International Journal of Biomedical and Health Sciences
Vol. 9, No. 2, June 30, 2013
Printed in Nigeria

0794-4748/2013 $5.00 + 0.00

http://www.asopah.org

IJBHS 9202

Aging and stem cell renewal

Haroldo Silva and Irina M Conboy[§].

Department of Bioengineering, University of California, Berkeley, California 94720, USA
[§] To whom correspondence should be addressed. E-mail: ude.yelekreb@yobnoci

ABSTRACT: Adult or organ stem cells present in mammalian organ systems are essential for the maintenance and repair of these organs throughout adult life. This key function of adult stem cells requires precise coordination of highly regulated molecular signaling to ensure proper cellular, tissue, and organ homeostasis. Such coordination deteriorates with age and consequentially, adult stem cells in the aged organism do not regenerate tissue damaged by stress, injury or attrition as efficiently as in the young. The molecular mechanisms associated with deficits in organ stem cell function with advancing age are for the most part unknown. Nonetheless, recent studies are beginning to shed light on the processes involved in stem cell aging, particularly in adult skeletal muscle stem cells, namely satellite cells. In this chapter, the current mechanisms believed to contribute to stem cell aging are reviewed, focusing on satellite cells and comparing them to hematopoietic stem cells as these cell types offer interesting perspectives regarding extrinsic versus intrinsic aging programs. Undoubtedly, knowledge of how organ stem cells change with advancing age will help in understanding the aging process itself and might provide novel therapeutic venues for the enhancement of tissue regeneration.

Stem cell aging and loss of tissue regenerative potential

Mammalian organ systems are repaired and maintained by dedicated subsets of resident cells that are collectively called adult or organ stem cells as well as progenitor or precursor cells. For the sake of convenience, all such cells (including satellite cells) will be henceforth referred to as stem cells even though it may not be the case for all organs and tissues. Similar to the embryonic stem cells that build organs, adult stem cells that regenerate organs are capable of symmetric and asymmetric divisions, self-renewal and differentiation. Coordinating these cell-fate decisions in adult tissues is critically important for the maintenance of cellular homeostasis and hence for organ function. This precise coordination of complex stem cell responses throughout adult life is regulated by evolutionary conserved signaling networks that cooperatively direct and control (1) the breakage of stem cell quiescence, (2) cell proliferation and self-renewal, (3) cell expansion and prevention of premature differentiation and finally, (4) the acquisition of the terminal cell fate. This highly regulated process of tissue regeneration recapitulates embryonic organogenesis with respect to the involvement of interactive signal transduction networks, such as Notch, Wnt, TGF-β, Shh and Ras/MAPK (Carlson *et al*., 2008; Wagers *et al*., 2005).

With advancing age the regenerative properties of organ stem cells deteriorate and the integration of the molecular signaling responsible for the productive responses of these cells becomes altered in ways that make tissue repair inefficient (Conboy *et al*., 2003; Molofsky *et al*., 2006; Rossi *et al*., 2007; Wagers *et al*., 2005). While the notion of an age-specific decline in regeneration has existed for a long time, the molecular and cellular determinants of this unfortunate outcome are not entirely understood and are a subject of active investigation. In recent years, the interconnected roles of the intrinsic and extrinsic/niche

based factors in the aging of tissue regeneration have begun to emerge, not only improving our understanding of the aging process, but also suggesting potential therapies for the enhancement of tissue repair in the old. The following discussion of stem cell aging mechanisms will be restricted, for the most part, to studies on adult skeletal muscle and hematopoietic stem cells. This review is by no means exhaustive and only highlights the major aging mechanisms reported in the literature for these two stem cell types.

The regeneration of skeletal muscle is a perfect example of a tissue that relies on life-long maintenance by endogenous stem cells, called satellite cells (Hawke *et al*., 2001; Mauro, 1961; Muir *et al*., 1965; Wagers *et al*., 2005). With aging, the process of muscle regeneration by resident stem cells becomes inefficient, which leads to a replacement of functional muscle by fatty and fibrous tissue (Brack *et al*., 2007; Marshall *et al*., 1989). This age-related, acquired muscle atrophy known as sarcopenia is phenotypically similar to congenital myopathies, where satellite cells struggle to keep up with the constant death of genetically deficient muscle fibers (Grounds, 1998; Gruenbaum *et al*., 2005; Radley *et al*., 2007; Smith *et al*., 2005).

Additionally, sarcopenia is associated with altered microtubule networks leading to disordered distribution of nuclei in old myofibers, which might introduce transport limitations to some cell compartments (Bruusgaard *et al*., 2006). Abnormalities in the microtubules may stem from nonenzymatic glycosylation and other posttranslational modifications of microtubule-associated proteins due to alterations in protein metabolism in old muscles (Bruusgaard *et al*., 2006). Irregular and fragmented nuclei are also found in aged myofibers, thus indicating that apoptotic events possibly triggered by accumulated DNA damage in these fibers are responsible at least in part by the loss of nuclei and muscle mass in the old (Bruusgaard *et al*., 2006). Moreover, sarcopenia has also been correlated to anatomic or functionally deficient muscle innervation in elderly individuals and indeed old animals have slow or impaired muscle reinnervation capacity as compared to young (Carlson *et al*., 1989; Choi *et al*., 1996).

The outstanding regeneration abilities inherent in adult skeletal muscle can be attributed almost exclusively to the small satellite cell population resident in this tissue (Hawke *et al*., 2001; Wagers *et al*., 2005). Satellite cells are located in a niche under the basal lamina but outside of the muscle fiber sarcolemma (Hawke *et al*., 2001; Le Grand *et al*., 2007; Wagers *et al*., 2005). Satellite cells were first identified in electron microscopic studies of frog skeletal muscle fibers (Mauro, 1961). These cells were first described as being "wedged" between the muscle fiber sarcolemma and the basement membrane, and this intimate association was persistent along the length of the frog tibialis anticus muscle fibers (Mauro, 1961). Interestingly, electron micrograph observations revealed that the surface of the myofiber is distorted inwards, with its myofibrils being pushed aside to accommodate the satellite cell and it was conjectured that these newly identified "dormant myoblasts" were present in all vertebrate skeletal muscles (Hawke *et al*., 2001; Mauro, 1961).

Later, more detailed studies on muscles derived from fruit bats and white mice revealed that satellite cells are uniformly distributed and indeed osmotically independent from muscle fibers (Muir *et al*., 1965). In addition, these mononucleate fusiform satellite cells possess a high nuclear-to-cytoplasmic ratio, few organelles and increased nuclear heterochromatin as compared to myonuclei (Hawke *et al*., 2001; Muir *et al*., 1965). These satellite cell features are consistent with its relatively quiescent and transcriptionally less active nature (Hawke *et al*., 2001). Satellite cell density depends on the age, species and type of myofiber, constituting about 30% of muscle nuclei in the neonate but only 2-4% in adult mice (Hawke *et al*., 2001). There is no significant decline in the satellite cell numbers in mice and humans (Conboy *et al*., 2003; Roth *et al*., 2000; Wagers *et al*., 2005) and their proliferative potential is nearly constant since satellite cells isolated from both young (9-year-old) and old (≥ 60-year-old) humans are capable of about 20 to 30 replications in vitro under standard growth conditions (Hawke *et al*., 2001; Renault *et al*., 2000). Also, mouse satellite cells isolated from young (3-6 mo), adult (7-10 and 11-13 mo), old (19-25 mo) and senile (29-33 mo) mice show the same proliferative capacity during short-term cultures in vitro, provided that the mitogenic milieu of older cells is properly enriched with FGF (Shefer *et al*., 2006). It has also been demonstrated that a minor subset of aged mouse satellite cells (22-30 mo) is as capable of self-renewal

and regeneration as young cells both in vitro and after myofiber engraftment into mdx-nude host mice (Collins *et al*., 2007).

Quiescent satellite cells are reported to express CD34 and Pax7, β1-integrin and CXCR4, but are also known to be a heterogeneous population with possible differences in myogenic potential among stem cell sub-populations (Collins *et al*., 2007; Cossu *et al*., 2007; Mitchell *et al*., 2005; Sherwood *et al*., 2004; Wagers *et al*., 2005). The activated satellite cell progeny (i.e., fusion-competent myoblasts) also express Pax7, β1-integrin and CXCR4, as well as desmin, Myf-5 and MyoD; and to this date, there is no known unique genetic marker of quiescent satellite cells and no clear understanding of how quiescence in these cells is established and maintained (Wagers *et al*., 2005). Another subset of myofiber-associated cells is $CD45^{+}$ leukocytes that become numerous in the injured muscle due to the inflammatory response, but are not themselves myogenic (Polesskaya *et al*., 2003; Sherwood *et al*., 2004; Wagers *et al*., 2005). Very little is known about age-specific changes in the profile of muscle stem cells and potential differences in the genetic marker expression. Hence, sub-population composition is yet to be determined with respect to satellite cells residing in young versus aged muscle. Nonetheless, advances are being made in identifying potential genetic markers for the satellite cell subpopulations, which are most likely generated via asymmetric (perpendicular to the muscle fiber) and symmetric (along the myofiber axis) muscle stem cell divisions (Cossu *et al*., 2007).

In contrast to the in vitro observations discussed above (Hawke *et al*., 2001; Renault *et al*., 2000; Shefer *et al*., 2006), satellite cells in aged muscles display an impaired ability to activate and proliferate in response to injury and represents one of the key age-specific defects in muscle repair (Conboy *et al*., 2002; Conboy *et al*., 2003; Wagers *et al*., 2005). Activation of these quiescent cells for proliferation is triggered by injury or attrition of mature muscle fibers. By 24 hours after muscle injury, satellite cells enter the G1/S phase of the cell cycle and robustly proliferate for the next 2-3 days (Hawke *et al*., 2001). This expansion of muscle stem cells is accompanied by their differentiation along the myogenic lineage; first into a pre-myoblast subset that expresses high levels of Pax3 and then into fusion-competent myoblasts that are $desmin^{hi}$, $pax7^{hi}$ and $pax3^{lo/-}$ (Wagers *et al*., 2005). Myf-5 was also reported to be up-regulated early during satellite cell activation and then to be down-regulated in the fusion-competent myoblasts (Brack *et al*., 2008). During this stage of de novo adult myogenesis, satellite cell progeny undergoes asymmetric cell divisions with respect to cell-fate determination and with respect to the segregation of template DNA strands (Conboy *et al*., 2007).

The process of muscle regeneration culminates in the production of de novo multinucleated myofibers. In mice, it has been well established in recent literature using standard injury models (cardiotoxin or dry ice) and a variety of techniques such as histology, immunofluorescence staining, Western Blotting, FACS, and high-throughput microarray analysis that muscle regeneration shifts from myogenic cell proliferation to myoblast differentiation events at around day 3 post-injury (Hawke *et al*., 2001; Yan *et al*., 2003). In fact, the highest levels of myogenic cell proliferation and expression of regulators of cell cycle progression and DNA replication are observed at 3 days after injury (Yan *et al*., 2003). Newly generated myofibers with their characteristic centrally-located nuclei, expressing embryonic myosin heavy chain and resulting from the fusion of satellite cell progeny (i.e., myoblasts), typically do not appear in massive numbers until 4 to 5 days after muscle injury (Hawke *et al*., 2001; Yan *et al*., 2003). However, it is still possible to detect a few nascent myofibers at earlier time points post-injury (Yan *et al*., 2003), especially around the periphery of the injury site where muscle was less damaged. In mice, no significant age-specific defect in this terminal differentiation, i.e. fusion of myoblasts into myotubes, is observed (Conboy *et al*., 2003).

The process of myogenic differentiation was reported to be regulated by an antagonistic balance between active Notch and Wnt/β-catenin signaling pathways (Brack *et al*., 2007; Brack *et al*., 2008; Conboy *et al*., 2002; Conboy *et al*., 2003). Specifically, active Notch allows cell proliferation and prevents premature differentiation by inhibiting Wnt signaling in muscle progenitor cells via the induction of GSK-3β, which in turn promotes the degradation of β-catenin (Brack *et al*., 2008; Conboy *et al*., 2002). Later on, the Notch antagonist Numb is upregulated, which inhibits Notch activity and allows for the Wnt pathway to promote differentiation into myoblasts and myotubes (Brack *et al*., 2008; Conboy *et al*.,

2002). Consequently, injections of exogenous Wnt3A into injured muscle at specific time points causes replacement of muscle with fibrous tissue because the expansion of myogenic progenitor cells terminates prematurely and thus not enough cells are available for regeneration, i.e. de novo myofiber production (Brack *et al*., 2007; Brack *et al*., 2008). This defect in muscle repair was also connected with a reported ability of Wnt to skew the myogenic cell fate of satellite cells into the fibroblast lineage (Brack *et al*., 2007). Thus, very interestingly, Wnt may both (1) promote myogenic lineage determination (Brack *et al*., 2008) and (2) inhibit myogenic cell fate (Brack *et al*., 2007), presumably, depending on the timing of Wnt signaling in the muscle niche.

The molecular regulatory mechanisms of cell fate decisions during regeneration of adult skeletal muscle are depicted in Figure 1.

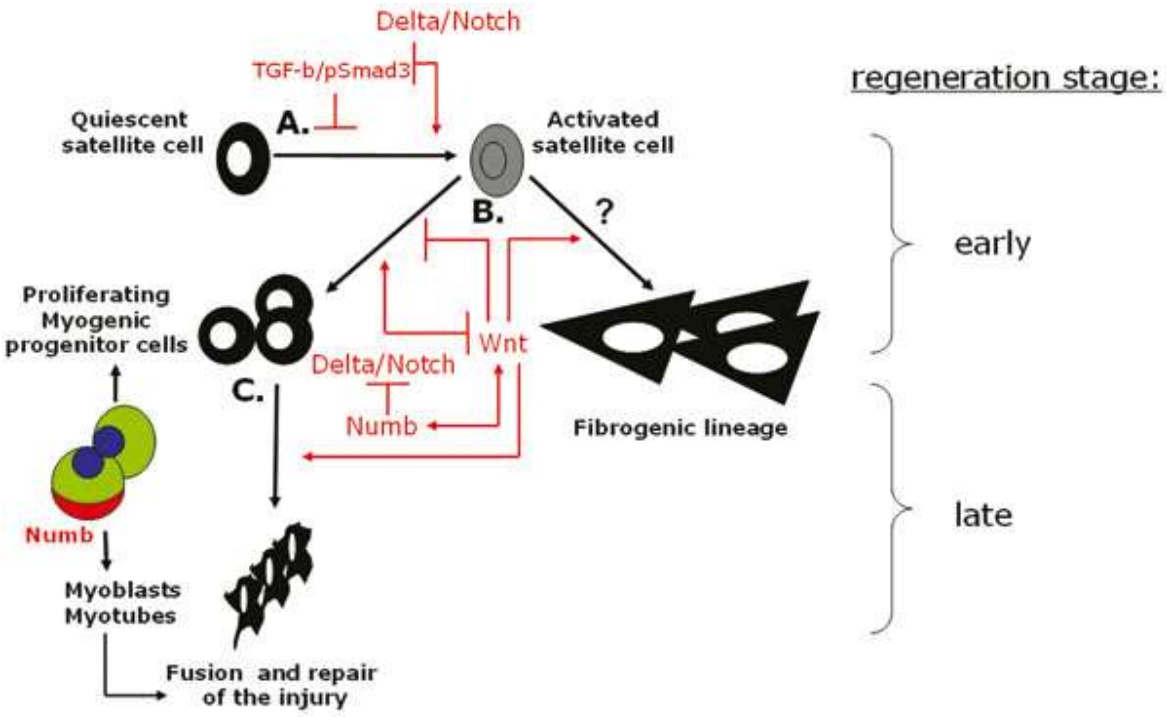

Figure 1: A model of signalling networks regulating myogenic cell-fate.

A. Activation of quiescent satellite cells to proliferate is induced by the upregulation of Notch ligand, Delta, on the surface of myofibers located near the injury site and on the satellite cells themselves. TGF-β/pSmad3 antagonize this process by keeping high levels of CDK inhibitors in satellite cells and the age-specific increase in pSmad3 accompanied by the decline in active Notch thus precludes satellite cell activation. **B.** Activated myogenic progenitor cells (progeny of satellite cells) proliferate without differentiation due to high levels of active Notch that inhibits Wnt signalling pathway. Wnt signaling may also skew the myogenic cell fate of satellite cells towards the fibroblast lineage in the early phase of the regenerative response. **C.** In the late stages of regeneration, differentiation of myogenic progenitor cells into fusion-competent myoblasts is induced by the up-regulation of Numb that inhibits Notch activation and thus, Wnt signalling is released to promote terminal myogenic cell fate. A representative picture of a myogenic progenitor cell that divides asymmetrically with respect to the levels of Numb is also shown in the insert. Cells with high Numb will go on to give rise to myoblasts and myotubes that replace damaged muscle; cells with low Numb continue to divide as pre-myoblast myogenic progenitors. Numb and Wnt might also re-enforce each other.

Aging of stem cell niches and intrinsic aging of stem cells

Individual myofibers are surrounded by a dynamic, collagen-rich interstitial connective tissue known as endomysium, comprised of a diverse array of extracellular matrix (ECM) components (Grounds *et al*., 2005). Linkages between the basal lamina and the endomysium are mediated by different adhesive and structural molecules that form a complex interconnected mesh (Grounds *et al*., 2005). Collagen VI, for instance, functions as a bridge between the basement membrane and the interstitial ECM via its ability to bind a variety of molecules such as integrins, collagen I and II, decorin as well as many basal lamina components including collagen IV and perlecan (Grounds *et al*., 2005; Sanes, 1982). Myogenic laminins (e.g., laminin 2/4) are a major component of the myofiber basement membrane and they also interact with the collagen IV network and perlecan (Grounds *et al*., 2005; Sanes, 1982). Perlecans and syndecans belong to the family of heparan sulfate proteoglycans, which are crucial in mediating binding between muscle regeneration-associated growth factors (e.g., FGF-2 and HGF) and their receptors (Cornelison *et al*., 2001; Langsdorf *et al*., 2007; Wagers *et al*., 2005).

Aging is invariably associated with a reduction in the regenerative capacity of organ stem cells, eventually leading to the accumulation of unrepaired, damaged tissues in the old organism (Janzen *et al*., 2006; Molofsky *et al*., 2006; Wagers *et al*., 2005). To the extent that this decay in stem cell function with age is caused by intrinsic molecular alterations (e.g., oxidative damage and decreased mitochondrial function) or extrinsic changes in the stem cell microenvironment is not entirely understood (Molofsky *et al*., 2006; Wagers *et al*., 2005). Interestingly, multiple lines of evidence exist to substantiate both intrinsic and extrinsic factors as mediators of the negative age-related changes in stem cell function depending on the organ stem cell niche under consideration.

In terms of extrinsic stem cell aging mechanisms, reports on adult skeletal muscle regeneration offer the most compelling case and many intriguing perspectives. It is well known that extensor digitorum longus (EDL) muscle autografts generate greater mass and develop higher maximum contractile force in young than old rats (Carlson *et al*., 1989). Moreover, cross-age transplantation experiments showed that the regenerative ability of young and old muscle grafts depended solely on the age of the host as young hosts allowed successful engraftment of both young and old muscles while both graft types failed to regenerate in old rats (Carlson *et al*., 1989). Similar results were obtained in minced muscle auto- and heterotransplants in anterior tibial muscles in mice (Zacks *et al*., 1982). Therefore these transplantation studies established that the extrinsic factor(s) present in the old host environment significantly limit the intrinsic muscle regeneration capacity, especially in the context of late regeneration events such as reinnervation and ultimately functional properties.

However, the specific local and/or systemic extrinsic factor(s) responsible for poor muscle regeneration in old hosts and, more importantly, how these factors influenced early regeneration events like satellite cell activation and proliferation, were still largely unknown (Carlson *et al*., 1989). Some extrinsic factors suggested to play a role in successful muscle regeneration include proper reinnervation (as evidenced by abnormal neuromuscular junction patterns observed in grafts into old animals), revascularization, hormones, growth factors, and biomechanical aspects (Carlson *et al*., 1989). Nonetheless, early muscle regeneration events up until the fusion stage are considered independent of innervation status and thus age-associated muscle denervation effects most likely play a minor role in deficient muscle repair after injury (Grounds, 1998; Zacks *et al*., 1982).

It was also suggested that the age-related decline in muscle regeneration was associated with a concurrent fall in phagocytic macrophage clearance activity during the early stages of muscle repair in SJL/J mice (Zacks *et al*., 1982). Co-culturing muscle minces with bone marrow cells in diffusion chambers implanted in the peritoneal cavity of mice resulted in faster regeneration as compared to chambers with muscle alone or muscle mixed with gold-pretreated (which impairs phagocytic activity) bone marrow (Yarom *et al*., 1977; Zacks *et al*., 1982). Indeed, both macrophage infiltration and muscle regeneration events after injury are slower in old than in young rats (Grounds, 1998; Sadeh, 1988). In humans, complement activation remains at normal levels but neutrophil mobilization is significantly

decreased in older subjects (Cannon *et al*., 1994). Age-associated deficits in macrophage activity have also been reported in a mouse model of cutaneous wound healing and faster wound healing was observed when young macrophages were applied to the wounds of old mice (Danon *et al*., 1989). Auto- and allograft muscle transplantation studies between SJL/J and BALB/c mice demonstrated that the superior regeneration capacity observed in SJL/J hosts correlated with their ability to recruit leukocytes faster than BALB/c hosts (Roberts *et al*., 1997). The impaired macrophage function observed in old SJL/J mice was eventually shown to be specific to males of this strain as female SJL/J and other four strains of mice did not show this phenotype (Grounds, 1987). Nevertheless, it is well established that the efficiency of the immune system deteriorates with age (Warren *et al*., 2008); and thus, a role for altered inflammatory cell function in deficient repair of old muscles cannot be ignored (Grounds, 1998). In fact, the immune response that is necessary for wound clearing overlaps with muscle regeneration, and the same cytokine, namely IL-4, positively regulates fusion of both macrophages and myoblasts in vitro and in vivo (Horsley *et al*., 2003).

Recent studies are shedding light on the role of local extrinsic factors and processes in the stem cell niche that are associated with alterations in myogenic capacity with age. It appears that these extrinsic factors present in the old environment have deleterious effects on early muscle regeneration events such as satellite cell activation and proliferation (Conboy *et al*., 2002; Conboy *et al*., 2003; Conboy *et al*., 2005). Old satellite cells have functional Notch receptors, but they fail to activate Notch signaling in response to injury due to a lack of concomitant, injury-stimulated Notch ligand Delta upregulation (Conboy *et al*., 2003; Wagers *et al*., 2005). Remarkably, muscle repair in old animals can be rejuvenated by forced Notch activation and, conversely, the regenerative processes of muscle in the young can be aged by inhibiting Notch signaling (Conboy *et al*., 2003; Wagers *et al*., 2005). Additionally, co-culture experiments of muscle fibers and young satellite cells or human embryonic stem cells (hESCs) showed that the regenerative potential and proliferative capacities of both stem cell types are significantly diminished when they are exposed to old local niches such as aged, dissociated myofibers (Carlson *et al*., 2007). Besides loss of Notch pathway activation with age, a recent study from our laboratory reveals that higher levels of TGF-β are present in aged satellite cell niches as compared to young (Carlson *et al*., 2008). Further analysis shows higher TGF-β pathway activation (i.e., elevated pSmad3) in old as compared to young satellite cells, and a physical competition between Notch and pSmad3 occurring at the promoters of multiple cyclin-dependent kinase (CDK) inhibitors (Carlson *et al*., 2008). In aged myofiber-associated niches, it is evident that the lack of Notch activation combined with TGF-β up-regulation lead to excessive pSmad3-mediated transcription of cell cycle inhibitors, which thus antagonize satellite cell proliferation and, at least in part, contribute to deficient muscle repair (Figure 1A).

Other components present in the satellite cell microenvironment, such as heparan sulfate proteoglycans, have been found essential in regulating satellite cell maintenance, activation, proliferation and differentiation during the muscle repair process (Cornelison *et al*., 2001; Langsdorf *et al*., 2007). Although to the best of our knowledge, no age-related alterations in these molecules have been established so far, it is worth noting that cellular infiltrates can induce syndecan expression in mammalian cells during the wound repair process (Gallo *et al*., 1994; Grounds, 1998) and thus the decreased inflammatory cell activity observed in old animals (Cannon *et al*., 1994; Danon *et al*., 1989; Grounds, 1998; Sadeh, 1988; Zacks *et al*., 1982) may affect the ability of muscle cells to express proteoglycans in these animals. On the other hand, twice as much endomysial collagen is found in 26-week-old as compared to 3-week-old wild-type and dystrophic mice (Marshall *et al*., 1989). Dystrophic animals in particular display not only an increased collagen content in both endomysium and perimysium (Marshall *et al*., 1989) but also an accumulation of atypical types of collagen (Alexakis *et al*., 2007; Grounds *et al*., 1993; Grounds, 1998; Marshall *et al*., 1989). In addition to collagen, the basal lamina surrounding satellite cells has also been reported to increase in aged muscle fibers (de Maruenda *et al*., 1978; Grounds, 1998; Snow, 1977). Another connective tissue-related change with age or disease includes alterations in the paracrine effect of fibroblast-derived growth factors on myoblast proliferation (Grounds, 1998; Quinn *et al*., 1990).

Besides local niche aging processes, age-related factors in the systemic niche also have to be considered in order to understand the mechanisms underlying skeletal muscle stem cell aging. Parabiotic pairing experiments, wherein animals share a common circulatory system, between young and old mice demonstrated that the regeneration capacity of aged satellite cells (and liver progenitor cells) can be rejuvenated by exposure to a young systemic milieu, without any recruitment of young cells from the shared circulation (Conboy *et al*., 2005; Wagers *et al*., 2005). Both in vivo heterochronic parabiosis and in vitro exposure to sera from young animals can restore Notch activation in old satellite cells, which are then able to proliferate and repair muscle as well as young cells (Carlson *et al*., 2007; Conboy *et al*., 2005; Wagers *et al*., 2005). On the other hand, old sera or a mixture of young and old sera can rapidly age the regenerative responses of both young satellite cells and hESCs (Carlson *et al*., 2007). The negative effects of old and heterochronic systemic milieu as well as of old local organ niches, on both mouse myogenic progenitor cells and hESCs, suggest that the extrinsic mechanisms of the age-associated regulation of stem cell responses are evolutionarily conserved across mammalian species and stem cell categories (Carlson *et al*., 2007). Furthermore, the same study demonstrated that hESCs secreted as of yet unidentified factors that significantly improved the myogenic potential of primary myoblasts in vitro as well as of young and old satellite cells both in vitro and in vivo (Carlson *et al*., 2007). Undoubtedly, the identification of the age-specific factors in young and old systemic niche environments, and the rejuvenating factors produced by hESCs, will reveal novel therapeutic avenues for regenerative medicine using cellular-, stem cell- and drug-based approaches.

Notably, since young satellite cells and hESCs were negatively affected when exposed to the old or heterochronic systemic milieu (Carlson *et al*., 2007), it can be inferred that it is not simply a lack of "positive" myogenic factors in the old circulation, but rather the presence of inhibitory factors in the aged systemic niche, that lead to a reduction in productive tissue repair. It would be interesting to investigate whether abnormal levels of soluble secreted molecules, such as TGF-β, that are characteristic of aged tissues (Carlson *et al*., 2008) lead to their systemic elevation in aged animals. In fact, old humans and rats have reduced serum levels of growth hormone and insulin-like growth factor-I (IGF-I) (Grounds, 1998). Alterations in the levels of such systemic factors may influence satellite cell behavior directly or indirectly via modulations of the immune system given that inflammatory cell activity is relevant to muscle regeneration, at least partially (Grounds, 1998).

Another potential age-specific candidate in the extrinsic systemic milieu of aged animals is the Wnt family of proteins. The decline in satellite cell regeneration capacity observed with age is also accompanied by increased tissue fibrosis (Alexakis *et al*., 2007; Grounds, 1998; Marshall *et al*., 1989), which appears to be associated with a myogenic-to-fibrogenic cell fate conversion of muscle stem cells, most likely via factors in the aged systemic environment that can bind to the Frizzled protein family (Brack *et al*., 2007). Accordingly, this lineage fate conversion appears to be driven by the activation of the canonical Wnt pathway in aged satellite cells as addition of exogenous Wnt or Wnt inhibitors can age the response of young satellite cells or rejuvenate old satellite cells, respectively, both in vitro and in vivo (Brack *et al*., 2007). In the mouse model of Duchenne muscular dystrophy, old mdx myoblasts seem to be reprogrammed to a profibrotic activity whereby collagen type I deposition impairs productive muscle regeneration and causes even more collagen synthesis, thus creating a major deleterious positive feedback mechanism (Alexakis *et al*., 2007). It is therefore also possible that Wnt signaling plays a role in the context of muscle degeneration associated with muscular dystrophies.

The location of satellite cells on the skeletal muscle fiber niche as well as the processes involved in the aging of satellite cell regenerative responses are schematically represented in Figure 2A.

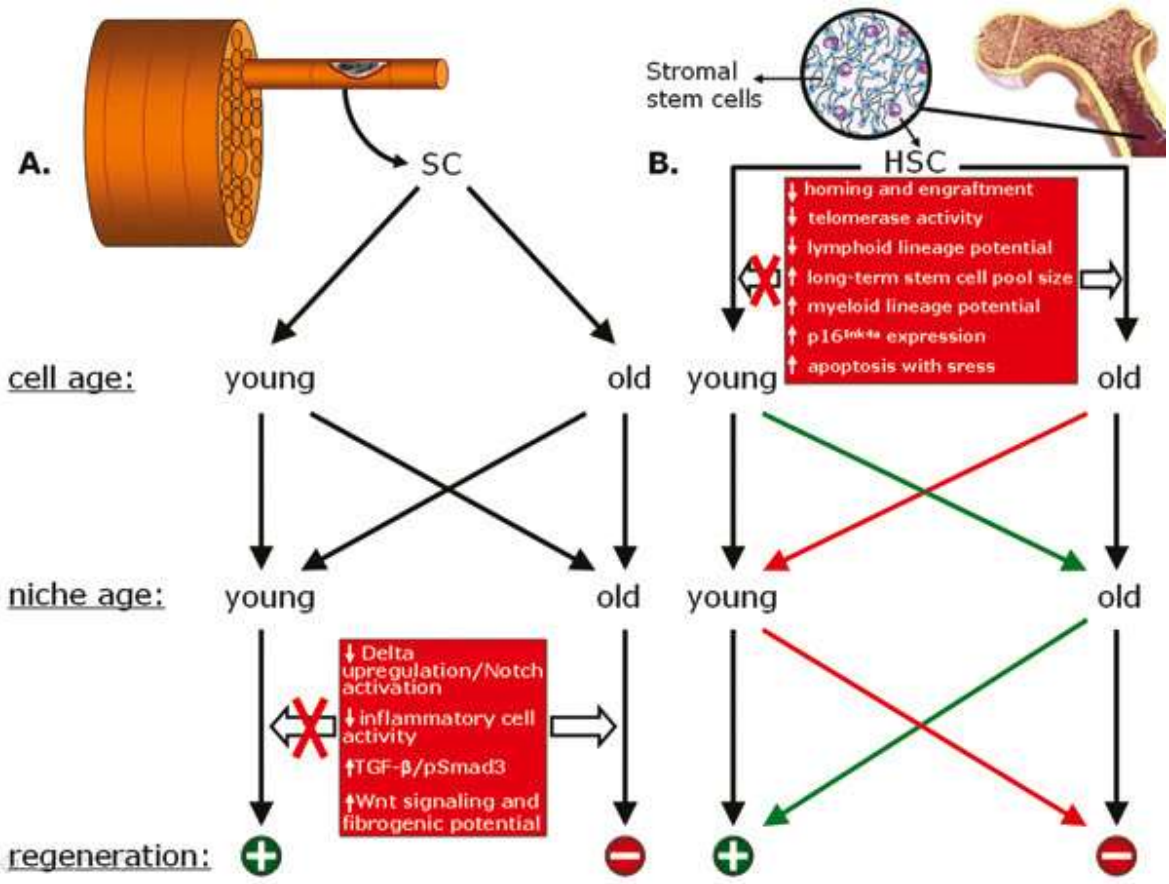

Figure 2: Extrinsic versus intrinsic aging mechanisms in satellite cells and hematopoietic stem cells.

Schematic depictions of satellite cell (SC) and hematopoietic stem cell (HSC) locations in the muscle fiber and bone marrow, respectively, and observed regenerative outcomes with respect to the age of the stem cell and its microenvironment or niche. **A.** Young or old SCs, when placed in contact with old systemic or local niches, both in vitro and in vivo, fail to generate productive tissue repair. Conversely, when SCs from young or old animals are immersed in a young microenvironment, both in vitro and in vivo, they regenerate muscle tissue appropriately. Thus the age of the extrinsic environment most likely determines the regenerative potential of SCs. The potential effects of the aged niche on SC responses are summarized in the red box. **B.** HSCs from young animals, when transplanted into either young or old hosts, produce successful regenerative responses while aged HSCs fail to regenerate properly regardless of the age of the host. Colored arrows indicate the procedure and proper outcomes of heterochronic HSC transplantations. Therefore it appears that, unlike SCs, HSC aging is probably regulated by intrinsic mechanisms that are unaffected by the age of the host environment. These prospective intrinsic aging mechanisms in HSCs are summarized in the red box.

In contrast to the case in satellite cells, mainly intrinsic factors appear to regulate the aging process of HSCs, which are the best characterized organ stem cells. Interestingly, the state of quiescence is not a unique feature of satellite cells, but is also typical of the least differentiated, long term hematopoietic stem cells (LT-HSCs) that have the highest capacity for self renewal. Furthermore, there is a larger body of knowledge on how quiescence is established and maintained in HSCs than in satellite cells. $CD34^{-}$ c-Kit^{+} Sca-1^{+} lineage marker-negative (Lin^{-}) ($CD34^{-}$KSL) HSCs represent only 0.004% of all mouse bone marrow mononuclear cells and about 40% of the $CD34^{-}$KSL population exhibit long-term repopulation capacity (Yamazaki *et al*., 2006). The majority of this cell population (about 94%) does not incorporate

Pyronin Y and does not express the Ki-67 proliferation marker, which indicates that most mouse LT-HSCs are in the G0 phase of the cell cycle (Yamazaki *et al*., 2006). Moreover, HSC entry into the quiescent state seems to be regulated by the PI3K–Akt–FOXO pathway via inhibition of lipid raft clustering (Yamazaki *et al*., 2006). However, the quiescent HSC state is associated with a reduction in checkpoint control and DNA damage responses in the context of repair or apoptosis, which leads to accumulation of genomic damage in these cells with age (Rossi *et al*., 2007). Indeed, microarray expression analysis showed that genes associated with genomic stability and chromatin remodeling were downregulated in old HSCs (Chambers *et al*., 2007). Thus it is possible that old HSCs fail to respond properly under stress or tissue repair conditions due to this age-related accrual of DNA damage (Rossi *et al*., 2007).

It was initially reported that the Thy-1^{10}Sca-1^{hi}Lin^{-}Mac-1^{-}CD4^{-}c-Kit^{+} LT-HSC population from mouse bone marrow both accumulated with age and entered the cell cycle more frequently in old animals (Morrison *et al*., 1996). However, later studies using the CD34^{-}KSL LT-HSC population have demonstrated that the percentage of cells in the quiescent state does not vary significantly with age (Chambers *et al*., 2007; Rossi *et al*., 2007; Sudo *et al*., 2000). Nonetheless, there is a marked accumulation of the HSC pool with age, most likely as a result of symmetric divisions (Sudo *et al*., 2000), but the presence of these extra HSCs is not beneficial since they present deficits in functional activity (Chambers *et al*., 2007; Sudo *et al*., 2000). These defective LT-HSCs are most likely the result of the increased DNA damage with age associated with the HSC quiescent state (Rossi *et al*., 2007). Additionally, the decline in expression of chromatin regulators and the subsequent epigenetic dysregulation observed in HSCs may actually be caused by environmental influences and lead to secondary aging effects, including higher cancer rates (Chambers *et al*., 2007). The nature of the age-associated defects present in HSCs will be discussed in more detail below.

Although most adult human cells have no detectable levels of telomerase, HSCs express low to moderate telomerase activity levels (Allsopp *et al*., 2002). Intriguingly, this readily detectable telomerase activity in the hematopoietic system is unable to prevent telomere shortening in lymphocytes in vitro and in aging peripheral blood leukocytes in vivo (Allsopp *et al*., 2002). Moreover, HSCs possess a finite replicative potential as they can be serially transplanted 5 to 7 times in mice, and their telomeres do shorten throughout the replicative aging process (Allsopp *et al*., 2002). Thus, one plausible hypothesis for the presence of telomerase in HSCs is to counter, at least partially, the deleterious effects of accelerated telomere shortening in HSC-derived hematopoietic lineages (Allsopp *et al*., 2002). Another possibility is that telomerase is only transiently activated in those particular hematopoietic cells that possess long-term replicative demands, to allow expansion of their replicative lifespan (Allsopp *et al*., 2002).

HSCs overexpressing telomerase may be serially transplanted no more than four times (close to wild-type HSCs) and in telomerase-deficient HSCs this number falls to only two times due to accelerated telomere shortening. This suggests that telomerase is required to avoid premature loss of telomeres, but other telomere-independent mechanisms are at work in regulating HSC regenerative potential (Park *et al*., 2004). Bmi1, a polycomb group member which is expressed at high levels in both HSCs and neural stem cells, may be part of these telomere-independent mechanisms as it was shown to regulate self-renewal and pool size of HSCs and most likely multiple types of somatic stem cells (Park *et al*., 2004). Bmi1 regulates HSC self-renewal by modulating key genes involved in stem cell fate decisions, survival and antiproliferation, including Ink4a locus genes (p16^{Ink4a} and p19^{Arf}), telomerase, and apoptosis inhibitor-6 (Park *et al*., 2004). These genes are associated with cell-cycle checkpoint programs that may contribute to organism aging and stem cell exhaustion via induced senescence or apoptosis (Janzen *et al*., 2006; Krishnamurthy *et al*., 2006; Molofsky *et al*., 2006; Orford *et al*., 2008; Park *et al*., 2004; Pelicci, 2004).

Although it has not been determined so far if Bmi1 expression is altered during stem cell transplantations and/or aging, at least one of its downstream targets, p16^{Ink4a}, which is an important regulator of cellular senescence, appears to accumulate in aged or stressed HSCs (Janzen *et al*., 2006; Orford *et al*., 2008; Park *et al*., 2004). Old mouse HSCs have impaired repopulating, homing and survival capabilities as compared to young, but old p16$^{-/}$ HSCs perform as efficiently as young wild-type HSCs in serial transplantation assays (Janzen *et al*., 2006; Orford *et al*., 2008). Similarly, reports on mouse

forebrain and pancreatic islets reveal that increased $p16^{Ink4a}$ expression also affected the regenerative capacity of these organs with age, and that p16-deficient animals were partially rescued from these negative age-associated phenotypes, and responded better to stress (Krishnamurthy *et al*., 2006; Molofsky *et al*., 2006).

Aged bone marrow has a decreased hematopoietic compartment, which is replaced by adipose tissue deposits, which are reminiscent of the replacement of functional muscle by fatty-fibrous tissue in the old (Gruver *et al*., 2007). Age-specific alterations in the cytokine milieu produced by and affecting the bone marrow are implicated in its morphological and stem cell output changes observed in the old, which is generally similar to the aging of muscle (Gruver *et al*., 2007). Examples of alterations in the cytokine and hormone networks with age include decreased systemic growth hormone, which can rescue proper cellularity and lower adiposity in the bone marrow of aged mice, diminished secretion of TNF by bone marrow-resident macrophages, and also bone marrow stromal cells themselves lower their levels of IL-7 secretion (Gruver *et al*., 2007). However, there is still no critical evidence that HSC numbers decline with age in the compromised hematopoietic compartment within the bone marrow (Gruver *et al*., 2007). In fact, as mentioned above, overall HSC numbers appear to increase in aged mice, and this effect is most likely intrinsic to LT-HSCs as evidenced in transplantation experiments from old to young animals(Park *et al*., 2004; Rossi *et al*., 2007). Nonetheless, it is known that many more old HSCs are necessary to completely reconstitute an ablated immune system, probably due to deficits in numerous HSC functions, including the lack of commitment to the lymphoid lineages (Gruver *et al*., 2007; Janzen *et al*., 2006; Rossi *et al*., 2007).

Unlike the case of skeletal muscle satellite cells, the age of the HSC niche seems of little relevance in regulating HSC behavior. When purified LT-HSCs from young and old mice were transplanted into young hosts, the total contribution from aged HSCs to B-, T- and myeloid cell lineage reconstitution was consistently lower than in mice receiving young HSCs (Rossi *et al*., 2005; Rossi *et al*., 2007). Additionally, this old LT-HSC-derived population had decreased peripheral B-lymphocyte numbers, but an increased proportion of myeloid cells (Rossi *et al*., 2005; Rossi *et al*., 2007). Conversely, transplantation of young purified LT-HSCs into young and old animals revealed that even in the aged bone marrow microniche, young HSCs produced B-cells at proper levels and thus scarce B-lymphopoiesis seems to be intrinsic to HSC aging and not due to the aging bone marrow microenvironment (Rossi *et al*., 2005; Rossi *et al*., 2007). Interestingly, aged mice possess lower levels of common lymphoid progenitors, thus substantiating the notion that the age-specific features observed in HSCs are transplantable and cell autonomous (Rossi *et al*., 2005; Rossi *et al*., 2007). The intrinsic properties inherent in HSC aging were further corroborated by comparing young and old purified LT-HSCs using whole genome microarray analysis, which demonstrated that lymphoid and myeloid specification genes were downregulated and upregulated, respectively, in aged animals (Rossi *et al*., 2005; Rossi *et al*., 2007).

Therefore, the emergence of age-related immune dysfunctions and myeloid leukemias are thought to be caused by abnormalities in the HSC developmental potential as these cells predominantly differentiate into myeloid lineages at the expense of lymphoid lineages in aged animals (Orford *et al*., 2008; Rossi *et al*., 2005; Rossi *et al*., 2007; Signer *et al*., 2007). This age-related myeloid leukemia is not associated with increased HSC cycling since the percentage of LT-HSCs in the G0 phase remains practically the same as animals age (Chambers *et al*., 2007; Rossi *et al*., 2007; Sudo *et al*., 2000). In fact, data from a mouse model of chronic myeloid leukemia (CML) wherein HSCs are transformed by the BCR-ABLP210 oncogene in adulthood shows that transformed bone marrow cells from young animals displayed both a myeloproliferative disorder (MPD) and B-lymphoid leukemia, whereas transformed old bone marrow cells represented a better mimicry of the disease phenotype found in humans since these old HSCs induced MPD with rare lymphoid contributions (Signer *et al*., 2007). Thus the observed predominance of CML as adult-onset leukemia can potentially be explained by intrinsic age-specific defects that accrue in B-lineage cells and thus impair lymphopoiesis (Signer *et al*., 2007). Similarly, the extremely low incidence of human T-cell leukemia present in the elderly may be explained by the age-associted decrease in T cell production (Min *et al*., 2005; Signer *et al*., 2007).

The location of the HSC niche in the bone marrow and the key mechanisms associated with their aging process are summarized in Figure 2B.

However, it is important to keep in mind that the bone marrow niche may not be physiological during transplantation procedures since this experimental approach requires lethal doses of irradiation, genetic alterations, or treatment with anti-c-Kit antibodies (Czechowicz *et al*., 2007; Janzen *et al*., 2006; Leung *et al*., 2007; Opferman *et al*., 2005; Park *et al*., 2004). Moreover, the observation from serial-transplantation experiments that the capacity of HSCs to replenish the ablated bone marrow of mice is finite may stem from the activation of non-physiological stress responses due to the transplantation procedure itself as well as the excessive proliferative demands and clonal selection pressure imposed on these cells (Park *et al*., 2004).

In summary, a variety of interactive signaling networks become altered in organ stem cells and in their differentiated niches during the aging process. Neither the satellite cell pool nor the HSC reserve pools decline with age, but their functional properties do deteriorate in the old. In contrast to HSCs, muscle stem cells are intrinsically capable of life-long maintenance and repair of skeletal muscle, but the functional ability of these stem cells to proliferate in response to tissue injury or attrition is severely affected by the aging of their local niches, i.e. differentiated myofibers and ECM. Remarkably, the behavior of old muscle stem cells can be rejuvenated in "young" environments. The mechanisms associated with the aging of both satellite cells and HSCs, as well as the observed results of iso- and heterochronic experiments for both types of stem cells, are summarized in Figure 2.

ACKNOWLEDGEMENTS: We apologize to the authors whose important contributions could not be included in this chapter, due to space restrictions. This work was supported by NIH R01 AG027252 to IMC and Chancellor's Fellowship for Graduate Study to HSS.

References

1. Alexakis C, Partridge T, Bou-Gharios G. Implication of the satellite cell in dystrophic muscle fibrosis: a self-perpetuating mechanism of collagen overproduction. Am. J. Physiol. Cell. Physiol. 2007;293:C661–9.
2. Allsopp R.C, Weissman I.L. Replicative senescence of hematopoietic stem cells during serial transplantation: does telomere shortening play a role? Oncogene. 2002;21:3270–3273.
3. Brack A.S, Conboy I.M, Conboy M.J, Shen J, Rando T.A. A temporal switch from notch to wnt signaling in muscle stem cells is necessary for normal adult myogenesis. Cell. Stem Cell. 2008;2:50–59.
4. Brack A.S, Conboy M.J, Roy S, Lee M, Kuo C.J, Keller C, Rando T.A. Increased Wnt signaling during aging alters muscle stem cell fate and increases fibrosis. Science. 2007;317:807–810.
5. Bruusgaard J.C, Liestol K, Gundersen K. Distribution of myonuclei and microtubules in live muscle fibers of young, middle-aged, and old mice. J. Appl. Physiol. 2006;100:2024–2030.
6. Cannon J.G, Fiatarone M.A, Fielding R.A, Evans W.J. Aging and stress-induced changes in complement activation and neutrophil mobilization. J. Appl. Physiol. 1994;76:2616–2620.
7. Carlson B.M, Faulkner J.A. Muscle transplantation between young and old rats: age of host determines recovery. Am. J. Physiol. 1989;256:C1262–6.
8. Carlson M.E, Conboy I.M. Loss of stem cell regenerative capacity within aged niches. Aging Cell. 2007;6:371–382.
9. Carlson M.E, Hsu M, Conboy I.M. Imbalance between pSmad3 and Notch induces CDK inhibitors in old muscle stem cells. Nature. 2008
10. Carlson M.E, Silva H.S, Conboy I.M. Aging of signal transduction pathways, and pathology. Exp. Cell Res. 2008;314:1951–1961.
11. Chambers S.M, Shaw C.A, Gatza C, Fisk C.J, Donehower L.A, Goodell M.A. Aging hematopoietic stem cells decline in function and exhibit epigenetic dysregulation. PLoS Biol. 2007;5:e201.
12. Choi S.J, Harii K, Asato H, Ueda K. Aging effects in skeletal muscle recovery after reinnervation. Scand. J. Plast. Reconstr. Surg. Hand Surg. 1996;30:89–98.

13. Collins C.A, Zammit P.S, Ruiz A.P, Morgan J.E, Partridge T.A. A population of myogenic stem cells that survives skeletal muscle aging. Stem Cells. 2007;25:885–894.
14. Conboy I.M, Conboy M.J, Smythe G.M, Rando T.A. Notch-mediated restoration of regenerative potential to aged muscle. Science. 2003;302:1575–1577.
15. Conboy I.M, Conboy M.J, Wagers A.J, Girma E.R, Weissman I.L, Rando T.A. Rejuvenation of aged progenitor cells by exposure to a young systemic environment. Nature. 2005;433:760–764.
16. Conboy I.M, Rando T.A. The regulation of Notch signaling controls satellite cell activation and cell fate determination in postnatal myogenesis. Dev. Cell. 2002;3:397–409.
17. Conboy M.J, Karasov A.O, Rando T.A. High incidence of non-random template strand segregation and asymmetric fate determination in dividing stem cells and their progeny. PLoS Biol. 2007;5:e102.
18. Cornelison D.D, Filla M.S, Stanley H.M, Rapraeger A.C, Olwin B.B. Syndecan-3 and syndecan-4 specifically mark skeletal muscle satellite cells and are implicated in satellite cell maintenance and muscle regeneration. Dev. Biol. 2001;239:79–94.
19. Cossu G, Tajbakhsh S. Oriented cell divisions and muscle satellite cell heterogeneity. Cell. 2007;129:859–861.
20. Czechowicz A, Kraft D, Weissman I.L, Bhattacharya D. Efficient transplantation via antibody-based clearance of hematopoietic stem cell niches. Science. 2007;318:1296–1299.
21. Danon D, Kowatch M.A, Roth G.S. Promotion of wound repair in old mice by local injection of macrophages. Proc. Natl. Acad. Sci. U. S. A. 1989;86:2018–2020.
22. de Maruenda E.C, Franzini-Armstrong C. Satellite and invasive cells in frog sartorius muscle. Tissue Cell. 1978;10:749–772.
23. Gallo R.L, Ono M, Povsic T, Page C, Eriksson E, Klagsbrun M, Bernfield M. Syndecans, cell surface heparan sulfate proteoglycans, are induced by a proline-rich antimicrobial peptide from wounds. Proc. Natl. Acad. Sci. U. S. A. 1994;91:11035–11039.
24. Grounds M.D. Age-associated changes in the response of skeletal muscle cells to exercise and regeneration. Ann. N. Y. Acad. Sci. 1998;854:78–91.
25. Grounds M.D. Phagocytosis of necrotic muscle in muscle isografts is influenced by the strain, age, and sex of host mice. J. Pathol. 1987;153:71–82.
26. Grounds M.D, Sorokin L, White J. Strength at the extracellular matrix-muscle interface. Scand. J. Med. Sci. Sports. 2005;15:381–391.
27. Grounds M.D, Yablonka-Reuveni Z. Molecular and cell biology of skeletal muscle regeneration. Mol. Cell Biol. Hum. Dis. Ser. 1993;3:210–256.
28. Gruenbaum Y, Margalit A, Goldman R.D, Shumaker D.K, Wilson K.L. The nuclear lamina comes of age. Nat. Rev. Mol. Cell Biol. 2005;6:21–31.
29. Gruver A.L, Hudson L.L, Sempowski G.D. Immunosenescence of ageing. J. Pathol. 2007;211:144–156.
30. Hawke T.J, Garry D.J. Myogenic satellite cells: physiology to molecular biology. J. Appl. Physiol. 2001;91:534–551.
31. Horsley V, Jansen K.M, Mills S.T, Pavlath G.K. IL-4 acts as a myoblast recruitment factor during mammalian muscle growth. Cell. 2003;113:483–494.
32. Janzen V, Forkert R, Fleming H.E, Saito Y, Waring M.T, Dombkowski D.M, Cheng T, DePinho R.A, Sharpless N.E, Scadden D.T. Stem-cell ageing modified by the cyclin-dependent kinase inhibitor p16INK4a. Nature. 2006;443:421–426.
33. Krishnamurthy J, Ramsey M.R, Ligon K.L, Torrice C, Koh A, Bonner-Weir S, Sharpless N.E. p16INK4a induces an age-dependent decline in islet regenerative potential. Nature. 2006;443:453–457.
34. Langsdorf A, Do A.T, Kusche-Gullberg M, Emerson C.P., Jr Jr, Ai X. Sulfs are regulators of growth factor signaling for satellite cell differentiation and muscle regeneration. Dev. Biol. 2007;311:464–477.
35. Le Grand F, Rudnicki M. Satellite and stem cells in muscle growth and repair. Development. 2007;134:3953–3957.
36. Leung C.G, Xu Y, Mularski B, Liu H, Gurbuxani S, Crispino J.D. Requirements for survivin in terminal differentiation of erythroid cells and maintenance of hematopoietic stem and progenitor cells. J. Exp. Med. 2007;204:1603–1611.
37. Marshall P.A, Williams P.E, Goldspink G. Accumulation of collagen and altered fiber-type ratios as indicators of abnormal muscle gene expression in the mdx dystrophic mouse. Muscle Nerve. 1989;12:528–537.
38. Mauro A. Satellite cell of skeletal muscle fibers. J. Biophys. Biochem. Cytol. 1961;9:493–495.
39. Min H, Montecino-Rodriguez E, Dorshkind K. Effects of aging on early B- and T-cell development. Immunol. Rev. 2005;205:7–17.

40. Mitchell P.O, Mills T, O'Connor R.S, Kline E.R, Graubert T, Dzierzak E, Pavlath G.K. Sca-1 negatively regulates proliferation and differentiation of muscle cells. Dev. Biol. 2005;283:240–252.
41. Molofsky A.V, Slutsky S.G, Joseph N.M, He S, Pardal R, Krishnamurthy J, Sharpless N.E, Morrison S.J. Increasing p16INK4a expression decreases forebrain progenitors and neurogenesis during ageing. Nature. 2006;443:448–452.
42. Morrison S.J, Wandycz A.M, Akashi K, Globerson A, Weissman I.L. The aging of hematopoietic stem cells. Nat. Med. 1996;2:1011–1016.
43. Muir A.R, Kanji A.H, Allbrook D. The structure of the satellite cells in skeletal muscle. J. Anat. 1965;99:435–444.
44. Opferman J.T, Iwasaki H, Ong C.C, Suh H, Mizuno S, Akashi K, Korsmeyer S.J. Obligate role of anti-apoptotic MCL-1 in the survival of hematopoietic stem cells. Science. 2005;307:1101–1104.
45. Orford K.W, Scadden D.T. Deconstructing stem cell self-renewal: genetic insights into cell-cycle regulation. Nat. Rev. Genet. 2008;9:115–128.
46. Park I.K, Morrison S.J, Clarke M.F. Bmi1, stem cells, and senescence regulation. J. Clin. Invest. 2004;113:175–179.
47. Pelicci P.G. Do tumor-suppressive mechanisms contribute to organism aging by inducing stem cell senescence? J. Clin. Invest. 2004;113:4–7.
48. Polesskaya A, Seale P, Rudnicki M.A. Wnt signaling induces the myogenic specification of resident CD45+ adult stem cells during muscle regeneration. Cell. 2003;113:841–852.
49. Quinn L.S, Ong L.D, Roeder R.A. Paracrine control of myoblast proliferation and differentiation by fibroblasts. Dev. Biol. 1990;140:8–19.
50. Radley H.G, De Luca A, Lynch G.S, Grounds M.D. Duchenne muscular dystrophy: focus on pharmaceutical and nutritional interventions. Int. J. Biochem. Cell Biol. 2007;39:469–477.
51. Renault V, Piron-Hamelin G, Forestier C, DiDonna S, Decary S, Hentati F, Saillant G, Butler-Browne G.S, Mouly V. Skeletal muscle regeneration and the mitotic clock. Exp. Gerontol. 2000;35:711–719.
52. Roberts P, McGeachie J.K, Grounds M.D. The host environment determines strain-specific differences in the timing of skeletal muscle regeneration: cross-transplantation studies between SJL/J and BALB/c mice. J. Anat. 1997;191(Pt 4):585–594.
53. Rossi D.J, Bryder D, Weissman I.L. Hematopoietic stem cell aging: mechanism and consequence. Exp. Gerontol. 2007;42:385–390.
54. Rossi D.J, Bryder D, Zahn J.M, Ahlenius H, Sonu R, Wagers A.J, Weissman I.L. Cell intrinsic alterations underlie hematopoietic stem cell aging. Proc. Natl. Acad. Sci. U. S. A. 2005;102:9194–9199.
55. Rossi D.J, Seita J, Czechowicz A, Bhattacharya D, Bryder D, Weissman I.L. Hematopoietic stem cell quiescence attenuates DNA damage response and permits DNA damage accumulation during aging. Cell. Cycle. 2007;6:2371–2376.
56. Roth S.M, Martel G.F, Ivey F.M, Lemmer J.T, Metter E.J, Hurley B.F, Rogers M.A. Skeletal muscle satellite cell populations in healthy young and older men and women. Anat. Rec. 2000;260:351–358.
57. Sadeh M. Effects of aging on skeletal muscle regeneration. J. Neurol. Sci. 1988;87:67–74.
58. Sanes J.R. Laminin, fibronectin, and collagen in synaptic and extrasynaptic portions of muscle fiber basement membrane. J. Cell Biol. 1982;93:442–451.
59. Shefer G, Van de Mark D.P, Richardson J.B, Yablonka-Reuveni Z. Satellite-cell pool size does matter: defining the myogenic potency of aging skeletal muscle. Dev. Biol. 2006;294:50–66.
60. Sherwood R.I, Christensen J.L, Conboy I.M, Conboy M.J, Rando T.A, Weissman I.L, Wagers A.J. Isolation of adult mouse myogenic progenitors: functional heterogeneity of cells within and engrafting skeletal muscle. Cell. 2004;119:543–554.
61. Signer R.A, Montecino-Rodriguez E, Witte O.N, McLaughlin J, Dorshkind K. Age-related defects in B lymphopoiesis underlie the myeloid dominance of adult leukemia. Blood. 2007;110:1831–1839.
62. Smith E.D, Kudlow B.A, Frock R.L, Kennedy B.K. A-type nuclear lamins, progerias and other degenerative disorders. Mech. Ageing Dev. 2005;126:447–460.
63. Snow M.H. The effects of aging on satellite cells in skeletal muscles of mice and rats. Cell Tissue Res. 1977;185:399–408.
64. Sudo K, Ema H, Morita Y, Nakauchi H. Age-associated characteristics of murine hematopoietic stem cells. J. Exp. Med. 2000;192:1273–1280.
65. Wagers A.J, Conboy I.M. Cellular and molecular signatures of muscle regeneration: current concepts and controversies in adult myogenesis. Cell. 2005;122:659–667.
66. Warren L.A, Rossi D.J. Stem cells and aging in the hematopoietic system. Mech. Ageing Dev. 2008

67. Yamazaki S, Iwama A, Takayanagi S, Morita Y, Eto K, Ema H, Nakauchi H. Cytokine signals modulated via lipid rafts mimic niche signals and induce hibernation in hematopoietic stem cells. EMBO J. 2006;25:3515–3523.
68. Yan Z, Choi S, Liu X, Zhang M, Schageman J.J, Lee S.Y, Hart R, Lin L, Thurmond F.A, Williams R.S. Highly coordinated gene regulation in mouse skeletal muscle regeneration. J. Biol. Chem. 2003;278:8826–8836.
69. Yarom R, Havivi Y. Acceleration of muscle regeneration by bone marrow cells. Experientia. 1977;33:195–197.
70. Zacks S.I, Sheff M.F. Age-related impeded regeneration of mouse minced anterior tibial muscle. Muscle Nerve. 1982;5:152–161.

Edited by: Gary Gilliland. Last revised June 9, 2008. Published on the Internet July 15, 2008. This chapter should be cited as: Silva, H. and Conboy, I.M., Aging and stem cell renewal (July 15, 2008), StemBook, ed. The Stem Cell Research Community, StemBook, doi/10.3824/stembook.1.11.1, http://www.stembook.org.

Bookshelf ID: NBK27025PMID: 20614587DOI: 10.3824/stembook.1.11.1