawke and Garry 2001; Cossu and Biressi 2005; Dhawan and Rando 2005; Holterman and Rudnicki 2005). The capacity for this regenerative response is primarily due to a mononuclear cell population termed satellite cells. In 1961, Alexander Mauro utilized ultrastructural techniques and identified the satellite cells as a rare cell population that is resident in adult skeletal muscle of the frog (Mauro 1961). These satellite cells were initially characterized as small, mononuclear cells that occupied a peripheral (or satellite) position in relation to the adjacent, larger multinucleated myofiber (Mauro 1961; Enesco and Puddy 1964; Moss and Leblond

1971). Using these morphological techniques, the satellite cells were observed to be intercalated between the basal lamina and the plasma membrane of the adjacent myofiber (Muir et al. 1965). In response to injury or disruption of the basal lamina, the satellite cells become activated and have a remarkable proliferative capacity. Ultimately, the satellite cells either fuse to form multinucleated myotubes or re-establish a residual pool of quiescent satellite cells that have the capability of supporting additional rounds of regeneration (Moss and Leblond 1971; Schultz and Jaryszak 1985; Bischoff 1994). However, this regenerative capacity is not unlimited, as exhaustion of the satellite cell population is an important factor in the deterioration and the demise of patients that have congenital myopathies such as Duchenne Muscular Dystrophy (DMD).

In response to a severe injury or a genetic disease such as DMD, recent studies have proposed that additional stem/progenitor cell populations may be recruited and/or have the capacity to participate in muscle regeneration and form functional myotubes (for reviews, see Hawke and Garry 2001; Cossu and Biressi 2005; Dhawan and Rando 2005; Holterman and Rudnicki 2005). The significance or the role of these stem/progenitor cells during development, disease, and regeneration is not well defined, but recent studies suggest that they not only contribute to muscle regeneration, they may also contribute to nonmuscle lineages and may serve as a vehicle for gene delivery or as a source for cell-based therapies (Hawke and Garry 2001; Cossu and Biressi 2005).

The present review will examine these issues in detail and outline the current understanding of the morphological and molecular regulation of stem cell and progenitor cell populations that participate in muscle regeneration. A discussion will focus on the genesis and molecular regulation of these stem/progenitor cells and highlight recent studies that challenge established paradigms. Importantly, this field of study remains rudimentary with regard to our understanding of the basic mechanisms that regulate the quiescence, activation, proliferation, differentiation, and self-renewal of these stem cell populations; we will highlight emerging topics of interest for this field.

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Skeletal muscle development during embryogenesis

A brief overview of muscle development during embryogenesis is warranted as studies suggest that a recapitulation of molecular networks occurs in developing and regenerating muscle. Skeletal muscle formation is derived from the paraxial mesoderm early during vertebrate embryogenesis (Buckingham et al. 2003). The paraxial mesoderm coalesces to form segmented, epithelial spheres referred to as somites that occupy paired structures on either side of the neural tube (Fig. 1A–C). The somite is further specialized to produce the dermomyotome (which is dorsal in location and generates the overlying skin and the skeletal muscle of the trunk and limbs) and the sclerotome (which is ventral in location and generates the skeleton) (Cossu et al. 1996; Miller et al. 1999; Pirskanen et al. 2000). Unlike the skeletal muscle of the torso and limbs, the genesis of head muscles is principally derived from paraxial head and prechordal mesoderm (Hauschka 1994; Christ and Ordahl 1995; Lu et al. 2002). The somites are formed in a rostral–caudal fashion, and approximately one pair of somites is formed every 2 h to ultimately produce a total of 60 pairs of somites in the developing mouse embryo (Figs. 1A–C, 2; Buckingham et al. 2003). Progenitors from the dermomyotome migrate in a dorsomedial fashion from the epaxial domain (which will ultimately generate the muscles of the back) or in a ventromedial fashion from the hypaxial domain (which will generate the intercostals, abdominal, and limb musculature) (Fig. 1C; Ordahl et al. 2000). These progenitors migrate beneath the dermomyotome to form the myotome and adopt a skeletal muscle fate. In response to cues from the adjacent notochord, neural tube, and lateral plate mesoderm, discrete gene expression in the progenitors results in withdrawal from the cell cycle and differentiation (Fig. 1). In addition, proliferating cells ($\text{Pax3}^+\text{Pax7}^+$ cells) from the central dermomyotome migrate directly to the myotome and continue to proliferate without expression of differentiation markers such as members of the MyoD family (Fig. 1C; Relaix et al. 2005). These results have challenged pre-existing notions that all myotomal cells withdraw from the cell cycle and differentiate.

Signaling factors have both permissive and repressive effects on gene expression in the epaxial and hypaxial domains of the myotome (Munsterberg and Lassar 1995; Rawls et al. 2000). For example, bone morphogenetic protein 4 (Bmp4) is released from the adjacent neural tube and the lateral plate mesoderm and has an inhibitory effect on gene expression (i.e., Myf5 and MyoD), whereas Sonic Hedgehog and Wnts (Wnt1, Wnt3, Wnt7a, and Wnt11) are released from the adjacent notochord, neural tube, and surface ectoderm, respectively, to activate gene expression in the myotome (Fig. 1B). Collectively, these and other signaling pathways regulate a hierarchical molecular program or cascade to coordinate a balance between proliferation, specification, and differentiation of the myogenic lineage during vertebrate development.

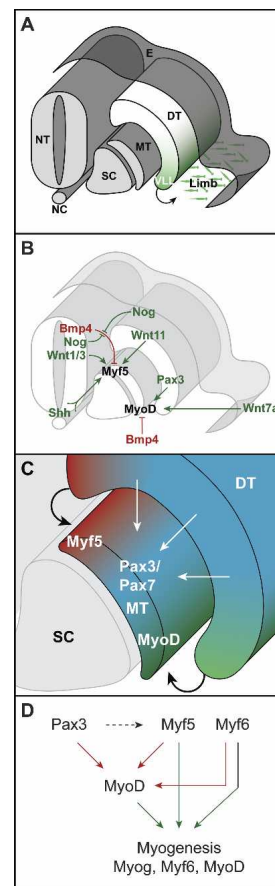


Figure 1. Developmental mechanisms direct limb myogenesis. (A) Schematic outlining the development of the somite from the paraxial mesoderm. Paired somites develop on either side of the notochord in a rostral–caudal direction. (B) In response to signals or cues from adjacent lineages (i.e., notochord, neural tube, surface ectoderm), segmentation of the somite occurs into the dermomyotome, myotome, and sclerotome that are coordinated by the regulation of gene expression. Dermomyotomal cells migrate in a dorsal fashion to give rise to the epaxial myotome (the source of trunk and back muscles) and in a ventral fashion (VLL, ventrolateral lip) to give rise to the hypaxial myotome (the source of limb muscle). Progenitors delaminate and migrate from the hypaxial myotome to the developing limb. (C) The epaxial myotome (Myf5 expressing cells) and the hypaxial myotome (MyoD-expressing cells) differentiate and activate the myogenic program. In contrast, proliferating cells from the central dermomyotomal region migrate to the central region of the myotome. These cycling cells do not express members of the MyoD family, and recent studies suggest that they are the source of a majority of the satellite cells in adult skeletal muscle. (D) Results of gene disruption studies support that Pax3, Myf5, and Myf6 (MRF4) are upstream regulators of MyoD during embryogenesis. (E) Surface ectoderm; (DT) dermomyotome; (MT) myotome; (SC) sclerotome; (NC) notochord; (NT) neurotube.

A genetic hierarchy of gene expression governs skeletal muscle development

The discovery of the basic helix–loop–helix (bHLH) family of transcription factors in developing skeletal muscle

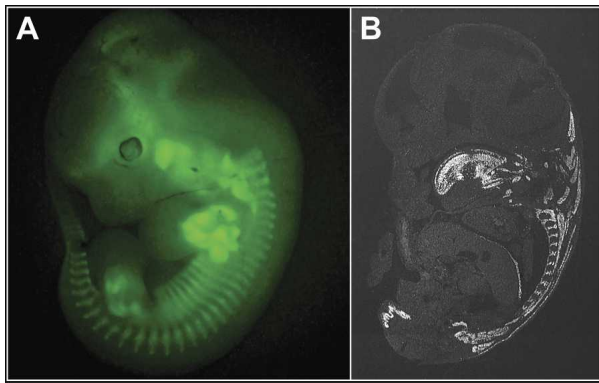


Figure 2. MyoD is expressed in somites and developing muscle during embryogenesis. (A) Whole-mount image of the MyoD promoter (containing the core enhancer and distal regulatory region)-GFP transgenic embryo at E11.5. Note expression in somites and limb muscles. (B) In situ hybridization of a parasagittal section of an E13.5 mouse embryo using a ^{35}S -labeled MyoD riboprobe. Note expression in back, intercostal, tongue, and limb muscle groups.

including MyoD (discovered in 1987), Myf5, myogenin, and Myf6 (MRF4) provided the foundation for a regulatory molecular cascade that directs myogenesis (Davis et al. 1987; Pinney et al. 1988; Tapscott et al. 1988; Braun et al. 1989; Edmondson and Olson 1989; Rhodes and Konieczny 1989; Sassoon et al. 1989; Wright et al. 1989; Weintraub 1993). These MyoD family members are expressed in somites and established skeletal muscle during embryogenesis (Fig. 2). In a coordinated fashion, they form heterodimeric DNA-binding complexes with other bHLH transcription factors such as the E2 gene family (E47 and E12) and bind a canonical DNA sequence (CANNTG, also referred to as an E box) to regulate an array of gene expression (Weintraub et al. 1989; Lassar et al. 1991; Martin et al. 1992). Utilization of gene disruption technologies has established the essential role of the MyoD family in myogenesis (Fig. 2; Braun et al. 1992; Rudnicki et al. 1992; Hasty et al. 1993; Nabeshima et al. 1993; Patapoutian et al. 1995; Zhang et al. 1995). Previous studies suggested that only MyoD and Myf5 were important to initiate muscle identity (Rudnicki et al. 1993; Kablar et al. 2003). More recently, however, studies support the notion that MyoD, Myf5, and Myf6 are all important for the specification of the skeletal muscle lineage, as triple-mutant embryos completely lacked myoblasts and skeletal muscle fibers (Kassar-Duchossoy et al. 2004). Furthermore, analysis of single and double-mutant embryos support the premise that Myf5 and Myf6 lie upstream of MyoD in the genetic hierarchy that governs skeletal muscle development (Fig. 1D; Kassar-Duchossoy et al. 2004). In contrast, the fourth member of this family has a distinct role in muscle development, as the inactivation of myogenin results in perturbed muscle differentiation and neonatal lethality (Hasty et al. 1993; Nabeshima et al. 1993).

Paired-box (Pax) transcription factors also function as key regulators of myogenesis. Pax3 exhibits broad ex-

pression in the developing embryo within the hypaxial dermomyotome, the neural tube, and neural crest derivatives. *Spotch* mice have a mutation that disrupts the *Pax3* gene, and embryos homozygous for the mutation are lethal by embryonic day 14.5 (E14.5) and have neural tube defects (exencephaly and spina bifida), neural crest cell defects, and somite defects (segmentation defects and loss of the hypaxial dermomyotome) resulting in migration failure of the muscle progenitors and an absence of limb muscles (Auerbach 1954; Franz et al. 1993; Bober et al. 1994; Goulding et al. 1994; Borycki et al. 1999). Previous studies have demonstrated that Pax3 is a transcriptional activator of the tyrosine kinase receptor Met (c-met), which functions in the delamination and migration of the muscle progenitors (Franz et al. 1993; Yang et al. 1996; Tajbakhsh et al. 1997; Dietrich et al. 1999; Brohmann et al. 2000). In support of these studies, embryos that lack Met also have an absence of limb muscles (Franz et al. 1993; Yang et al. 1996; Tajbakhsh et al. 1997; Dietrich et al. 1999; Brohmann et al. 2000). Combinatorial matings to produce embryos lacking both Pax3 and Myf5 result in an absence of body wall and limb muscle. Studies further support a regulatory network where Pax3 is genetically upstream of the MyoD family members (i.e., MyoD) (Fig. 1D; Maroto et al. 1997; Tajbakhsh et al. 1997).

Recent studies reveal a partially overlapping embryonic expression pattern between the Pax3 and Pax7 (Borycki et al. 1999). Furthermore, knock-in or replacement technologies that target the *Pax3* or the *Pax7* locus reveal that most of the Pax3 functions can be replaced by its paralog, Pax7, with the exception of limb muscle development (Relaix et al. 2004). Importantly, Pax7-deficient embryos have normal muscle development, suggesting that it is nonessential for embryonic muscle formation (Mansouri et al. 1996). Furthermore, gene disruption studies have identified additional regulators of myogenesis that function downstream of muscle specification, including the homeodomain transcriptional repressor *Msx1* and the homeodomain transcription factor *Lbx1* (results in the absence of selected limb muscles) (Wang and Sassoon 1995; Bendall et al. 1999; Brohmann et al. 2000; Gross et al. 2000). Collectively, these transcriptional regulators govern the specification of the skeletal muscle lineage in the somite, the progenitor cell migration from the hypaxial domain of the dermomyotome to the limb (from the 20- to the 31-somite stage in the forelimb), the condensation of the myoblasts into pre-muscle masses, and the formation of primary and secondary myofibers (Hawke and Garry 2001; Cossu and Biressi 2005).

Somitic origin of the satellite cell population

The embryonic origin of muscle stem cells that reside in adult skeletal muscle has been extensively explored using a spectrum of transplantation and genetic strategies (Cossu 1997; Cossu and Mavilio 2000). Previous studies suggest that muscle stem/precursor cells including the myogenic satellite cell population originate principally

from the somite (Fischel 1895; Le Douarin and Barq 1969; Christ et al. 1974; Armand et al. 1983; Schultz and McCormick 1994; Ordahl et al. 2000). Recent fate mapping studies support the results of early experiments and exploit the ability to manipulate the chick embryo (Gros et al. 2005; Schienda et al. 2006). In recent studies, the investigators either electroporated green fluorescent protein (GFP) into the cells of the somite, or in a separate series of experiments they grafted quail cells (which can be easily distinguished and identified in the chick muscle) within the chick somite (Gros et al. 2005; Schienda et al. 2006). Following birth, the majority (but not all) of the satellite cells were of quail origin, supporting the hypothesis that a majority of the satellite cells are derived from the central region of the dermomyotome of the somite. Alternative origins for the satellite cell population have also been proposed; these include the bone marrow or vascular components (i.e., endothelium, pericyte, mesoangioblast, etc.) (discussed below, see Fig. 3). A somitic versus a nonsomitic origin for the satellite cell population need not be mutually exclusive, as alternative sources may contribute to a greater or lesser extent in response to growth-promoting environments or in response to a severe injury or associated with disease.

Myogenic stem cell identity

Since the discovery of the satellite cell population in adult skeletal muscle, intense efforts have been directed toward the definition of molecular markers that identify this cell population. Satellite cells lack expression of the

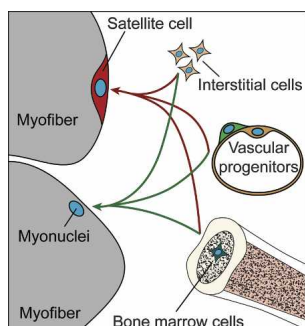


Figure 3. Somitic and nonsomitic contributions to the satellite cell pool and myofibers. Recent studies establish that the majority of the satellite cells are derived from the somite ($Pax3^+/Pax7^+$ cells located in the central region of the myotome). Other stem cell/progenitor cell populations that also contribute to the satellite cell pool and muscle regeneration include interstitial cells (muscle derived stem cells or MDSC, SP cells, $Cd45^+/Scal^+$ cells, $Scal^+$ cells, $Cd34^+$ cells, etc.), bone marrow cells (hematopoietic stem cells, mesenchymal stem cells, multipotent adult progenitor cells, etc.), vascular progenitors (mesoangioblasts, pericytes, endothelial progenitors), or other lineages (i.e., neural stem cells). It is unclear whether the interstitial or non-muscle stem cell population may be a more significant source for muscle regeneration in the diseased or myopathic state (characterized by a severe, chronic injury).

myogenic regulatory factors, including members of the Myod family (Hawke and Garry 2001). Recent studies have utilized an array of transgenic and gene disruption strategies to identify and further characterize the satellite cell population. Factors that have a restricted expression pattern and serve as markers for the satellite cells in adult skeletal muscle include cell surface receptors, adhesion proteins, growth factors, and transcription factors (Fig. 4).

Receptors and adhesion proteins

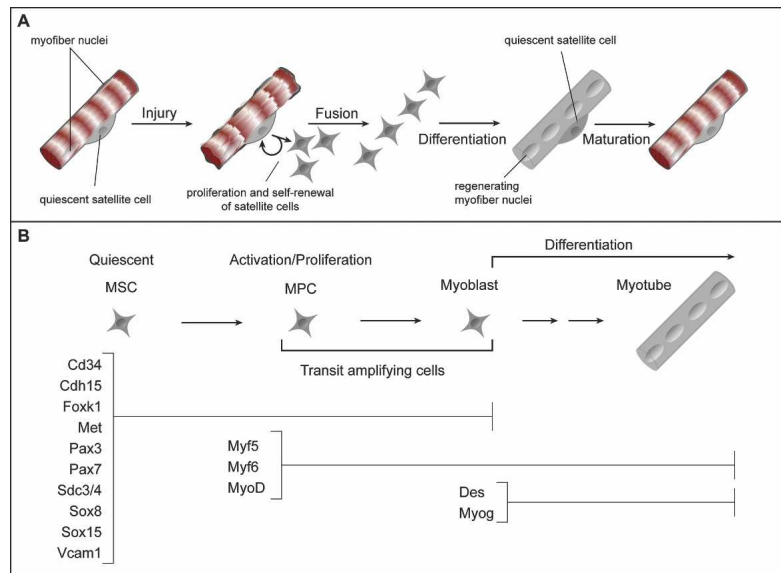
Met is a tyrosine kinase receptor for the multifunctional cytokine ligand, hepatocyte growth factor (Hgf) (Andermarcher et al. 1996). This tyrosine kinase receptor is expressed broadly during development in the myotome of the somite and neural crest derivatives and is localized to the quiescent satellite cell population in adult skeletal muscle (Andermarcher et al. 1996). Embryos lacking Met are nonviable and have an absence of limb musculature, presumably due to the failure of precursor migration from the somite (Bladt et al. 1995; Andermarcher et al. 1996; Maina et al. 1996). Expression of Met appears to uniformly label the quiescent satellite cell pool (Cornelison and Wold 1997).

M-cadherin (Cdh15) is a calcium-dependent cell adhesion molecule that is expressed in a subpopulation of the quiescent satellite cells and is up-regulated more broadly in activated satellite cells during muscle regeneration (Irintchev et al. 1994; Cornelison and Wold 1997; Beauchamp et al. 2000). Proposed functions for this integrin include the anchoring of the satellite cell to its location and/or a role in facilitating the migration of the satellite cell to areas of injury to mediate repair (Irintchev et al. 1994; Bischoff 1997; Beauchamp et al. 2000). While mice lacking m-cadherin have normal muscle development and regeneration, other cadherin proteins may substitute for the absence of m-cadherin, further suggesting the redundancy of these adhesion factors (Hollnagel et al. 2002). Other integrins and adhesion proteins that have been used as markers for satellite cells include VCAM-1 and NCAM (Covault and Sanes 1986; Jesse et al. 1998).

The sialomucin Cd34 is a cell surface glycoprotein that is expressed on endothelial cells and serves as a marker for hematopoietic stem and progenitor cells (Young et al. 1995; Cheng et al. 1996). Mice lacking Cd34 are viable, suggesting that it is nonessential for stem cell function (Krause et al. 1994). Cd34 is expressed in a subpopulation of satellite cells, but it is not restricted to this lineage in adult skeletal muscle (Beauchamp et al. 2000). Rather, expression of Cd34 may be associated with a specific stage or state of the satellite cell population, and therefore its use as a marker for satellite cells must be used with caution (Lee et al. 2000).

Recent studies by the Olwin laboratory (Cornelison et al. 2001) have identified the transmembrane heparin sulfate proteoglycans syndecan-3 (Sdc3) and syndecan-4 (Sdc4) as important satellite cell factors in the developing embryo and in adult muscle (Fig. 4). Using a targeted

Figure 4. Gene expression identifies stem cell and progenitor cell populations in adult skeletal muscle. (A) Schematic outlining the role of satellite cells during muscle regeneration. In response to an injury, the quiescent satellite cell is activated by factors (including Fgfs, Hgf, activated Notch or NICD, Tnf- α) and up-regulates MyoD expression within 2 h of injury. Recent studies support that satellite cells undergo self-renewal (to repopulate the residual pool) and proliferate to produce myoblasts that fuse to form newly regenerated myofibers (characterized by the central location of the nucleus). (B) Schematic outlining the gene expression of the myogenic stem cell pool (MSC or satellite cells), myogenic progenitor cells (MPC or those characterized by expression of MyoD, Myf5, or Myf6), myoblasts (characterized by myogenin or desmin expression), and the multinucleated myotube. Additional studies will be necessary to dissect the gene expression and establish the hierarchy of the heterogeneous satellite (MSC) pool. MPC and myoblasts may be equivalent to the transit amplifying cells described in skin and gut. (Sdc3/4) Syndecan 3 and 4; (Cdh15) m-cadherin; (Myog) myogenin; (Des) desmin; (Met) c-met.



gene disruption strategy, distinct satellite cell defects were associated with the loss of either syndecan protein (Cornelison et al. 2004). Syndecan-3-null mice were shown to exhibit impaired locomotion, hyperplasia of satellite cells and myocytes, extensive fatty infiltrates, and fibrosis of the skeletal muscle. Aspects of this phenotype are further observed in other dystrophic muscle models (Bell and Conen 1968). In contrast, the syndecan-4-null satellite cells have impaired activation, proliferation, and differentiation of the mutant satellite cells resulting in a perturbed regenerative response to injury (Cornelison et al. 2004). Future studies will be needed to explore the role of each of these syndecans in satellite cell signal transduction in response to stimuli associated with growth, aging, and injury.

Nuclear factors

Transcription factors govern molecular cascades that ultimately regulate the fate of cell populations. *Foxk1* is a member of the *forkhead*/winged helix transcription factor family and is expressed in the quiescent and proliferating satellite cell population during the latter stages of embryogenesis, postnatal, and adult skeletal muscle (Fig. 4; Garry et al. 1997, 2000). Members of the *forkhead*/winged helix transcription factor family regulate cell fate, patterning, and cell cycle kinetics of stem cell and progenitor cell populations. Using an array of biochemical techniques, we have demonstrated that *Foxk1* is an upstream regulator of the cyclin-dependent kinase inhibitor *p21^{CIP}* in the satellite cell population (Garry et al. 2000; Hawke et al. 2003). Mice lacking *Foxk1* are growth retarded and have a severe impairment in skeletal muscle regeneration. The impairment of skeletal muscle regeneration is due to decreased numbers of satellite cells and impaired cell cycle kinetics (Hawke et al. 2003).

Recent studies suggest that Sox transcription factors are upstream regulators of *Foxk1*. Sox transcription factors are found in all metazoan species and play key roles in embryonic development. Sox factors contain a DNA-binding domain (i.e., HMG domain) that doubles as both the DNA-binding moiety and the major interface for protein-protein interaction (Wilson and Koopman 2002). Therefore, specificity of the Sox factor is, in part, dependent on the factors that partner with Sox proteins either to activate or repress transcription from target promoters (Beranger et al. 2000; Wilson and Koopman 2002; Schmidt et al. 2003). Sox8 and Sox15 are expressed in the satellite cell population in adult skeletal muscle (Fig. 4; Schmidt et al. 2003; Lee et al. 2004). Biochemical and overexpression studies suggest that these Sox factors inhibit myogenesis through the transcriptional repression of MyoD family members (Schmidt et al. 2003). Moreover, mice lacking Sox15 are viable but appear to have impaired skeletal muscle regeneration (Lee et al. 2004). Utilizing a yeast two-hybrid assay, recent studies report that Sox factors may interact with Paired-box transcription factors to coregulate gene expression (Wilson and Koopman 2002).

Elegant studies undertaken by the Buckingham laboratory have targeted the *Pax3* locus using the GFP reporter (Relaix et al. 2005). Analysis of this reporter model revealed that *Pax3* and its paralog, *Pax7*, are coexpressed in a majority (~87%) of the myotomal cells of the somite during embryogenesis (Relaix et al. 2005). Moreover, a majority of these *Pax3⁺Pax7⁺* myotomal cells were proliferating cells that sharply contrasted with the decreased proliferative index of the myotomal cells that expressed MyoD or Myf5. During the latter stages of development, these *Pax3⁺Pax7⁺* cells lacked MyoD expression and served as progenitors that subsequently formed skeletal muscle (Relaix et al. 2005). Furthermore, these *Pax3*-GFP cells assumed a satellite cell position (i.e., be-

neath the basal lamina) (Fig. 5) in the E18.5 embryo and in adult skeletal muscle, further emphasizing an essential role for Pax transcription factors for the specification of a myogenic fate (Montarras et al. 2005). Pax7 mutant mice have normal muscle development, and while satellite cells are present initially, they are not maintained during the postnatal period, suggesting a role for Pax7 in the maintenance (or as an antiapoptotic factor) of the satellite cell (Mansouri et al. 1996; Seale et al. 2000; Oustanina et al. 2004; Relaix et al. 2006). Additional studies verify that the Pax7 mutant mouse has a severe impairment in muscle regeneration (Kuang et al. 2006; Relaix et al. 2006).

The satellite cell niche and the influence of permissive and repressive factors

Satellite cells are abundant during the neonatal period, as estimates suggest that upward of 30% of nuclei in the neonatal hindlimb skeletal muscle are sublaminar satellite cells (Snow 1977; Bischoff 1994). Following the growth period where satellite cells fuse to myofibers, this cell population is reduced to 2%–5% of the hindlimb nuclei in adult skeletal muscle (the number of satellite cells is dependent on species, age, and muscle fiber type) (Fig. 5; Snow 1977; Allam 1981; Campion et al. 1981; Hawke and Garry 2001). Future initiatives for this field will evaluate the relationship between neonatal versus adult satellite cells (i.e., the definition of the molecular regulation of the respective cell populations), the heterogeneity of the satellite cell pool in adult skeletal muscle (i.e., the definition of a hierarchy of satellite cells), and the relationship of satellite cells resident in oxidative slow-twitch muscle groups (i.e., soleus muscle) compared with those cells resident in the fast-twitch glycolytic muscles (i.e., extensor digitorum longus muscle).

The myogenic satellite cell has an anatomically defined specialized niche (Fig. 5) that ultimately governs the state of this cell population (i.e., quiescence, activation, proliferation, etc.) (Fig. 6). The adjacent differentiated myofiber, innervating motor neurons, infiltrating inflammatory cells, and the vascularization collectively

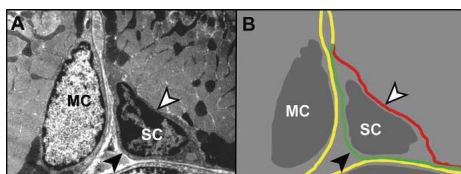


Figure 5. The satellite cells have a specialized niche in adult skeletal muscle. (A) Electron micrograph of adult skeletal muscle demonstrating the myocyte nucleus (MC) and the satellite cell nucleus (SC). Note that the satellite cell is characterized by its size (i.e., small), high nuclear to cytoplasm ratio, relative absence of cytoplasmic organelles, and increased nuclear heterochromatin representing a quiescent state of the cell. (B) Schematic of A emphasizing that the satellite cell lies between the basal lamina (black arrowhead or green line) and the sarcolemma (white arrowhead or red line).

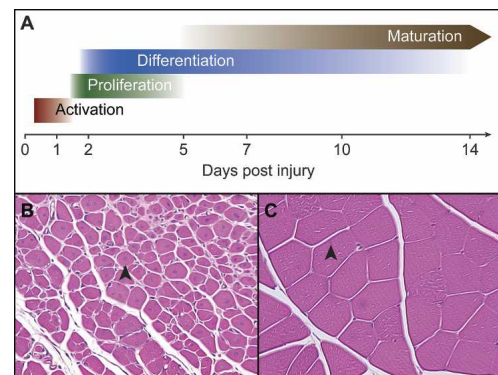


Figure 6. Muscle repair is characterized by discrete stages of regeneration. (A) Schematic outlining the stages of regeneration including the activation of satellite cells (within 2 h of injury), satellite cell proliferative (or transit amplifying cell) stage (cellular proliferation peaks at days 2–3 following injury), differentiation (characterized by the formation of centronucleated myofibers), and maturation. (B) Following an intramuscular injection of cardiotoxin (a myonecrotic agent), ~70%–90% of the muscle is destroyed. Regeneration by stem/progenitor cells results in the formation of small, centronucleated (slightly basophilic) myofibers between 5 and 7 d post-injury (arrowhead marks the centronucleus of the newly regenerated myofiber). (C) Hematoxylin and eosin-stained transverse section of post-injured skeletal muscle reveals restoration of the cellular architecture within ~2 wk of injury. The nucleus occupies a peripheral position in fully mature myofibers.

establish the niche in which the satellite cell resides (Schmalbruch and Hellhammer 1977; Gibson and Schultz 1982; Wokke et al. 1989; Brown and Stickland 1993). The release of cytokines, neurotrophic factors, growth factors, or oxygen tension (which mediates the hypoxia-inducible gene program such as Hif1 α , Hif2 α , NO, Vegf, etc.) collectively orchestrates and modulates the status of the satellite cell pool. For example, recent studies have established that a hypoxic microenvironment maintains an undifferentiated state of selected cell populations. In a series of experiments, the induction of Hif1 α was shown to activate Notch downstream genes to maintain the stem/progenitor cell state (Gustafsson et al. 2005).

Skeletal muscle is a source for insulin-like growth factors (Igf1 and Igf2) that function as hormones and as paracrine factors (Allen and Boxhorn 1989; LeRoith et al. 1992). A detailed analysis has been undertaken for the functional roles for Igf1 in skeletal muscle, which are multiple and complex. This complexity is attributable to the four isoforms for Igf1 that originate through genetic and protein processing. The use of mouse genetics has established roles for Igf1 in the modulation of inflammation and decreased scar formation mediated in part by the down-regulation of Tgfb during muscle regeneration (Barton et al. 2002; Shavlakadze et al. 2004). Transgenic overexpression of Igf1 in skeletal muscle restores the regenerative capacity of aging skeletal muscle through the promotion of satellite cell activation, satellite cell proliferation, and the recruitment of nonmuscle stem cells

from the bone marrow (Barton-Davis et al. 1998; Musaro et al. 2001, 2004). These functional roles for Igf1 are mediated by a number of signaling pathways in skeletal muscle including the calcineurin/NFAT pathway to mediate hypertrophy, PI3K/Akt/mTOR to increase protein synthesis and promote cell survival, and mitogen-activated protein kinase kinase (MAPKK) pathway to promote satellite cell activation and proliferation (Mourkioti and Rosenthal 2005; Song et al. 2005). Further studies will be necessary to further explore the role of Igf1 isoforms on the regulation of stem cell activity and examine clinical applications for the use of recombinant human Igf1 for the treatment of myopathies (Mourkioti and Rosenthal 2005).

The Tgfb superfamily stimulates and represses stem cell activity and regeneration. Myostatin (Gdf8) is a member of the Tgfb family that is expressed in skeletal muscle satellite cells and myoblasts (McCroskery et al. 2003). Bovine (Belgian Blue and Piedmontese) and genetic murine models that lack myostatin have extensive muscle hypertrophy referred to as a double-muscling phenotype (Kambadur et al. 1997; McPherron et al. 1997). Using isolated fiber preparations and satellite cell/myoblast cultures, data suggest that myostatin may function to maintain satellite cell quiescence and repress self-renewal in part through the induction of p21^{CIP} (Cdkn1a) (McCroskery et al. 2003). Recent studies further suggest that the modulation of growth-inhibitory factors such as myostatin in myopathic models results in increased muscle regeneration (McCroskery et al. 2005). These preclinical studies have led to the use of small molecule inhibitors of myostatin in clinical trials.

Hgf or Scatter factor (SF) is a 90-kDa protein that is tethered to the extracellular matrix in skeletal muscle and is released in response to mechanical stretch or injury by a nitric oxide (NO)-dependent mechanism (Michalopoulos and Zarnegar 1992; Miller et al. 2000; Sheehan et al. 2000; Anderson and Pilipowicz 2002; Tatsumi et al. 2002; Tatsumi and Allen 2004). The activated Hgf is a ligand for the c-met receptor and is a potent activator of the satellite cell population promoting cell cycle re-entry (from the G0 quiescent state to G1) by transducing the p38 MAPK and PI3K signaling pathways (Cornelison and Wold 1997; Tatsumi et al. 1998; Weston et al. 2003; Jones et al. 2005; Lluís et al. 2006; Wozniak et al. 2005). Unresolved issues include the definition of the mechanism of NO-mediated release of Hgf as well as the role of NO and Hgf on non-satellite cell progenitors that participate in muscle regeneration.

Fibroblast growth factors have multiple isoforms and are released from damaged myofibers to further promote the proliferation of activated satellite cells (Clegg et al. 1987; Clarke et al. 1993; Johnson and Allen 1995; Cornelison et al. 2001, 2004; Yablonka-Reuveni and Anderson 2006). Transduction of the FGF signal is mediated through one of four transmembrane tyrosine kinase receptors (Fgfr1–Fgfr4) that are expressed on the satellite cell membrane and requires heparin sulfate to mediate the intracellular signal (Rapraeger et al. 1991; Cornelison et al. 2001). Previous studies have established that the

role of Fgfs on satellite cell proliferation is mediated via the Raf/ERK signaling pathway (Jones et al. 2001). Furthermore, studies have explored the modulatory effects of Fgfs (including Fgf6) on myogenic differentiation (Seed and Hauschka 1988; Rando and Blau 1994; Sheehan and Allen 1999; Cornelison et al. 2001; Armand et al. 2003). Fgf6 is relatively restricted to the myogenic lineage and is induced in response to injury (Goetsch et al. 2003). Independent efforts to genetically ablate Fgf6 have resulted in a variable phenotype with one group reporting a normal phenotype and another group reporting a severe regenerative defect in the absence of Fgf6 (Floss et al. 1997; Fiore et al. 2000). These differential phenotypic results remain unresolved but may be due to strain differences and the presence of modifier genes. Additional studies will be necessary to explore the collective interaction of Fgfs and other growth factors in the regulation of the satellite cell fate in response to injury and regeneration. These additional factors include, but are not limited to, Pdgf, Egf, Lif, Tnf- α , Tgfb, NO, Il4, etc. (Nathan 1987; Austin and Burgess 1991; Kurek et al. 1997; Anderson 2000; Horsley et al. 2003; Li 2003).

Self-renewal of myogenic stem cell populations

Skeletal muscle has the capacity for complete regeneration and restoration of the cellular architecture in response to repeated injuries. This ability to withstand multiple injuries implies that the satellite cell pool is replenished during the regenerative process (Fig. 5A; Moss and Leblond 1971; Schultz and Jaryszak 1985; Schultz 1996). Previous pulse-chase experiments (using tritiated thymidine or BrdU to label cells in S phase of the cell cycle as a measure of cellular proliferation) have suggested that the satellite cell pool was heterogeneous and promoted the notion that a pool of satellite cells maintained a residual pool consistent with a self-renewal mechanism (Moss and Leblond 1971; Schultz 1996). These studies further supported the presence of a cycling pool of satellite cells that may be similar to the transit amplifying cell (TAC) population described in other lineages (i.e., skin and gut) (Blanpain et al. 2004; Tajbakhsh 2005). More recent studies using cultured myofibers demonstrate that activated satellite cells principally differentiate and express MyoD family members (Fig. 5B). In contrast, activated satellite cells may exit the cell cycle, re-establish a quiescent state, and be stimulated to re-enter the cell cycle, suggesting that satellite cells are capable of self-renewal or replenishment of a residual pool of cells (Halevy et al. 2004; Olguin and Olwin 2004; Zammit et al. 2004). Direct evidence for a self-renewal mechanism for the satellite cell pool was established following the transplantation of genetically labeled myofibers (genetically labeled with the LacZ reporter) into the hindlimb musculature of the irradiated *mdx* myopathic mouse model. In this study, radiation ablation of the dystrophic muscle inactivated the endogenous muscle stem cells. Collins et al. (2005) observed that the transplantation of one myofiber containing as few as seven satellite cells gave rise to >100 new myofi-

bers containing >25,000 differentiated donor myonuclei. Importantly, these transplanted satellite cells gave rise to anatomically distinct satellite cells that participated in the repopulation of myofibers following a newly induced injury with a myotoxin (Collins et al. 2005). The mechanism that directs the self-renewal mechanism remains to be determined, but studies suggest that the transcription factor, Pax7, or the Notch/Numb signaling pathway may participate in these cell fate decisions (Conboy and Rando 2002; Halevy et al. 2004; Olguin and Olwin 2004). Further studies will unravel the mechanisms that direct the self-renewal process, define the proliferative capacity of the satellite cell population *in vivo*, and define a hierarchical satellite cell cascade. It is likely that a stem cell/progenitor cell hierarchy comparable to the hematopoietic system exists for the satellite cell pool (i.e., stem cells vs. transit amplifying progenitors vs. progenitors) (Weissman 2000). The definition of this satellite cell hierarchy will serve as a platform for cell-based therapies.

Repositories of stem cell and progenitor cell populations for repair of skeletal muscle

While studies have clearly established the myogenic potential of satellite cells, other cell populations have been shown to participate in limited muscle regeneration. These stem cell populations either reside in skeletal muscle or may be recruited from nonmuscle pools in response to signals or cues associated with injury and regeneration (Fig. 3). Selected cell populations will be highlighted as cellular sources for muscle regeneration.

Previous studies have established that Cd45, a hematopoietic-restricted marker, identifies a cell population that has a myogenic capacity following induction by the Wnt signaling pathway (Polesskaya et al. 2003). Moreover, these Cd45⁺:Sca1⁺ (Ly6a) cells lack a myogenic potential when isolated from unperturbed skeletal muscle but acquire a myogenic potential when isolated from injured muscle (Polesskaya et al. 2003). Using genetic mouse models, studies demonstrated that the Cd45⁺:Sca1⁺ cells, in adult skeletal muscle, require Pax7 for myogenesis during regeneration (Seale et al. 2004).

The bone marrow is a further source of stem cell populations that has myogenic potential. Using genetically labeled mouse models, marrow-derived cells have been shown to be recruited to injured muscle and to generate fully differentiated myofibers (Ferrari et al. 1998). Bone marrow-derived multipotent adult progenitors (Cd13⁻/Sca1⁻/Flk1⁻/Cd45⁻/Cd31⁻) are capable of forming differentiated myotubes *in vitro* and *in vivo* following the delivery into murine muscle (Jiang et al. 2002; Muguruma et al. 2003; Reyes et al. 2005). Studies undertaken in the Blau laboratory (LaBarge and Blau 2002; Corbel et al. 2003) have demonstrated that GFP-labeled bone marrow-derived cells become satellite cells that are capable of myogenesis and the formation of labeled myofibers. Further support of these results was undertaken using parabiotic joined mice. The parabiotic mouse model joins two genetically distinct mice that develop a common

vascular system, and these studies demonstrated that bone marrow-derived cells formed skeletal myofibers in injured and physiologically stressed muscle in the absence of other injuries (i.e., irradiation damage) (Sherwood et al. 2004; Palermo et al. 2005).

Side population (SP) cells constitute a stem cell/progenitor cell population that resides in adult tissues including bone marrow and skeletal muscle (Goodell et al. 1996, 1997; Meeson et al. 2004). Using a DNA-binding dye (Hoechst33342) and dual-wavelength flow cytometry, SP cells are identified based on their ability to efflux the Hoechst33342 dye (Goodell et al. 1996, 1997; Montanaro et al. 2004). The ability to efflux this DNA-binding dye is due to the multidrug resistance protein, Abcg2 (Zhou et al. 2001; Martin et al. 2004). Previous studies have established that SP cells are capable of myogenesis *in vitro* and *in vivo* (Gussoni et al. 1999; Asakura et al. 2002; Bachrach et al. 2004; Meeson et al. 2004). SP cells increase in number following muscle injury, have a distinct molecular signature, and participate in muscle regeneration (Meeson et al. 2004). Muscle SP cells are characterized as Sca1^{high} and Cd45^{low} (>80% of the SP cells express Sca1 and ~10%–15% of the SP cells express Cd45) (Gussoni et al. 1999; Meeson et al. 2004). SP cells in skeletal muscle have been shown to be decreased in number (Meeson et al. 2004) or have normal numbers (Seale et al. 2000) in genetic null mouse models. Recent studies undertaken by the Kunkel laboratory (Schienda et al. 2006) utilizing different types of labeling techniques in chick and mouse reveal that at least a subpopulation of skeletal muscle SP cells is derived from Pax3⁺ hypaxial somitic cells. Future studies will further explore the developmental origin of all muscle SP cells and the relationship of the SP cells to vascular progenitors and satellite cell populations.

Vascular constituents have been shown to have a myogenic potential (Fig. 3). Cossu's laboratory (De Angelis et al. 1999; Minasi et al. 2002; Sampaoli et al. 2003) has demonstrated that vessel-associated progenitors (mesoangioblasts) isolated from the dorsal aorta have myogenic potential and are capable of participating in muscle regeneration. In support of these results, fate-mapping studies revealed that descendants of Flk1 (Kdr)-expressing cells contributed to the skeletal muscle lineage generating labeled myofibers (Motoike et al. 2003). Flk1 is the receptor for vascular endothelial growth factor and is expressed in the earliest progenitors of the endothelial and hematopoietic lineages (Motoike et al. 2003). Other vascular components such as endothelial progenitors and pericytes have also been proposed as having myogenic potential (Tavian et al. 2005).

Additional stem cell populations that have been isolated from adult skeletal muscle include muscle-derived stem cells (MDSC that are Cd34⁺/Sca1⁺), Sca1⁺ cells, Cd34⁺ cells, and neural stem cells (neurospheres), which all have myogenic potential (Galli et al. 2000; Lee et al. 2000; Tamaki et al. 2002, 2005; Deasy et al. 2005; Mitchell et al. 2005). These studies emphasize the capacity of stem cell/progenitor cell populations to undergo the self-renewal, increased proliferation (up to 300 dou-

blings), and reprogramming associated with culture conditions (Galli et al. 2000; Lee et al. 2000; Tamaki et al. 2002, 2005; Deasy et al. 2005; Mitchell et al. 2005). Additional studies will be necessary to define the hierarchy of these stem cell/progenitor cell populations, their relationship to satellite cells, and their capacity to participate in the growth, maintenance, and regeneration of skeletal muscle in response to injury and disease.

Plasticity and potential of stem cells and progenitor cells in adult skeletal muscle

Multipotentiality or plasticity is a characteristic of stem cell and progenitor cell populations. Recent studies have clearly demonstrated that satellite cells and other progenitor cell populations that are resident in adult skeletal muscle are capable of generating other mesodermal derivatives (Hu et al. 1995; Jackson et al. 1999; Asakura et al. 2001; Holst et al. 2003). These studies demonstrate that myogenic stem/progenitors are capable of generating nonmuscle lineages including blood derivatives, vascular components, osteoblasts, and adipocytes in response to specific signals (Jackson et al. 1999). For example, satellite cells that are cultured in the presence of bone morphogenic proteins (i.e., Bmp2) promote the osteogenic molecular program with an induction of the master transcriptional regulators Runx2 and Osterix (Fux et al. 2004). Similarly, intense interest has recently focused on the transdifferentiation of muscle progenitors to the adipogenic lineage. This interest is fueled by the observation that myopathic skeletal muscle is characterized by the replacement of myofibers by adipose tissue. Induction of the master regulators peroxisome proliferating activating receptor- γ (PPAR γ) and CCAAT-enhancer binding protein- α (Cebpa) in satellite cells results in the transdifferentiation to the adipogenic lineage. While the regulatory cascade for adipogenesis in myogenic progenitors is incompletely defined, signaling pathways, such as the Wnt/ β -catenin, the Rho GTPase, and IL-15 pathways, have been implicated in this process (Ross et al. 2000; Taylor-Jones et al. 2002; Sordella et al. 2003; Akimoto et al. 2005; Quinn et al. 2005; Vertino et al. 2005). In addition to the mesodermal derivatives, myogenic stem/progenitor cell populations may have a broader potential and may generate lineages from other germ layers such as the neuronal lineage (Tamaki et al. 2005). An alternate but not mutually exclusive possibility is that satellite cells can be directed toward a mesenchymal alternative differentiation (MAD) program prior to the generation of nonmuscle lineages (Shefer et al. 2004). Future studies will be necessary to fully decipher the capacity of the myogenic progenitors *in vivo* to generate other lineages within the regenerating skeletal muscle (i.e., vasculature, peripheral nerve, etc.) and other lineages (i.e., myocardial, neuronal, etc.). These studies will enhance our understanding of regeneration and may serve as a platform for progenitor cell-based therapies for non-skeletal muscle diseases (i.e., cardiomyopathies).

Regenerative mechanisms

Skeletal muscle is a highly regenerative tissue that is second only to bone marrow with regards to its regenerative capacity. Numerous injury models have been proposed to examine skeletal muscle regenerative mechanisms, including crush, freeze, and chemical injuries. Perhaps the most reproducible injury utilizes chemical agents including cardiotoxin, notexin, or barium chloride (d'Albis et al. 1988; Garry et al. 1997; Cornelison et al. 2004). In response to a chemical-induced injury, a well orchestrated cellular and molecular response is observed (Fig. 6). Immediately following injury, myofibers hyalinize, vacuolate, and lyse (Goetsch et al. 2003). Morphological analysis reveals interstitial edema with neutrophils that release trophic factors to activate the satellite cells within 2 h of injury (Fig. 6). A marked inflammatory response is characterized by the presence of lymphocytes and macrophages that begin to phagocytose necrotic myofibers (Goetsch et al. 2003). Following activation of the satellite cell population, they re-enter the cell cycle and demonstrate a significant proliferative capacity between 2 and 3 d following injury. This proliferative period is followed by a differentiation phase where myoblasts withdraw from the cell cycle and form small basophilic centronucleated myotubes (the hallmark of skeletal muscle regeneration) (Fig. 6; Goetsch et al. 2003). Fusion of myoblasts and further growth of the newly regenerated centronucleated myofibers ultimately results in restoration of the cellular architecture within an ~2-wk period (Goetsch et al. 2003).

Similarly, the molecular signature of regenerating muscle is coordinated and complex. Using transcriptome analyses, numerous studies have characterized the molecular profile of gene expression that governs discrete stages of stem cell and progenitor cell populations during muscle regeneration. Hoffman's laboratory (Zhao and Hoffman 2004) undertook an extensive transcriptome analysis as they interrogated 27 regenerative time periods following cardiotoxin-induced muscle injury. In addition, studies using microarray analysis have focused on cell cycle kinetics, the extracellular matrix, or mouse models that have ongoing degeneration-regeneration cycles (Tseng et al. 2002; Goetsch et al. 2003; Porter et al. 2003; Yan et al. 2003; Turk et al. 2005). Collectively, these and other studies demonstrate the induction of MyoD and Myf6 within 2–6 h of injury, corresponding to their role in activation of the satellite cell population (Grounds et al. 1992; Megeney et al. 1996; Nicolas et al. 1996; Garry et al. 2000). Myf5 is delayed in expression, peaks within 5 d of injury, and has a similar expression pattern to myogenin. The Notch/Numb, Fgf, and Neuregulin pathways were dynamically regulated in addition to the extracellular matrix factors tenascin C, thymosin B4, and MMPs, which have multiple roles including the modulation of cellular migration of the satellite cell pool (Goetsch et al. 2003; Turk et al. 2005). Transcriptional regulators including Paired-box factors (Pax3 and Pax7), Forkhead, and Sox family members are up-regulated during the repair and regenerative period (Goetsch et al.

2003; Turk et al. 2005). This strategy has provided a global analysis of the molecular regulation of stage-specific gene expression during the degeneration–regeneration period and has provided a foundation to further define regulatory cascades that govern the regenerative process.

Muscle diseases and aging

Congenital and acquired myopathies are common and deadly. The most common lethal myopathic disease is DMD, which is an X-linked recessive disease that afflicts ~1:3500 males. In 1986, the Kunkel laboratory identified dystrophin as the disease-causing gene (Hoffman et al. 1987). Dystrophin is 2.4 Mb in size and is the largest known mammalian gene (Hoffman et al. 1987). DMD-afflicted patients are diagnosed early in childhood. This progressive muscle-wasting disease affects striated muscle including limb muscles, diaphragm, and heart (Watkins and Cullen 1988). The final stages of disease are characterized by cardiorespiratory failure, and death usually occurs in the teenage years or early 20s. The most common mouse model for DMD is the dystrophin mutant *mdx* mouse model that was described in 1984 (Bulfield et al. 1984). The phenotypic changes in the *mdx* mouse model are less pronounced compared with the DMD patients, but the mutant mouse has ongoing cycles of degeneration and regeneration of skeletal muscle (peaking at 3–10 wk of age) and an increase in fat and fibrosis of the skeletal muscle (Bell and Conen 1968; DiMario et al. 1991; Matsuda et al. 1995; Straub et al. 1997; Briguët et al. 2004). The *mdx* mice also have spinal abnormalities (i.e., kyphosis) and a dilated cardiomyopathy (Briguët et al. 2004; Laws and Hoey 2004; Quinlan et al. 2004). A genetic mouse model that may have a more severe myopathy and limited survival is the utrophin–dystrophin double-mutant mice (Deconinck et al. 1997). Studies suggest that the double-mutant mice may more accurately represent the pathobiology observed in the DMD patient (Deconinck et al. 1997).

Recent studies have established an important role for Lamin A/C and emerin in satellite cell differentiation (Bakay et al. 2006; Frock et al. 2006; Melcon et al. 2006). Mutations within Lamin A are associated with Emery-Dreifuss and Limb-Girdle muscular dystrophy patients. Mice lacking lamin A/C have impaired myogenic differentiation as a result of perturbed pathways or networks regulated by the retinoblastoma and MyoD genes (Bakay et al. 2006; Frock et al. 2006; Melcon et al. 2006). These studies underscore the role of Lamin A/C and emerin for the coordinated regulation of cell cycle kinetics and terminal differentiation.

Utilizing a gene disruption strategy, additional genetic mouse models have been generated that have myopathic or regenerative defects including dystrophin–glycoprotein complex (DGC) mutant mice (i.e., sarcoglycan mutants), sarcomeric mutant mice (i.e., desmin-null mice), Pax7-null mice, Foxk1-null mice, and syndecan-4-null mice (Garry et al. 2000; Seale et al. 2000; Allikian et al. 2004; Cornelison et al. 2004; McNally and MacLeod 2005; Barresi and Campbell 2006). These knockout and

other transgenic models will have utility for the study of muscle regeneration and serve as models to test therapeutic strategies to promote function and survival (Yasuda et al. 2005).

Accumulating evidence has established that age-related myopathies (i.e., sarcopenia) also have impaired regenerative defects. A number of the regenerative defects associated with aged muscle are due to the macro- and microenvironment (Carlson and Faulkner 1989, 1996; Coggan et al. 1992; Chakravarthy et al. 2000). Previous studies utilizing a transgenic strategy to overexpress Igf1 have demonstrated increased satellite cell proliferation, mobilization of nonmuscle stem cells, and improved regeneration in skeletal muscle of aged mice (Musaro et al. 2001, 2004; Mourkioti and Rosenthal 2005). Mechanistically, the impaired proliferative capacity of satellite cells that reside in aged muscle has been shown to be due, in part, to perturbed Notch signaling, as forced expression of activated Notch restored the regeneration capacity of old (or aged) muscle (Conboy et al. 2003; Luo et al. 2005). Further studies undertaken by the Rando laboratory have utilized parabiosis to surgically join young and old mice to establish a shared circulatory system (Conboy et al. 2005). This strategy established that unknown circulating factors in young mice restore both the Notch signaling in satellite cells and muscle regeneration in aged mice (Conboy et al. 2005; Luo et al. 2005). Additional studies will be necessary to decipher the factors that modulate aged satellite cells as therapeutic targets for sarcopenia.

Future perspectives

In summary, skeletal muscle has a remarkable regenerative capacity due to resident stem cell populations. Recent studies have begun to define the genesis of the satellite cell pool and the regulatory cascades that direct discrete stages of the satellite cell pool. Future studies will further define the molecular regulation of these stages and define the hierarchy of stem cells and progenitors (i.e., transient amplifying cells) that reside in adult skeletal muscle. These results will enhance our understanding of somatic stem cell biology and serve as a platform for cell-based therapies directed toward patients with congenital birth defects and debilitating myopathies.

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