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Age-Associated Changes in Skeletal Muscle Regeneration: Effect of Exercise

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Abstract

Aim of the present short review is to provide a comprehensive update on age-associated skeletal muscle damage, regeneration, and effect of endurance and resistance type of exercise training on muscle regeneration. Decrease in muscle quantity and quality leads to disability in the aging population. The degradation rate of muscle proteins during aging increased about two times, and muscle strength and motor activity decreased at the same time. Aging induced sarcopenia is a result of decreased synthesis and increased degradation of muscle proteins, which leads to the slower turnover rate of these proteins, especially contractile proteins, and this, in turn, leads to the decrease in muscle strength. Muscle damage is mainly caused by excessive strain in contracting fibre and aging muscle is particularly sensitive to it. The decreased synthesis and increased degradation rate of contractile proteins are in accordance with the increase destructive processes in muscle and lead to the decrease in the regeneration capacity and development of sarcopenia in the elderly. Exercise training increases muscle mass, oxidative capacity, contracile quality, regeneration capacity and via this, physiological functioning of skeletal muscle is improved in the elderly.

Keywords

Aging, Muscle Damage, Regeneration, Exercise

1. Introduction

Aging is a physiological process that includes a gradual decrease in skeletal muscle mass, strength, and endurance coupled with an ineffective response to tissue damage [1]. Aging and a reduced physical level are mainly responsible for the progressive decline in several physiological capacities in the elderly [2]. Decrease in the protein synthesis rate is affected by the translational process occurring in older human skeletal muscle,

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whereas the transcriptional process appears to be unaltered when compared with those in younger men [3]. Skeletal muscle fibers have a remarkable capacity to regenerate [3] [4], and this depends on the number of satellite cells under the basal lamina of fibers and their oxidative capacity [5]. Autografting of skeletal muscle in old rodents shows that regeneration proceeds at a significantly slower rate in comparison with young animals [6]. A decrease in the number of satellite cells has been shown in fast-twitch muscle fibers of elderly subjects [7]. In sarcopenic muscle, the decrease in the satellite cell pool and the length of telomeres might explain the higher prevalence of muscle injuries and delayed muscle regeneration [2]. Functionally heterogeneous satellite cells with different properties may be recruited for different tasks, for example, muscle regeneration [8]-[10]. After severe damage, muscles in old rodents did not regenerate as well as muscles in adults [6]. The decreased regeneration capacity of muscles has shown due to extrinsic causes rather than an intrinsic limitation of muscles, but it is a combination of both extrinsic and intrinsic factors that contribute to reduced skeletal muscle regeneration [11] [12]. A contraction-induced muscle injury to weightbearing muscles in old rodents causes deficits in muscle mass and force [13]. The degradation rate of contractile proteins in rat skeletal muscle during aging increased about two times, and muscle strength and motor activity decreased at the same time [14]. Aging induced sarcopenia is a result of decreased synthesis and increased degradation of myofibrillar proteins, which leads to the slower turnover rate of muscle proteins, especially contractile proteins, and this, in turn, leads to the decrease in muscle strength [14]-[16]. Increasing dietary protein intake in combination with the use of anabolic agents attenuates muscle loss [15]. In essence, sarcopenia is an imbalance between protein synthesis and degradation rate [17].

Effective exercise training in the elderly increases both muscle oxidative capacity and contractile property, enhancing their life quality by improving muscle functional capacity and plasticity.

The aim of this review is to provide a comprehensive update on age-associated skeletal muscle damage and regeneration, effect of endurance and resistance type of exercise training and to analyze the mechanisms which underly muscle damage and regeneration.

2. Muscle Weakness in Elderly

During aging the physical system suffers to a different extent and rate in diverse parts of the body. This results in reduced functional reserve, a decrease in vital capacity, deterioration of the capillaty blood supply, and a decrise of muscle mass [18].

Sarcopenia has been considered to be a minor modifiable risk factor for health outcomes, and it plays a significant role in the etiology of disability [19] [20]. Aging and inactivity or disuse is associated with a decline in muscle mass, structure, and strength [15] [21]. A sedentary lifestyle, bed rest, spaceflight, and hindlimb suspension lead the skeletal muscle to microcirculatory disturbances, atrophy, protein loss, changes in contractile properties, and fibertype switching [15] [22]-[24]. In both young and aged skeletal muscle, oxidative stress increases in response to inactivity [25] and may have an important role in mediating muscle atrophy. Inactivity results in a decrease in the number of myonuclei and an increase in the number of apoptotic myonuclei in skeletal muscle [26]. Heat-shock protein (HSP) 70 inhibits caspase-dependent and caspase-independent apoptotic pathways and may function in the regulation of muscle size via the inhibition of necrotic muscle fiber distribution and apoptosis in aged muscle [27]. The decline in elderly muscle mass primarily results from type II fiber atrophy and loss in the number of these muscle fibers (**Figure 1**). Increased variability in fiber size, accumulation of nongrouping, scattered, and angulated fibers, and the expansion of extracellular space are characteristics of muscle atrophy [28]. Beyond the loss of muscle size due to reduced fiber number and myofibrillar proteins that underlie muscle weakness in the elderly [29], impairments in neural activation have been found, as well as potential alterationsin other muscular properties that may reduce contractile quality defined as a reduction in involuntary force production per unit muscle size [30]-[32]. The functional and structural decline of the neuromuscular system is a recognized cause of decreased strength, impaired performance of daily activities, and loss of independence in the elderly [33]. Loss of muscle strength in older adults is weakly associated with the loss of lean body mass [34]. It means that muscle weakness in older adults is more related to impairments in neural activation and/or reductions in the intrinsic force generating capacity of skeletal muscle [33].

3. Muscle Damage

Certain intracellular mechanisms are associated with muscle damage both in young and old, such as calcium

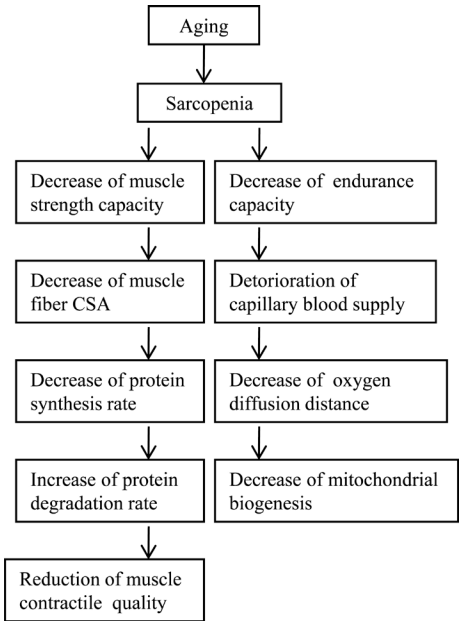

Figure 1. Effect of aging on skeletal muscle. CSA: cross sectional area.

overload, free radical formation and a decrease in energy supply. A fall in cellular adenosine triphosphate (ATP) content is associated with apoptosis and muscle ATP levels can decrease in response to stress [35]. The release of cellular proteins occurs when cellular ATP falls below a critical level, and interference in the energy supply to the muscle membrane is an important factor leading to enzyme efflux [36] [37]. The ability to alter mitochondrial content and function is an important adaptive response of the skeletal muscle. Skeletal muscle regeneration is accompanied by a marked stimulation of mitochondrial biogenesis concomitant with the onset of muscle fibre differentiation [38].

Muscle damage during exercise increases energy and protein needs [39]. Contracting muscle fibres release cytokines, which in turn create many effects in other organs, including the brain. Sooner or later, all these different mechanisms create sensations of fatigue and exhaustion in the mind of the exercising subject [40]. Long lasting exercise induces an anti-inflammatory effect in skeletal muscle, especially in fast twitch (FT) muscle fibres and a pro-inflammatory effect in adipose tissue [41]. This effect contributes to increased lipolysis to provide energy for the exercising muscle. Cytokines play an important role in the exercise induced immune reaction and exercise related metabolic and cellular signal transduction, and they are also capable of increasing HSP synthesis [42]. It is possible that HSP may act as a cytokine in reaction to long lasting exercise, stimulate tumour necrosis factor-alpha (TNF-α), interleukin (IL)-β, and IL-8 in monocytes, and activate CD 14-dependent and Ca^{2+}-dependent pathways [43]. Leukemia inhibitory factor (LIF) has been shown as a trauma factor for injured skeletal muscle due to its myotrophic action and in response to muscle injury together with IL-6 they are upregulated in injured muscle fibres and mononuclear cells at the site of the muscle injury [44]. High concentration of pro-inflammatory cytokine TNF-α promotes damage and impairs skeletal muscle [44]. Exercise caused muscle damage in elderly is more related with muscle fibers with low oxidative capacity.

4. Endurance Training Caused Muscle Damage

Endurance exercise training (ET) results in regulation of enzyme systems of Krebs cycle, electron trsnsport chain, capillary supplay, changes in key metabolic enzymes involved in fatty acid activation, and increased oxygen uptake [45]. ET does not result in hypertrophy of skeletal muscle fibers involved in the exercise response because the level of force production is relatively small compared to their maximal force-generating [46]. ET causes most changes in type I and IIA muscle fibres (**Figure 2**). The day following ET, significant destructive changes are in the myofibrils of these fibers. This damage includes the destruction of myosin and actin filaments and the disturbance of the regularity of Z-disc in some sarcomeres [47]. In some A-discs, myosin

filaments are absent and the destruction may cover the whole sarcomere. These structural changes are in accordance with biochemical ones [48]. Small structural rearrangements take place in type IIB fibres during ET as these fibers are less recruited. The number of mitochondria in type IIB fibers during ET does not increase significantly; they are located in small groups near nuclei and between myofibrils on the level of Z-disc, but not in each sarcomere [49]. As oxidative capacity of skeletal muscle decreasas in the elderly, endurance exercise has shown to be effective in its restoration as it stimulates mitochondrial biogeneses (**Figure 2**) and improves their functional parameters [50]. The higher oxidative capacity in trained elderly people is related to an increase in the abilities of cardiovascular system and to the lesser extent to an increase in muscle mitochondrial concentration [51]. Under conditions of hypoxia the connection between mitochondria and sarcomeres are disturbed as sarcomeric components disintegrate the muscle fiber structure and cause cell injury and death [52]. Aging and reduced physical level are responsible for the decline in several physiological capacities in the elderly. The degradation of muscle contractile proteins increased about two times in aging induced sarcopenic muscle, protein synthesis rate, muscle strength and motor activity decreased at the same time [14]. During adaptation of skeletal muscle to the ET changes in isform composition of main muscle contractile protein myosin, points to the transformation of the contractile apparatus in accordance with the increase in muscle oxidative capacity [53]. During the adaptation of elderly skeletal muscle to the ET these changes in FT skeletal muscle points to the transformation of the muscle contractile apparatus in accordance with the increase in muscle oxidative capacity. This adaptational process shows coordination between changes in oxidative capacity and contractile apparatus in skeletal muscle during adaptation to ET primarily in relation to muscle metabolism [54].

5. Resistance Training Caused Muscle Damage

Resistance training (RT) cause an increase in the cross-sectional area (CSA) of the whole muscle and individual muscle fibers, and an increase in myofibrillar size and number (**Figure 2**). The hypertrophy response is related to activation of satellite cells in the early stages of training [55]. Structural changes in skeletal muscle during RT

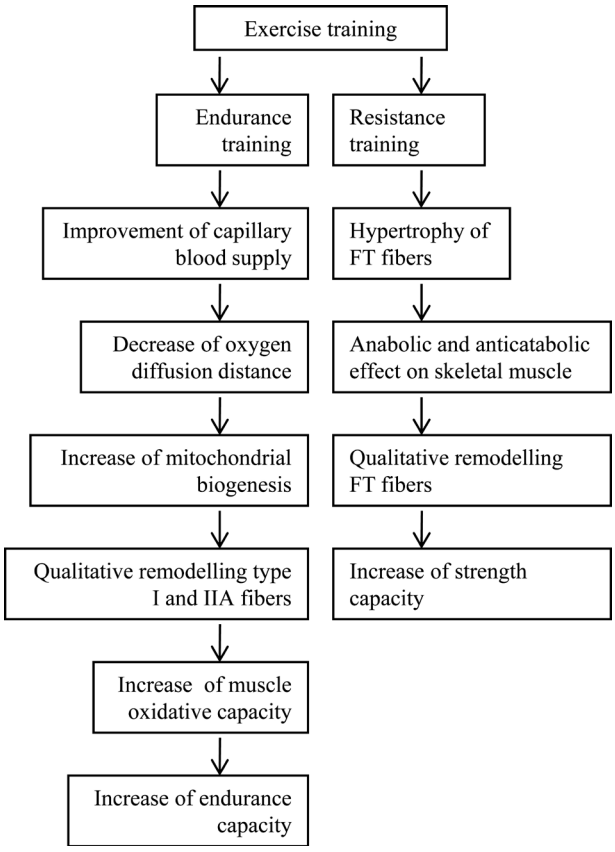

Figure 2. Effect of exercise training on aging muscle.

are fibre specific. FT fibres are more vulnerable to damage than slow-twitch (ST) [56]. In RT, type IIX/IIB fibres have twisted myofibrils in a relatively small area and they have lost connection with the neighbouring structures [49]. Damage caused by RT in skeletal muscle is also stimulus for regeneration due to muscle growth and promoting signalling events arising from the mechanical deformation of fibres, hormones and immune/inflammatory responses. The focal denervation of muscle fibers during exercise is reversable and accompanied by by regeneration of new axonal terminals growing into pre-existing synaptic grooves. RT enhances the synthesis rate of myofibrillar proteins, not of sarcoplasmic proteins, and this is related to the mammalian target of rapamycin complex by activating proteins with mitogen activated protein kinase signalling [57]. Structural changes with exercise induced muscle damage are associated with the influence of gene expression strengthening the muscle, protecting the tissue against further injury [58], and an increased protein turnover rate [49]. RT increased the synthesis rate of myofibrillar proteins in ageing FT muscle. The slowdown of the turnover rate of contractile proteins with age approximately one third is caused both by the decreased protein synthesis rate and the intensification of the protein degradation rate. Although mechanical activity changes the turnover rate of contractile proteinsin both young and old, the turnover rate changes in old age are relatively slower than than in young.

6. Muscle Regeneration

Under the basal lamina, skeletal muscle contains quiescent mononucleated cells—satellite cells (Sc) characterized by their high level of Pax7 expression. Sc which soon after muscle damage activate, divide, proliferate, undergo myogenic differentiation, maturation and form new muscle fibres [59] [60]. Sc, which develop into myoblasts, contain a lot of ribosomes, branching granular sarcoplasmic reticulum with widened canals and a well developed Golgi apparatus [49]. Sometimes Sc also contain centrioles, which confirms that these cells are divided by mitosis. In some of these Sc, sarcoplasm close to the nucleus contains bundles of filaments, which may turn out to be myofilamets [61].

Many growth factors are produced in injured skeletal muscle (**Figure 3**) and influence its regeneration [60] [62]. Leukaemia inhibitory factor (LIF) stimulates skeletal muscle Sc proliferation and is involved in muscle hypertrophy and regeneration during exercise [63]. Peroxisome proliferator activated receptor isoform δ (Ppar δ) gene, which regulates skeletal muscle oxidative capacity via Sc proliferation [64] as well as injury induced myokine insulin-like 6 (Insl6) [65] also support muscle regeneration.

The fact that Sc play a direct role in fast-to-slow fibre transition shows that considerable adaptive capacity resides in myonuclei [66]. The location of Sc in the postsynaptic region is evidence of the plastic regenerative capacity of this region [49]. If necessary, this kind of cells can join the muscle fibres and increase the area of the

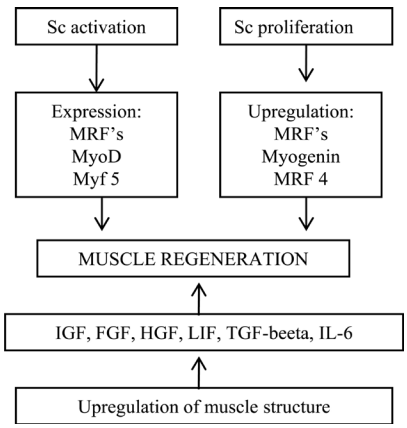

Figure 3. Regulation of damaged skeletal muscle regeneration. Exercise stimulates muscle regeneration process via Sc fusion with damaged fibers, or the formation of new muscle fibers as a result of myoblasts' fusion in order to maintain myonuclear domain size.
Sc: satellite cells; MRFs: muscle regulatory factors; MyoD: myoblast determination protein; Myf 5: myogenetic factor; MRF 4: myogenic regulatory factor; IGF: insulin-like growth factor; FGF: fibroblasts growth factor; HGF: hepatocyte growth factor; LIF: leukemia inhibitory factor; TGF: transforming growth factor; IL: interleukin.

synapse and the number of nuclei in the region. ST oxidative muscle fibres contain a large number of Sc in comparison with FT glycolytic fibres [67]. In exercising muscle, Sc are able to leave the fibre and form a new population of myogenic cells and are later ready to form new muscle fibres [49]. Regeneration capacity is higher in type I and IIA muscle fibres, where the oxidative capacity and insulin stimulated glucose uptake is higher in comparison with type IIB/IIX fibres [37] [68].

7. Effect of Endurance Training on the Muscle Regeneration

Exercise training has the ability to influence the function of muscle fibres modifying their structure and metabolism and promoting the release of growth factors and other signalling molecules, such as nitric oxide, which work through the paracrine system to activate Sc [47]. ST oxidative (type I) muscle fibres contain a large number of myonuclei and Sc compared with FT glycolytic (IIB) fibres [67] [69]. Fast to slow fibre transition has been shown to be associated with increases in Sc activation, content and fusion to transforming fibres, especially within the IIB fibres [70] [71]. The number of Sc in very different stages of development under the basal lamina of type I and FT oxidative-glycolytic (type IIA) muscle fibres increases during ET [47] [61] [72]. Adenosine monophosphate-activated protein kinase (AMPK) is activated in response to ET [73] and related to the metabolic adaptation of skeletal muscle both in young and old. AMPK function includes glucose transport, glycogen metabolism, fatty acid oxidation and transcriptional regulation of structural muscle genes [74]. α_1 isoform of AMPK is the regulator of skeletal muscle growth and α_2 isoform regulates metabolic adaptation [75]. Increased mitochondrial biogeneses via AMPK is accompanied by supression of the myofibrillar protein synthesis through pathways mediated by mitogen activated protein kinase (MAPK), nuclear factor kappa B (NF-κB) mammalian target of rapamycin (mTOR) and tuberous sklerosis complex (TSC) [57] [76]. Insulin-like growth factor (IGF) I expression is higher in ST fibers [77] [78] and myostatin in fibers with higher oxidative capacity (type I and IIA) [79]. The components of the degradation system of muscle proteins, such as ubiquitin ligases muscle atrophy F-box (MAFbx) and muscle ring finger (MuRF) are about two fold higher in fibers with higher oxidative capacity [76] and in elderly. It was shown that the number of Sc in rat skeletal muscle increased about 3.5 times during ET [80]. Both oxidative capacity and Sc number in muscle fibers, which determine muscle regenerative capacity, are higher in young than in old muscle. Protein turnover in skeletal muscle is relatively slow, especially contractile proteins and endurance exercise training stimulates protein turnover [48]. The turnover rate of myosin heavy chain (MyHC) and myosin light chain (MyLC) isoforms provides a mechanism by which the type and amount of protein changes in accordance with the needs of the contractile machinery during adaptation to ET [81]. ET mainly increases the number of Sc under the basal lamina of type I and IIA fibres and increases the regeneration capacity of these fibres [49]. The mechanism associated with activity-induced shifts in myosin expression is the key to understanding the plasticity of skeletal muscle as the hypertrophied muscle fibre has adapted to a chronic overload *via* an alteration in its phenotype [82]. The mechanisms involved in regulating changes in the myosin expression and in the muscle mass may have different sensitivities to mechanical load [83].

8. Effect of Resistance Training on the Muscle Regeneration

RT increases the CSA of the whole muscle and individual muscle fibres, and increases myofibrillar size and number [45]. The hypertrophy response to RT is related to the activation of Sc in the early stage of training [55]. RT causes fiber hypertrophy in two ways: damged fibers regenerate as a result of the fusion with Sc [84] as it is proved by the incorporation of 3H thymidine into the nucleus of the muscle fiber [85], and via Sc activation under the basal lamina, devision and after that myosymplasts fuse with each other and form myotubes [86]. RT also causes other morphological adaptations, such as hyperplasia, changes in muscle fine architecture, in myofilament density and in the structures of connective tissue [55]. RT mainly causes an increase in the CSA of IIX/IIB and IIA fibres. Structural changes in skeletal muscle during RT are fibre specific. RT enhances the synthesis rate of myofibrillar proteins, not of sarcoplasmic proteins, and this is related to the mammalian target of rapamycin complex by activating proteins with mitogen activated protein kinase signalling [57]. Recovery from intensive RT caused damages is slower as a result of age, whereas there are no age related differences in recovery from less damaging metabolic fatigue [86]. Recovery from RT, during which the power of exercise increases less than 5% per session, causes hypertrophy of both FT and ST muscle fibres and an increase in the myonuclear number. This is achieved via Sc fusion with damaged fibres or the formation process of new muscle

fibres as a result of myoblasts' fusion in order to maintain myonuclear domain size [85]. RT increases the level of IGF-I and mechano-growth factor (MGF) in skeletal muscle and these factors support faster recovery of muscle tissue [37].

9. Conclusion

The decreased synthesis and increased degradation rate of contractile proteins are in accordance with the increase destructive processes in muscle and lead to the decrease in the regeneration capacity and development of sarcopenia in elderly. Muscle damage is mainly caused by excessive strain in contracting fibre and aging muscle is particularly sensitive to it. Several factors play a role in injured skeletal muscle and influence its regeneration. So, LIF stimulates skeletal muscle Sc proliferation and is involved in muscle hypertrophy and regeneration during exercise. Ppar δ gene, which regulates skeletal muscle oxidative capacity *via* Sc proliferation, and injury induced myokine Insl6 also support muscle regeneration. Oxidative muscle fibres contain a large number of myonuclei and Sc compared with glycolytic fibres. The number of Sc under the basal lamina of type I and type IIA muscle fibres increases during ET and these cells are in very different stages of development. Sc number also increases during RT. The paired box transcription factor Pax7 plays a critical role in regulating the specification of Sc and in maintaining the Sc population via selfrenewal process. An increase in Sc is related to several factors expressing different genes and FT muscle hypertrophy. IGF-I have a role in the hypertrophy of muscle fibres through the stimulation of the differentiation of Sc. The MGF level increases with the increase in the number of Sc in muscle fibres during RT. Mitochondrial biogenesis increases during ET via AMP-activated AMPK which is accompanied by suppression of the myofibrillar protein synthesis through pathways mediated by MAPK and NF-kB. As a result of exercise training muscle fibres with higher oxidative capacity contain more Sc, myonuclei, mitochondria, mRNA, and have higher total ribosomal RNA content. IGF-I expression is also higher in ST fibres. Myostatin, the expression inhibitor of muscle hypertrophy, is higher in FT IIB fibres. The proteasome-, lysosome- and Ca^{2+}-mediated protein degradation is more intensive in fibres with higher oxidative capacity during and after exercise training. The components of the degradation system of muscle proteins, such as ubiquitin ligases MAFbx and MuRF, are higher in muscle fibres with higher oxidative capacity. Both oxidative capacity and Sc number in muscle fibres play an important role in skeletal muscle regeneration. Muscle protein synthesis and degradation are balanced in ET so that fibre size does not increase. ET improves the energetic potential of skeletal muscle and supports the effective functioning of the myofibrillar apparatus. Activation of AMPK in response to ET includes an induction of glucose transport, glycogen metabolism, fatty acid oxidation and transcriptional regulation of structural genes and α_1 isoform of AMPK, which regulates skeletal muscle growth. This work adds an essential contribution to the understanding of physicians and exercise therapists about the effect of character of exercise training on aging muscle, its regeneration capacity and mechanisms of regulation.

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Author Contributions

Teet Seene and Priit Kaasik designed, participated in interpretation of data and final approval of the manuscript.

Disclosure Statement

The authors declare no conflict of interest.

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Abbreviations

AMPK: adenosine monophosphate-activated protein kinase
ATP: adenosine triphosphate
CSA: cross-sectional area
ET: endurance training
FT: fast-twitch
HSP: heat shock protein
IGF: insulin-like growth factor
IL: interleukin
LIF: leukemia inhibitory factor
MAFbx: ubicuitin ligases muscle atrophy F-box
MAPK: mitogen activated protein kinase
MGF: mechano growth factor
MuRF: muscle ring finger
MyHC: myosin heavy chain
MyLC: myosin light chain
mTOR: mammalian target of rapamycin
NF-κB: nuclear factor kappa B
Ppar: peroxisome proliferator activated
RT: resistance training
Sc: satellite cell
ST: slow-twitch
TNF: tumor necrosis factor
TSC: tuberous sclerosis complex