Published in final edited form as:

Am J Phys Med Rehabil. 2009 February ; 88(2): 145–155. doi:10.1097/PHM.0b013e3181951fc5.

The Effect of Muscle Loading on Skeletal Muscle Regenerative Potential: An Update of Current Research Findings Relating to Aging and Neuromuscular Pathology

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Abstract

Skeletal muscle is a dynamic tissue with a remarkable ability to continuously respond to environmental stimuli. Among its adaptive responses is the widely investigated ability of skeletal muscle to regenerate after loading or injury or both. Although significant basic science efforts have been dedicated to better understand the underlying mechanism controlling skeletal muscle regeneration, there has been relatively little impact in the clinical approaches used to treat skeletal muscle injuries and wasting. The purpose of this review article is to provide an overview of the basic biology of satellite cell function in response to muscle loading and to relate these findings in the context of aging and neuromuscular pathology for the rehabilitation medicine specialist.

Keywords

Stem Cells; Satellite Cells; Skeletal Muscle; Regeneration; Exercise

Muscle cells function to contract. It is well known that environmental cues resulting from disease or exercise stimulate the regenerative cascade within the skeletal muscle. However, the mechanism underlying the signaling of regenerative cells remains largely unknown. An improved understanding of these processes may help in the development of targeted rehabilitation strategies to counteract the effects of aging or neuromuscular pathology or both. With this in mind, the purpose of this review article, aimed at the rehabilitation medicine specialist, is to provide an overview of the basic biology of satellite cell function in response to muscle loading and to relate these findings in the context of age-related sarcopenia and dysfunction of the neuromuscular system.

General Events Surrounding Skeletal Muscle Fiber Regeneration

Muscles can be damaged by trauma, disease, or even some types of exercises; the most notable exercise-induced damage is in response to eccentric exercise.^{1–3} Skeletal muscle healing after injury or microtrauma caused by exercise has been divided into four interrelated and time-dependent phases.^{4,5} These phases are necrosis/degeneration, inflammation, repair, and scar-tissue formation (fibrosis). Necrosis/degeneration of the myofiber is characterized by disruption of the plasma membrane and basal lamina, resulting in an ingress of extracellular calcium⁶ and subsequent autogenic degradation of the damaged muscle fiber unit. Within the first day of injury, the area is invaded by inflammatory cells such as mononuclear cells, activated macrophages, and T-lymphocytes.^{7–9} The subsequent secretion of growth factors and cytokines further promotes increased blood flow to the area and enhances the inflammatory response. Muscle regeneration begins once the phagocytic inflammatory cells have cleared away necrotic tissue, and it has been shown that inflammatory cell blockage impairs muscle regeneration.^{10,11} For example, nonsteroidal anti-inflammatory drug administration reduces important macrophage-secreted factors that may play a role in myoblast proliferation and differentiation.^{12,13} Therefore, the initial benefit of the inhibition of myofiber degeneration may be at the expense of functional muscle regeneration at later time points. The reader is referred to Prisk and Huard¹⁴ for a review of the role of the inflammatory process in skeletal muscle repair.

Active muscle regeneration typically occurs within 7–10 days from the time of injury, peaks at 2 wks, and gradually declines until 3–4 wks.^{4,15} Simultaneously, scar-tissue formation peaks around the second week postinjury, although collagen I and III deposition has been observed as early as 3 days after injury.¹⁵ During the repair process, muscle regeneration and scar-tissue formation seem to be in competition, as each vie for muscle area.¹⁷ Significant efforts have been dedicated to the development of biological therapies aimed at minimizing skeletal muscle scar-tissue formation with the intention of indirectly enhancing regeneration.^{18–21} The regenerative processes occurring in skeletal muscle will be the main subject of the remainder of this review.

The Satellite Cell

Given the postmitotic nature of human myofiber nuclei,²² another progenitor cell population is necessary for regeneration to occur. The main cells in the regeneration of damaged skeletal muscle fibers are satellite cells, although it has been shown that the first week of recovery after injury or unloading does not require satellite cell activation.^{23,24} In fact, satellite cell activation seems to account for only half of the force restoration after eccentric contraction-induced injury.²³ Our laboratory has isolated a population of neonatal muscle-derived stem cells, which contain the ability to proliferate in vivo for an extended period of time, demonstrate strong capacity for self-renewal, undergo multipotent differentiation, and display immune-privileged behavior.²⁵ Furthermore, these cells display improved regeneration capacity in skeletal muscle when compared with satellite cells.²⁵ The reader is referred to Peault et al.²⁶ for a review of stem and progenitor cells in skeletal muscle development.

Satellite cells are unspecialized, mononucleated cells that, in an uninjured state, are interposed in a quiescent state between the muscle fiber itself and the basal lamina, which surrounds the muscle fiber.²⁷ In human skeletal muscle, satellite cell content varies between muscles with different functional properties and between individuals with different physical activity levels and ages.^{28,29} In the human vastus lateralis muscle, the number of satellite cells per fiber cross-section does not differ between type I and type II muscles fibers.³⁰

In response to injury or overloading (as in exercise), satellite cells are activated, at which point they are considered to be myoblasts. Within the scaffold of the original damaged myofiber's basal lamina, myoblasts assemble together and fuse to form a new myofiber (Fig. 1) (reviewed in Ref. 31). Each myoblast contributes a small amount of cytoplasm and a new nucleus to the myofiber syncytium. It seems that satellite cell proliferation is necessary to contribute myonuclei for myofiber hypertrophy to occur after muscle overloading.^{32–34} Importantly, satellite cells not only demonstrate an ability to fuse together, or with existing myofibers, but they are also self-renewing.^{28,37} This is essential to re-instate a residual pool of satellite cells, such that these cells are available for future rounds of regeneration or hypertrophy. In cases where the satellite pool is not adequately replenished, such as in Duchenne Muscular Dystrophy ^{38,39} or in aging,^{40,41} regeneration is impaired.

It has been suggested that there are two subsets of satellite cells, the first of which is capable of rapid differentiation (just 4–8 hrs from the time of injury), as evidenced by early myogenic marker expression, and another subset that demonstrates stem cell-like properties and undergoes prolonged self-renewal before terminal differentiation.⁴² Muscle stem cells are defined as cells that possess the ability to produce both new muscle stem cells as well as myoblast and myofiber progeny, without themselves expressing markers of muscle differentiation. Muscle-derived stem cells have the ability to differentiate into endothelial and neural lineages that alter neural and vascular supply to the targeted skeletal muscle that may enhance regeneration (reviewed in Reference 43). The differentiation of these cells into the various tissues seems to be dependent on environmental signaling.

A variety of alterations in the surrounding environment of the satellite cell, including mechanical and growth factors, as well as hormonal signaling might regulate the activation and proliferation of satellite cells.²⁸ Satellite cell replication is initiated in response to secretion of inflammatory cytokines and growth factors (including insulin growth factor [IGF]-1, hepatocyte growth factor, basic fibroblast growth factor, nerve growth factor, leukemia inhibitory factor, and platelet-derived growth factors). Hepatocyte growth factor promotes satellite cell activation but delays cellular differentiation, possibly through the inhibition of myogenic regulatory factors, such as MyoD.⁴⁴ IGF-1, on the other hand, is one of the few myogenic regulators that seem to stimulate both satellite cell proliferation and differentiation (reviewed in Ref. 45). IGF-1 also has an antiapoptotic effect, attributed to the suppression of caspases and the activation of Akt, an important cellular survival factor.⁴⁶ Not surprisingly, it has been demonstrated, using in vivo animal models, that IGF-1 gene overexpression or infusion results in the maintenance of muscle girth after denervation ⁴⁷ and in an improved regeneration after injury.^{48,49}

The Effect of Exercise/Muscle Loading on Satellite Cell Activation/Stem Cell Mobilization in Healthy Skeletal Muscle—Why Is It Important for Skeletal Muscle Regeneration?

Exercise in humans can induce the activation and proliferation of satellite cells.⁵⁰ Exercise-induced release of inflammatory substances or growth factors or both is an important trigger of satellite cell activation (reviewed in Ref. 28). It has been recently shown that the number of satellite cells is enhanced on day 8 after a 36-km run in a group of endurance runners.⁵¹ When a group of runners received 100-mg indomethacin (a nonspecific cyclooxygenase inhibitor), however, there were no changes in satellite cell number.⁵¹ Therefore, the ingestion of nonsteroidal anti-inflammatory drugs attenuates the exercise-induced increase in satellite cell number and may affect hypertrophic or regenerative capacity or both. Several studies have demonstrated increases in satellite cell numbers after the execution of various training regimes. The effect of resistance training on satellite cell activation and proliferation in human skeletal muscle has been most widely investigated (reviewed in Reference 28). One study by Kadi and Thornell⁵⁰ demonstrated that 10 wks of strength training resulted in a 46% increase in the number of satellite cells of healthy individuals, when compared with pretraining baseline measures. This increase in the number of satellite cells was concurrent with a 70% increase in the myonuclear number, indicating that, in response to resistance exercise, satellite cells were not only recruited for myofiber hypertrophy but also produced daughter cells to replenish the reservoir of satellite cells. These findings were supported by later studies.^{52–54} Interestingly, the rise in satellite cell count seems to be maintained for a period of up to 60 days after resistance training, with values returning to pretraining values at 90 days.²⁹

Although most of the studies regarding training effect and satellite cell quantification have been performed using resistance exercise protocols, endurance training has also been shown to significantly increase the satellite cell number in the skeletal muscle of healthy individuals. After 14 wks of 45-min bouts of bicycle ergometry performed 4 times/wk, there was an observed 29% increase in the satellite cell number of the vastus lateralis muscle,⁵³ supporting the evidence that aerobic exercise is capable of activating and recruiting quiescent satellite cells.⁵⁵ This shows that nondamaging aerobic exercises can induce satellite cell proliferation, and the occurrence of muscle damage is not required for the exercise-induced satellite cell activation. However, for both resistance and endurance training effects, it remains to be determined whether this increase in satellite cell count translates directly to an increased skeletal muscle regenerative capacity after injury.

Muscle loading through chronic low-frequency electrical stimulation has also shown a relative increase in the number of satellite cells present in the skeletal muscle of rats,⁵⁶ even in the absence of myofibrillar damage.⁵⁶ Chronic low-frequency electrical stimulation has been shown to stimulate fast-to-slow fiber-type transformation⁵⁷ and hypoxia and skeletal muscle angiogenesis, possibly through the up-regulation of hepatocyte growth factor and vascular endothelial growth factor (VEGF).^{58–61} The enhanced vascularity of the stimulated muscle may play a role in the activation of satellite cells.

Potential Mechanism Behind Satellite/Stem Cell Activation After Exercise

Some ultrastructural muscle damage can be evidenced in human models using excessively high mechanical load. However, most resistance-exercise protocols do not induce extensive muscle damage, and the occurrence of extensive fiber necrosis has rarely been reported in response to exercise. Therefore, the magnitude of changes in satellite cells seen in exercised human skeletal muscle cannot be solely attributed to muscle fiber damage. The release of inflammatory substances, cytokines, and growth factors from active skeletal muscle, and also from the surrounding connective tissue during exercise, probably represent important triggers of satellite cell activation, as previously mentioned.

It is clear that skeletal muscle undergoes a certain level of tissue hypoxia as a result of exercise training. Morici et al.⁶² speculated that hypoxia, or other factors secreted by skeletal muscle working at a very high workload, may induce systemic stem cell mobilization, which are then recruited to participate in muscle regeneration. In vitro, it has been shown that physiologic hypoxia stimulates myoblast proliferation (reviewed in Ref. 63). Among other things, hypoxia is a very potent stimulator of angiogenic growth factor secretion, and VEGF is a marker of hypoxic activation (reviewed in Ref. 64).

The increased secretion of VEGF in response to exercise has been well documented.^{62,65} VEGF stimulates satellite cell proliferation⁶⁶ and migration,⁶⁷ and promotes the formation of centrally nucleated fibers (an indicator of myofiber regeneration).⁶⁸ It seems that exercising skeletal muscles may be exposed to increased nutrient and mitogen diffusion that accompanies increased blood flow to the area, thereby increasing satellite cell activation.⁶⁹ In a study by Christov et al.,⁶⁶ satellite cell numbers in human skeletal muscle were shown to correlate linearly with capillarization. Specifically, in different normal muscle types expressing varying levels of vascularity, satellite cell niches were found to be juxtavascular and were nonrandomly associated with capillary localization. Accordingly, myopathy resulting in decreased vascularity was associated with a proportionate decrease satellite count, whereas muscle biopsies obtained from heavy-trained athletes demonstrated a concomitant increase in both number of capillaries and satellite cells per myofiber. However, these results were based on the analysis of only a handful of biopsies. Further investigations to determine the relationship between skeletal muscle capillarity and the presence of satellite cells are warranted.

Another component involved in the exercise-induced increase in satellite cell count and activation is IGF-1. Exercise results in increased IGF-1 levels, both locally and systemically. The IGF-1 splice variant secreted locally, mechanogrowth factor (MGF), seems to participate in promoting transcriptional factors important for myoblast proliferation and satellite cell activation³² while inhibiting terminal myotube differentiation.⁷⁰ MGF is distinguished from IGF-IEa, another IGF isoform that is secreted systemically by the liver in response to exercise. In contrast to MGF, IGF-IEa increases the mitotic index and enhances terminal differentiation of myotubes.⁷⁰ Not surprisingly, a difference in the actions of each of these isoforms is concomitant with variability in the timing of secretion. Hill and Goldspink found that after injury and exercise, MGF is rapidly expressed (days 1–4) and that gene splicing seems to switch to expression of the IGF-IEa variant at greater than 7 days.⁷¹

On the other hand, myostatin, a transforming growth factor-[beta]1 superfamily member, and negative regulator of skeletal muscle growth, directly inhibits the regenerative capacity of satellite and muscle stem cells.^{72,73} Moreover, it has been shown that myostatin stimulates, in vitro, fibroblast proliferation and the differentiation toward myofibroblasts.⁷⁴ Therefore, myostatin seems to simultaneously inhibit myogenic regeneration while stimulating fibrosis formation during the healing process. Importantly, myostatin gene expression has been shown to decrease after resistance and eccentric exercise.^{75–77} This down-regulation may play a role in exercise-induced muscle hypertrophy.

How Soon After Exercising Are Changes in Satellite Cell Count Evident?

It has been shown that there is a considerable increase in labeled satellite cells in the skeletal muscle of adult rats just 24 hrs after a bout of treadmill running.^{78,79} Similar results have been seen in humans after a single bout of high-intensity exercise.^{80,81} Crameri et al.⁸¹ investigated the number of satellite cells present after a single bout of one-legged high-intensity exercise, as compared with the contralateral, unexercised side. Vastus lateralis biopsies from bilateral lower limbs were obtained on days 2, 4, and 8 postexercise. A significant increase in the average number of satellite cells was observed 4 and 8 days after cessation of the exercised limb, although the increased number of satellite cells was evident on day 2. Interestingly, seven of eight of the subjects tested demonstrated no evidence of myofiber damage, suggesting that an exercise-induced growth factor secretion is the main player for satellite cell proliferation. This also suggests that myofiber damage is not required for satellite cell activation or proliferation. However, on the basis of the lack of significant difference in the markers of terminal differentiation of activated satellite cells in the exercised vs. control legs, authors suggested that multiple bouts of exercise or myofiber damage may be necessary for the differentiation of activated satellite cells.

Aging

A progressive decline in muscle strength may be the greatest contributing factor leading to an impaired physical function with age. Age-associated muscle atrophy has been shown to begin as early as the mid-twenties, after which time the rate of muscle decline accelerates.⁸² Sarcopenia, and age-related reduction in number and size of muscle fibers, seems to be responsible for the decrease in muscle mass.⁸³ Weakness ensues, resulting in an impaired mobility,⁸⁴ an increased risk for falls,⁸⁵ and a decreased physical functioning.⁸⁶ In addition, increasing age typically results in a decreased overall regenerative capacity, which contributes to decreased muscle mass,⁸⁷ increased susceptibility to muscle damage,^{88,89} an impairment of skeletal muscle regeneration in response to injury,^{87,90,91} and a prolonged recovery.^{92,93}

It has been said that “all ageing phenomena—tissue deterioration, cancer, and propensity to infections—can be interpreted as signs of ageing at the level of somatic stem cells.”⁹⁴ Along these lines, aged skeletal muscle has been characterized by a significant decrease in the number of satellite cells per muscle fiber.^{40,41} In humans, a significant decline in satellite cell count is observed after 70 yrs of age,⁴⁰ and it has been recently shown that satellite cells obtained from aged skeletal muscle have an increased susceptibility for

programmed cell death when exposed to a pro-apoptotic milieu.⁹⁵ Along these lines, it has been shown that although satellite cells largely retain their myogenic capacity,^{95,96} some studies have shown that satellite cells from aged animals demonstrate a decreased proliferative capacity.^{97–99} However, the activity levels of the subjects from these studies were poorly defined. On the other hand, in a recent study by Ponsot et al.³⁵ investigating the skeletal muscle regenerative potential of young (25 ± 4 yrs) and old (75 ± 4 yrs) individuals with comparable physical activity levels, the replicative potential of myonuclei (as determined by telomere length) seems to be qualitatively maintained with increasing age. Therefore, the cellular niche characterizing aged skeletal muscle may play a greater role in defining the regenerative potential of aged skeletal muscle.

Carlson and Faulkner⁸⁷ found that, when extensor digitorum muscles harvested from young animals were transplanted into old hosts, the young muscles demonstrated a regenerative capacity comparable with old muscles. Conversely, when old extensor digitorum muscles were transplanted into young hosts, the old transplanted muscles did not show any significant difference in regenerative capacity, when compared with young muscles.⁸⁷ Along these lines, Conboy et al.¹⁰⁰ performed a study in which aged muscles were exposed to circulating factors typical of young animals. It was found that old muscles exposed to a young environment resulted in a significantly increased regenerative capacity of the cells. These studies suggest that the dysfunction of muscle regeneration seen in senescent skeletal muscle is not a dysfunction of the muscle fibers or muscle fiber receptors. Instead, authors hypothesized that systemic factors supporting regeneration in young animals control critical molecular pathways that control the regenerative capacity of satellite cells.¹⁰⁰

One of the main players in characterizing the environmental milieu is, of course, the vascular system. Aging has been associated with a decline in skeletal muscle capillarity,^{36,101,102} although some reports have shown that capillarization is maintained, or even increased, with aging.^{103,104} However, Davidson et al.¹⁰⁴ examined the number of capillaries/fiber, and, therefore, the relative increase they observed may be attributed to a loss in myofiber number. Other variations in methodology to quantify capillarization, age ranges defining young vs. elderly, and the types of species studied may also contribute to the reported discrepancies related to the effect of age on skeletal muscle vascularity. Importantly, aging has also been associated with declines in VEGF mRNA levels,¹⁰² which may further help explain decreases in resident satellite cell counts.

Both endurance and resistance exercise have been shown to counteract the age-related declines in satellite cell counts in elderly individuals (for review, see Ref. 28), supporting the continued plasticity of skeletal muscle with aging. However, it has been shown that the extent to which the number of satellite cells per fibers is increased 24 hrs after a single bout of resistance exercise is significantly dampened in older men, compared with young male counterparts.⁸⁰ Along these lines, a markedly lower expression of MGF in response to loading, and therefore decreased satellite cell activation, has been demonstrated in both older rodent¹⁰⁵ and human¹⁰⁶ skeletal muscles. In contrast, others have demonstrated comparable satellite cell increases with chronic training in the elderly⁵⁴ as compared with young individuals.²⁹

It remains to be determined whether exercise-or electrical stimulation -induced increases in satellite cell counts are associated with an increased regenerative capacity in elderly skeletal muscle and could, therefore, present an effective modality to counteract the effects of sarcopenia. However, it is becoming increasingly apparent that elderly individuals who participate in regular physical activity will be better positioned for a better, more complete skeletal muscle repair after muscle injury in addition to the widely publicized cardiovascular and endocrine benefits of exercise.

Duchenne Muscular Dystrophy

In certain neuromuscular diseases, such as muscular dystrophies, muscle fibers are strikingly more susceptible to damage as compared with normal counterparts. Since declines in muscle strength and endurance are often among the most debilitating symptoms, the decision regarding if and how much to exercise an individual with myopathy becomes difficult. Individuals with Duchenne Muscular Dystrophy experience an increased rate of degeneration of skeletal muscle fibers as a result of the lack of dystrophin, leading to repeated cycles of degeneration-regeneration, and ultimately an impaired skeletal muscle regenerative capacity as a result of decreased satellite cell self-renewal. The decreased satellite cell self-renewal may be explained by the fact that fibroblasts found in dystrophic muscle have been shown to secrete increased levels of IGF-1-binding proteins, thereby diminishing the IGF-1 supply available for satellite cell activation.¹⁰⁷ Consequently, dystrophic muscle fibers become inflamed, necrotic, and fibrotic, ultimately resulting in muscle wasting, muscle weakness, and muscle fatigue.^{108,109}

Although the past couple of decades have led to an increased understanding of the pathogenesis of muscular dystrophy, effective therapeutic interventions aimed at improving skeletal muscle quality and function in these individuals remain limited. Surprisingly, few efforts have been dedicated to investigate the effect of exercise on skeletal muscle function in individuals with Duchenne Muscular Dystrophy. There has been a debate for several years regarding the benefits and detriments of strengthening exercises for individuals with Duchenne Muscular Dystrophy. On one end of the spectrum, low-intensity strengthening exercises may counteract the progressively deteriorating muscle weakness that accompanies the absence of the structural protein dystrophin. It seems, however, that exercising dystrophic muscle, especially in the advanced form of the disease, may lead to an accelerated weakness (reviewed in Ref. 110), possibly a product of the impaired regenerative capacity resulting from the decreased satellite cell count. The restoration of dystrophin and satellite cell count seems to be a prerequisite for effective improvement in skeletal muscle function through the use of rehabilitation approaches. With this in mind, cellular therapies, such as muscle-derived stem cell transplantation, hold great promise to restore the reservoir of regenerative cells, making muscle more responsive to exercise-or stimulation -induced benefits.

Muscle Unloading/Denervation

Aging, frailty, and chronic illness may all result in decreased physical activity, which is associated with muscle wasting, decreased ability to perform activities of daily living, and,

ultimately, a decreased quality of life. Clearly, muscle unloading retards skeletal muscle growth and has been shown to result in not only skeletal muscle atrophy but also a concomitant decrease in the number of satellite cell counts.^{111–114} Hindlimb unloading experiments conducted in murine models have shown a rapid and significant decline in satellite cell proliferative capacity and activation,^{112,115} evident just 24 hrs after unloading.¹¹³ Two weeks of hindlimb suspension has been shown to result in a decreased differentiation capacity of myogenic precursor cells, and this is concomitant with decreased mRNA expression of myogenic markers.²⁴ Return to normal loading in healthy muscle consequently results in a complete regeneration of skeletal muscle fibers and a recovery of muscle mass ^{114,116} as well as a reversal of the deleterious effects of unloading on satellite cell regenerative capacity.²⁴ In elderly animals, on the other hand, it has been reported that hindlimb immobilization may result in a decrease in the proliferative potential of satellite cells, which is not restored even up to 11 wks of recovery.¹¹⁷ However, the application of IGF-1 after remobilization increased satellite cell proliferative capacity and was associated with increased muscle mass.¹¹⁷ This has considerable clinical implications, as the effects of prolonged bed rest may prove to be irreversible in an aged population. A nonweight-bearing status is often prescribed to individuals after joint replacement or fractures, for example, even though a failure to return to previous mobility status after such a period of unweighting is not uncommon.

In contrast to hindlimb unloading, after peripheral nerve transection, there is an initial phase of rapid satellite cell proliferation that is followed by a drastic decrease in satellite cell counts at later time points.^{111,118,119} This subsequent decline in satellite cell numbers may be explained by an increased susceptibility to apoptotic cell death after chronic denervation.¹²⁰ Furthermore, it has been shown that myogenesis in denervated rat skeletal muscle is characterized by poorly developed myofiber contractile systems with small fiber diameters.¹²¹ It has been suggested that, rather than a complete necrosis of muscle fibers after denervation, it is more likely that fibers go through cycles of necrosis and regeneration.¹²² However, because of the absence of neural stimulation, regenerated myofibers never mature into functioning contractile elements. It seems that muscle atrophy after unloading or denervation may be mitigated by the application of electric stimulation. Electron microscopy studies of rat skeletal muscle that was chronically, electrically stimulated after denervation demonstrated more regular sarcomeres and large increases in force production, when compared with nonstimulated denervated counterparts.¹²² However, in humans, it is very difficult to get an effective muscle contraction after denervation using electrical stimulation. In these cases, the muscle needs to be stimulated directly rather than stimulating the motor nerve. This requires much more current to get an action potential, and it is usually not tolerated by the patient.

Areas for Future Research

As our knowledge of the mechanisms underlying satellite cell activation and proliferation in response to injury, aging, and neuromuscular pathology is not yet complete, there are several areas for future research. The relationship between skeletal muscle vascularity and satellite cell activation or proliferation or both is an important area of investigation. Several neurologic conditions within both the central and peripheral nervous system may indirectly

and directly affect the skeletal muscle and thereby the satellite cells. This could be one important factor leading to an impaired neuromuscular function, with muscle hypotrophy and muscle weakness, for example, after stroke, inflammatory nervous system disorders, spinal cord injuries, and diseases in the motor unit. The processes that influence the satellite cells in these conditions are largely unknown. An increased understanding of these underlying mechanisms may help guide the development of clinical applications to enhance skeletal muscle regeneration by using targeted modalities, such as electrical stimulation and exercise, in addition to pharmacologic interventions and dietary recommendations.

Acknowledgments

This work was supported by grants from the Claude D. Pepper Older Americans Independence Center and the Foundation for Physical Therapy and by the NIH K12 for Physical and Occupational Therapists -The Comprehensive Opportunities in Rehabilitation Research Training program.

We thank Mary Synnott for graphical assistance.

References

1. Irintchev A, Wernig A. Muscle damage and repair in voluntarily running mice: Strain and muscle differences. *Cell Tissue Res.* 1987; 249:509–21. [PubMed: 3664601]
2. Friden J, Sfikianos PN, Hargens AR. Muscle soreness and intramuscular fluid pressure: Comparison between eccentric and concentric load. *J Appl Physiol.* 1986; 61:2175–9. [PubMed: 3804924]
3. Wernig A, Irintchev A, Weisshaupt P. Muscle injury, cross-sectional area and fibre type distribution in mouse soleus after intermittent wheel-running. *J Physiol.* 1990; 428:639–52. [PubMed: 2231427]
4. Huard J, Li Y, Fu FH. Current concepts review-muscle injuries and repair: Current trends in research. *J Bone Joint Surg Am.* 2002; 84:822–32. [PubMed: 12004029]
5. Hurme T, Kalimo H, Lehto M, et al. Healing of skeletal muscle injury: An ultrastructural and immunohistochemical study. *Med Sci Sports Exerc.* 1991; 23:801–10. [PubMed: 1921672]
6. Jones DA, Jackson MJ, McPhail G, et al. Experimental mouse muscle damage: The importance of external calcium. *Clin Sci.* 1984; 66:317–22. [PubMed: 6420110]
7. Fielding RA, Manfredi TJ, Ding W, et al. Acute phase response in exercise. III. Neutrophil and IL -1 beta accumulation in skeletal muscle. *Am J Physiol.* 1993; 265(1 pt 2):R166–R172. [PubMed: 8342683]
8. Tidball JG. Inflammatory cell response to acute muscle injury [review; 118 references]. *Med Sci Sports Exerc.* 1995; 27:1022–32. [PubMed: 7564969]
9. Frenette J, Cai B, Tidball JG. Complement activation promotes muscle inflammation during modified muscle use. *Am J Pathol.* 2000; 156:2103–10. [PubMed: 10854231]
10. Chazaud B, Sonnet C, Lafuste P, et al. Satellite cells attract monocytes and use macrophages as a support to escape apoptosis and enhance muscle growth. *J Cell Biol.* 2003; 163:1133–43. [PubMed: 14662751]
11. Lescaudron L, Peltekian E, Fontaine-Perus J, et al. Blood borne macrophages are essential for the triggering of muscle regeneration following muscle transplant. *Neuromuscul Disord.* 1999; 9:72–80. [PubMed: 10220861]
12. Bondesen BA, Mills ST, Kegley KM, et al. The COX-2 pathway is essential during early stages of skeletal muscle regeneration. *Am J Physiol Cell Physiol.* 2004; 287:C475–C483. [PubMed: 15084473]
13. Shen W, Li Y, Tang Y, et al. NS-398, a cyclooxygenase-2-specific inhibitor, delays skeletal muscle healing by decreasing regeneration and promoting fibrosis. *Am J Pathol.* 2005; 167:1105–17. [PubMed: 16192645]
14. Prisk V, Huard J. Muscle injuries and repair: The role of prostaglandins and inflammation [review; 140 references]. *Histol Histopathol.* 2003; 18:1243–56. [PubMed: 12973691]

15. Kaariainen M, Jarvinen T, Jarvinen M, et al. Relation between myofibers and connective tissue during muscle injury repair [review; 31 references]. *Scand J Med Sci Sports*. 2000; 10:332–7. [PubMed: 11085560]
16. Cao B, Zheng B, Jankowski R, et al. Muscle stem cells differentiate into hematopoietic lineages in vitro and in vivo. *Mol Biol Cell*. 2002; 13:120A.
17. Li Y, Huard J. Differentiation of muscle-derived cells into myofibroblasts in injured skeletal muscle. *Am J Pathol*. 2002; 161:895–907. [PubMed: 12213718]
18. Chan YS, Li Y, Foster W, et al. Antifibrotic effects of suramin in injured skeletal muscle after laceration. *J Appl Physiol*. 2003; 95:771–80. [PubMed: 12730151]
19. Chan YS, Li Y, Foster W, et al. The use of suramin, an antifibrotic agent, to improve muscle recovery after strain injury. *Am J Sports Med*. 2005; 33:43–51. [PubMed: 15610998]
20. Fukushima K, Badlani N, Usas A, et al. The use of an antifibrosis agent to improve muscle recovery after laceration. *Am J Sports Med*. 2001; 29:394–402. [PubMed: 11476375]
21. Negishi S, Li Y, Usas A, et al. The effect of relaxin treatment on skeletal muscle injuries. *Am J Sports Med*. 2005; 33:1816–24. [PubMed: 16157846]
22. Snow MH. An autoradiographic study of satellite cell differentiation into regenerating myotubes following transplantation of muscles in young rats. *Cell Tissue Res*. 1978; 186:535–40. [PubMed: 627031]
23. Rathbone CR, Wenke JC, Warren GL, et al. Importance of satellite cells in the strength recovery after eccentric contraction-induced muscle injury. *Am J Physiol Regul Integr Comp Physiol*. 2003; 285:R1490–R1495. [PubMed: 12920057]
24. Mitchell PO, Pavlath GK. Skeletal muscle atrophy leads to loss and dysfunction of muscle precursor cells. *Am J Physiol Cell Physiol*. 2004; 287:C1753–C1762. [PubMed: 15329339]
25. Qu-Petersen Z, Deasy B, Jankowski R, et al. Identification of a novel population of muscle stem cells in mice: Potential for muscle regeneration. *J Cell Biol*. 2002; 157:851–64. [PubMed: 12021255]
26. Peault B, Rudnicki M, Torrente Y, et al. Stem and progenitor cells in skeletal muscle development, maintenance, and therapy [review; 145 references]. *Mol Ther*. 2007; 15:867–77. [PubMed: 17387336]
27. Mauro A. Satellite cell of skeletal muscle fibers. *J Biophys Biochem Cytol*. 1961; 9:493–5. [PubMed: 13768451]
28. Kadi F, Charifi N, Denis C, et al. The behaviour of satellite cells in response to exercise: What have we learned from human studies? [review; 54 references]. *Pflugers Arch*. 2005; 451:319–27. [PubMed: 16091958]
29. Kadi F, Schjerling P, Andersen LL, et al. The effects of heavy resistance training and detraining on satellite cells in human skeletal muscles. *J Physiol*. 2004; 558(pt 3):1005–12. [PubMed: 15218062]
30. Kadi F, Charifi N, Henriksson J. The number of satellite cells in slow and fast fibres from human vastus lateralis muscle. *Histochem Cell Biol*. 2006; 126:83–7. [PubMed: 16283361]
31. Carlson BM, Faulkner JA. The regeneration of skeletal muscle fibers following injury: A review [review; 109 references]. *Med Sci Sports Exerc*. 1983; 15:187–98. [PubMed: 6353126]
32. Hill M, Wernig A, Goldspink G. Muscle satellite (stem) cell activation during local tissue injury and repair. *J Anat*. 2003; 203:89–99. [PubMed: 12892408]
33. Rosenblatt JD, Yong D, Parry DJ. Satellite cell activity is required for hypertrophy of overloaded adult rat muscle. *Muscle Nerve*. 1994; 17:608–13. [PubMed: 8196703]
34. Snow MH. Satellite cell response in rat soleus muscle undergoing hypertrophy due to surgical ablation of synergists. *Anat Rec*. 1990; 227:437–46. [PubMed: 2393096]
35. Ponsot E, Lexell J, Kadi F. Skeletal muscle telomere length is not impaired in healthy physically active old women and men. *Muscle Nerve*. 2008; 37:1–6.
36. Coggan AR, Spina RJ, King DS, et al. Histochemical and enzymatic comparison of the gastrocnemius muscle of young and elderly men and women. *J Gerontol*. 1992; 47:B71–B76. [PubMed: 1573181]

37. Collins CA, Partridge TA. Self-renewal of the adult skeletal muscle satellite cell. *Cell Cycle*. 2005; 4:1338–41. [PubMed: 16177569]
38. Webster C, Blau HM. Accelerated age-related decline in replicative life-span of Duchenne muscular dystrophy myoblasts: Implications for cell and gene therapy. *Somat Cell Mol Genet*. 1990; 16:557–65. [PubMed: 2267630]
39. Heslop L, Morgan JE, Partridge TA. Evidence for a myogenic stem cell that is exhausted in dystrophic muscle. *J Cell Sci*. 2000; 113(pt 12):2299–308. [PubMed: 10825301]
40. Kadi F, Charifi N, Denis C, et al. Satellite cells and myonuclei in young and elderly women and men. *Muscle Nerve*. 2004; 29:120–7. [PubMed: 14694507]
41. Snow MH. The effects of aging on satellite cells in skeletal muscles of mice and rats. *Cell Tissue Res*. 1977; 185:399–408. [PubMed: 597854]
42. Rantanen J, Hurme T, Lukka R, et al. Satellite cell proliferation and the expression of myogenin and desmin in regenerating skeletal muscle: Evidence for two different populations of satellite cells. *Lab Invest*. 1995; 72:341–7. [PubMed: 7898053]
43. Peng H, Huard J. Muscle-derived stem cells for musculoskeletal tissue regeneration and repair [review; 83 references]. *Transpl Immunol*. 2004; 12:311–19. [PubMed: 15157924]
44. Miller KJ, Thaloer D, Matteson S, et al. Hepatocyte growth factor affects satellite cell activation and differentiation in regenerating skeletal muscle. *Am J Physiol Cell Physiol*. 2000; 278:C174–C181. [PubMed: 10644525]
45. Florini JR, Ewton DZ, Coolican SA. Growth hormone and the insulin-like growth factor system in myogenesis [review; 465 references]. *Endocr Rev*. 1996; 17:481–517. [PubMed: 8897022]
46. Lawlor MA, Rotwein P. Insulin-like growth factor-mediated muscle cell survival: Central roles for Akt and cyclin-dependent kinase inhibitor p21. *Mol Cell Biol*. 2000; 20:8983–95. [PubMed: 11073997]
47. Shavlakadze T, White JD, Davies M, et al. Insulin-like growth factor I slows the rate of denervation induced skeletal muscle atrophy. *Neuromuscul Disord*. 2005; 15:139–46. [PubMed: 15694135]
48. Kasemkijwattana C, Menetrey J, Somogyi G, et al. Development of approaches to improve the healing following muscle contusion. *Cell Transplant*. 1998; 7:585–98. [PubMed: 9853587]
49. Kasemkijwattana C, Menetrey J, Bosch P, et al. Use of growth factors to improve muscle healing after strain injury. *Clin Orthop Relat Res*. 2000; 370:272–85. [PubMed: 10660723]
50. Kadi F, Thornell LE. Concomitant increases in myonuclear and satellite cell content in female trapezius muscle following strength training. *Histochem Cell Biol*. 2000; 113:99–103. [PubMed: 10766262]
51. Mackey AL, Kjaer M, Dandanell S, et al. The influence of anti-inflammatory medication on exercise-induced myogenic precursor cell responses in humans [see comment]. *J Appl Physiol*. 2007; 103:425–31. [PubMed: 17463304]
52. Roth SM, Martel GF, Ivey FM, et al. Skeletal muscle satellite cell characteristics in young and older men and women after heavy resistance strength training. *J Gerontol A Biol Sci Med Sci*. 2001; 56:B240–B247. [PubMed: 11382785]
53. Charifi N, Kadi F, Feasson L, et al. Effects of endurance training on satellite cell frequency in skeletal muscle of old men. *Muscle Nerve*. 2003; 28:87–92. [PubMed: 12811778]
54. Mackey AL, Esmarck B, Kadi F, et al. Enhanced satellite cell proliferation with resistance training in elderly men and women. *Scand J Med Sci Sports*. 2007; 17:34–42. [PubMed: 17305939]
55. Appell HJ, Forsberg S, Hollmann W. Satellite cell activation in human skeletal muscle after training: Evidence for muscle fiber neof ormation. *Int J Sports Med*. 1988; 9:297–9. [PubMed: 3182162]
56. Putman CT, Dusterhoft S, Pette D. Changes in satellite cell content and myosin isoforms in low - frequency-stimulated fast muscle of hypothyroid rat. *J Appl Physiol*. 1999; 86:40–51. [PubMed: 9887111]
57. Schuler M, Pette D. Fiber transformation and replacement in low-frequency stimulated rabbit fast-twitch muscles. *Cell Tissue Res*. 1996; 285:297–303. [PubMed: 8766166]
58. Nagasaka M, Kohzaki M, Fujii T, et al. Effect of low-voltage electrical stimulation on angiogenic growth factors in ischaemic rat skeletal muscle. *Clin Exp Pharmacol Physiol*. 2006; 33:623–7. [PubMed: 16789930]

59. Hudlicka O, Brown MD, May S, et al. Changes in capillary shear stress in skeletal muscles exposed to long-term activity: Role of nitric oxide. *Microcirculation*. 2006; 13:249–59. [PubMed: 16627367]
60. Zhao M, Huai B, Wang E, et al. Electrical stimulation directly induces pre-angiogenic responses in vascular endothelial cells by signaling through VEGF receptors. *J Cell Sci*. 2004; 117:397–405. [PubMed: 14679307]
61. Brutsaert TD, Gavin TP, Fu Z, et al. Regional differences in expression of VEGF mRNA in rat gastrocnemius following 1 hr exercise or electrical stimulation. *BMC Physiol*. 2002; 2:8. [PubMed: 12086595]
62. Morici G, Zangla D, Santoro A, et al. Supramaximal exercise mobilizes hematopoietic progenitors and reticulocytes in athletes. *Am J Physiol Regul Integr Comp Physiol*. 2005; 289:R1496–R1503. [PubMed: 16020520]
63. Li X, Zhu L, Chen X, et al. Effects of hypoxia on proliferation and differentiation of myoblasts. *Med Hypotheses*. 2007; 69:629–36. [PubMed: 17395396]
64. Huang LE, Bunn HF. Hypoxia-inducible factor and its biomedical relevance [review; 80 references]. *J Biol Chem*. 2003; 278:19575. [PubMed: 12639949]
65. Gavin TP, Westerkamp LM, Zwetsloot KA. Soleus, plantaris and gastrocnemius VEGF mRNA responses to hypoxia and exercise are preserved in aged compared with young female C57BL/6 mice. *Acta Physiol*. 2006; 188:113–21.
66. Christov C, Chretien F, Abou-Khalil R, et al. Muscle satellite cells and endothelial cells: Close neighbors and privileged partners. *Mol Biol Cell*. 2007; 18:1397–409. [PubMed: 17287398]
67. Germani A, Di Carlo A, Mangoni A, et al. Vascular endothelial growth factor modulates skeletal myoblast function. *Am J Pathol*. 2003; 163:1417–28. [PubMed: 14507649]
68. Arsic N, Zacchigna S, Zentilin L, et al. Vascular endothelial growth factor stimulates skeletal muscle regeneration in vivo. *Mol Ther*. 2004; 10:844–54. [PubMed: 15509502]
69. Roberts P, McGeachie JK. The effects of pre-and posttransplantation exercise on satellite cell activation and the regeneration of skeletal muscle transplants: A morphometric and autoradiographic study in mice. *J Anat*. 1992; 180(pt 1):67–74. [PubMed: 1452483]
70. Yang SY, Goldspink G. Different roles of the IGF-I Ec peptide (MGF) and mature IGF-I in myoblast proliferation and differentiation [erratum appears in FEBS Lett 2006;580:2530]. *FEBS Lett*. 2002; 522:156–60. [PubMed: 12095637]
71. Hill M, Goldspink G. Expression and splicing of the insulin-like growth factor gene in rodent muscle is associated with muscle satellite (stem) cell activation following local tissue damage. *J Physiol*. 2003; 549(pt 2):409–18. [PubMed: 12692175]
72. McCroskery S, Thomas M, Maxwell L, et al. Myostatin negatively regulates satellite cell activation and self-renewal. *J Cell Biol*. 2003; 162:1135–47. [PubMed: 12963705]
73. Nozaki M, Li Y, Zhu J, et al. Improved muscle healing after contusion injury by the inhibitory effect of suramin on myostatin, a negative regulator of muscle growth. *Am J Sports Med*. 2008; 36:2354–62. [PubMed: 18725651]
74. Zhu J, Li Y, Shen W, et al. Relationships between transforming growth factor-beta1, myostatin, and decorin: Implications for skeletal muscle fibrosis. *J Biol Chem*. 2007; 282:25852–63. [PubMed: 17597062]
75. Willoughby DS. Effects of heavy resistance training on myostatin mRNA and protein expression [see comment]. *Med Sci Sports Exerc*. 2004; 36:574–82. [PubMed: 15064583]
76. Costa A, Dalloul H, Hegyesi H, et al. Impact of repeated bouts of eccentric exercise on myogenic gene expression. *Eur J Appl Physiol*. 2007; 101:427–36. [PubMed: 17641910]
77. Hulmi JJ, Ahtiainen JP, Kaasalainen T, et al. Postexercise myostatin and activin IIb mRNA levels: Effects of strength training. *Med Sci Sports Exerc*. 2007; 39:289–97. [PubMed: 17277593]
78. Darr KC, Schultz E. Exercise-induced satellite cell activation in growing and mature skeletal muscle. *J Appl Physiol*. 1987; 63:1816–21. [PubMed: 3693217]
79. Jacobs SC, Wokke JH, Bar PR, et al. Satellite cell activation after muscle damage in young and adult rats. *Anat Rec*. 1995; 242:329–36. [PubMed: 7573980]
80. Dreyer HC, Blanco CE, Sattler FR, et al. Satellite cell numbers in young and older men 24 hours after eccentric exercise. *Muscle Nerve*. 2006; 33:242–53. [PubMed: 16315322]

81. Cramer RM, Langberg H, Magnusson P, et al. Changes in satellite cells in human skeletal muscle after a single bout of high intensity exercise. *J Physiol.* 2004; 558(pt 1):333–40. [PubMed: 15121802]
82. Lexell J, Taylor CC, Sjostrom M. What is the cause of the ageing atrophy? Total number, size and proportion of different fiber types studied in whole vastus lateralis muscle from 15-to 83 -year-old men. *J Neurol Sci.* 1988; 84:275–94. [PubMed: 3379447]
83. Lexell J. Human aging, muscle mass, and fiber type composition [review; 55 references]. *J Gerontol A Biol Sci Med Sci.* 1995; 50:11–16. [PubMed: 7493202]
84. Rantanen T, Guralnik JM, Ferrucci L, et al. Coinpairments: Strength and balance as predictors of severe walking disability. *J Gerontol A Biol Sci Med Sci.* 1999; 54:M172–M176. [PubMed: 10219007]
85. Tinetti ME. Factors associated with serious injury during falls by ambulatory nursing home residents. *J Am Geriatr Soc.* 1987; 35:644–8. [PubMed: 3584769]
86. Rantanen T, Era P, Heikkinen E. Physical activity and the changes in maximal isometric strength in men and women from the age of 75 to 80 years [see comment]. *J Am Geriatr Soc.* 1997; 45:1439–45. [PubMed: 9400552]
87. Carlson BM, Faulkner JA. Muscle transplantation between young and old rats: Age of host determines recovery. *Am J Physiol.* 1989; 256(6 pt 1):C1262–C1266. [PubMed: 2735398]
88. Brooks SV, Faulkner JA. Contractile properties of skeletal muscles from young, adult and aged mice. *J Physiol.* 1988; 404:71–82. [PubMed: 3253447]
89. Zerba E, Komorowski TE, Faulkner JA. Free radical injury to skeletal muscles of young, adult, and old mice. *Am J Physiol.* 1990; 258(3 pt 1):C429–C435. [PubMed: 2316631]
90. Jarvinen M, Aho AJ, Lehto M, et al. Age dependent repair of muscle rupture. A histological and microangiographical study in rats. *Acta Orthop Scand.* 1983; 54:64–74. [PubMed: 6829284]
91. Brooks SV, Faulkner JA. Contraction-induced injury: Recovery of skeletal muscles in young and old mice. *Am J Physiol.* 1990; 258(3 pt 1):C436–C442. [PubMed: 2316632]
92. Dedrick ME, Clarkson PM. The effects of eccentric exercise on motor performance in young and older women. *Eur J Appl Physiol.* 1990; 60:183–6.
93. McBride TA, Gorin FA, Carlsen RC. Prolonged recovery and reduced adaptation in aged rat muscle following eccentric exercise. *Mech Ageing Dev.* 1995; 83:185–200. [PubMed: 8583836]
94. Ho AD, Wagner W, Mahlknecht U. Stem cells and ageing. The potential of stem cells to overcome age-related deteriorations of the body in regenerative medicine. *EMBO Rep.* 2005; 6:S35–S38. [PubMed: 15995659]
95. Jejurikar SS, Henkelman EA, Cederna PS, et al. Aging increases the susceptibility of skeletal muscle derived satellite cells to apoptosis. *Exp Gerontol.* 2006; 41:828–36. [PubMed: 16942852]
96. Allen RE, McAllister PK, Masak KC. Myogenic potential of satellite cells in skeletal muscle of old rats: A brief note. *Mech Ageing Dev.* 1980; 13:105–9. [PubMed: 7431999]
97. Mouly V, Aamiri A, Bigot A, et al. The mitotic clock in skeletal muscle regeneration, disease and cell mediated gene therapy [review; 87 references]. *Acta Physiol Scand.* 2005; 184:3–15. [PubMed: 15847639]
98. Decary S, Mouly V, Hamida CB, et al. Replicative potential and telomere length in human skeletal muscle: Implications for satellite cell-mediated gene therapy. *Hum Gene Ther.* 1997; 8:1429–38. [PubMed: 9287143]
99. Schultz E, Lipton BH. Skeletal muscle satellite cells: Changes in proliferation potential as a function of age. *Mech Ageing Dev.* 1982; 20:377–83. [PubMed: 7166986]
100. Conboy IM, Conboy MJ, Wagers AJ, et al. Rejuvenation of aged progenitor cells by exposure to a young systemic environment. *Nature.* 2005; 433:760–4. [PubMed: 15716955]
101. Parizkova J, Eiselt E, Sprynarova S, et al. Body composition, aerobic capacity, and density of muscle capillaries in young and old men. *J Appl Physiol.* 1971; 31:323–5. [PubMed: 5111849]
102. Croleary AN, Zwetsloot KA, Westerkamp LM, et al. Lower capillarization, VEGF protein, and VEGF mRNA response to acute exercise in the vastus lateralis muscle of aged vs. young women. *J Appl Physiol.* 2005; 99:1872–9. [PubMed: 16024519]

103. Denis C, Chatard JC, Dormois D, et al. Effects of endurance training on capillary supply of human skeletal muscle on two age groups (20 and 60 years). *J Physiol.* 1986; 81:379–83.
104. Davidson YS, Clague JE, Horan MA, et al. The effect of aging on skeletal muscle capillarization in a murine model. *J Gerontol A Biol Sci Med Sci.* 1999; 54:B448–B451. [PubMed: 10568528]
105. Owino V, Yang SY, Goldspink G. Age-related loss of skeletal muscle function and the inability to express the autocrine form of insulin-like growth factor-1 (MGF) in response to mechanical overload. *FEBS Lett.* 2001; 505:259–63. [PubMed: 11566187]
106. Hameed M, Orrell RW, Cobbold M, et al. Expression of IGF-I splice variants in young and old human skeletal muscle after high resistance exercise [see comment]. *J Physiol.* 2003; 547(pt 1): 247–54. [PubMed: 12562960]
107. Melone MA, Peluso G, Galderisi U, et al. Increased expression of IGF-binding protein-5 in Duchenne muscular dystrophy (DMD) fibroblasts correlates with the fibroblast-induced downregulation of DMD myoblast growth: An in vitro analysis. *J Cell Physiol.* 2000; 185:143–53. [PubMed: 10942528]
108. Ervasti JM, Campbell KP. Membrane organization of the dystrophin-glycoprotein complex. *Cell.* 1991; 66:1121–31. [PubMed: 1913804]
109. Ibraghimov-Beskrovnaya O, Ervasti JM, Leveille CJ, et al. Primary structure of dystrophin-associated glycoproteins linking dystrophin to the extracellular matrix. *Nature.* 1992; 355:696–702. [PubMed: 1741056]
110. Ansved T. Muscular dystrophies: Influence of physical conditioning on the disease evolution [review; 58 references]. *Curr Opin Clin Nutr Metab Care.* 2003; 6:435–9. [PubMed: 12806218]
111. Viguie CA, Lu DX, Huang SK, et al. Quantitative study of the effects of long-term denervation on the extensor digitorum longus muscle of the rat. *Anat Rec.* 1997; 248:346–54. [PubMed: 9214552]
112. Darr KC, Schultz E. Hindlimb suspension suppresses muscle growth and satellite cell proliferation. *J Appl Physiol.* 1989; 67:1827–34. [PubMed: 2600016]
113. Schultz E, Darr KC, Macius A. Acute effects of hindlimb unweighting on satellite cells of growing skeletal muscle. *J Appl Physiol.* 1994; 76:266–70. [PubMed: 8175516]
114. Wanek LJ, Snow MH. Activity-induced fiber regeneration in rat soleus muscle. *Anat Rec.* 2000; 258:176–85. [PubMed: 10645965]
115. Mozdziak PE, Pulvermacher PM, Schultz E. Muscle regeneration during hindlimb unloading results in a reduction in muscle size after reloading. *J Appl Physiol.* 2001; 91:183–90. [PubMed: 11408429]
116. Booth FW. Regrowth of atrophied skeletal muscle in adult rats after ending immobilization. *J Appl Physiol.* 1978; 44:225–30. [PubMed: 632162]
117. Chakravarthy MV, Davis BS, Booth FW. IGF-I restores satellite cell proliferative potential in immobilized old skeletal muscle. *J Appl Physiol.* 2000; 89:1365–79. [PubMed: 11007571]
118. McGeachie J, Allbrook D. Cell proliferation in skeletal muscle following denervation or tenotomy: A series of autoradiographic studies. *Cell Tissue Res.* 1978; 193:259–67. [PubMed: 719719]
119. Rodrigues AC, Schmalbruch H. Satellite cells and myonuclei in long-term denervated rat muscles. *Anat Rec.* 1995; 243:430–7. [PubMed: 8597289]
120. Jejuri SS, Marcelo CL, Kuzon WM Jr. Skeletal muscle denervation increases satellite cell susceptibility to apoptosis. *Plast Reconstr Surg.* 2002; 110:160–8. [PubMed: 12087247]
121. Borisov AB, Dedkov EI, Carlson BM. Abortive myogenesis in denervated skeletal muscle: Differentiative properties of satellite cells, their migration, and block of terminal differentiation. *Anat Embryol.* 2005; 209:269–79. [PubMed: 15761724]
122. Schmalbruch H, al Amood WS, Lewis DM. Morphology of long-term denervated rat soleus muscle and the effect of chronic electrical stimulation. *J Physiol.* 1991; 441:233–41. [PubMed: 1816373]

Figure 1.