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Muscle damage and regeneration: Response to exercise training

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ABSTRACT

Exercise training influences the function of skeletal muscle, modifying fibre structure, metabolism and promoting the release of growth factors and other signalling molecules. The number of satellite cells under the basal lamina of type I and type IIA muscle fibres increases during endurance training and under the basal lamina of both type II fibres during resistance training. An increase in satellite cells is related to several factors expressing different genes and type II muscle fibre hypertrophy. Insulin-like growth factor-I has a role in the hypertrophy of muscle fibres through the stimulation of the differentiation of satellite cells. The increased mitochondrial biogenesis via adenosine myophosphate-activated protein kinase is accompanied by the suppression of myofibrillar protein synthesis through pathways mediated by mitogen-activated protein kinases and the nuclear factor kappa B. Insulin-like growth factor-I expression is higher in type I fibres. Myostatin, the expression inhibitor of muscle hypertrophy, is higher in type II fibres. The proteasome-, lysosome- and Ca^{2+}-mediated protein degradation is more intensive in fibres with higher oxidative capacity. Both, oxidative capacity and satellite cells number in muscle fibres play important roles in skeletal muscle regeneration. In this review, we explore the regeneration capacity changes in different types of skeletal muscle fibres in response to resistance, endurance and overtraining.

Keywords: Skeletal Muscle; Regeneration Capacity; Resistance; Endurance and Overtraining

1. INTRODUCTION

The contemporary exercise training process does not simply consist in repetitive exercise but encompasses regular regeneration as an integral part of a successful training program. Systematic recovery periods in the training process are necessary to achieve an augmentation for further performance improvement. Exercise-induced skeletal muscle damage mainly follows unaccustomed and sustained metabolically demanding training processes [1]. Muscle fibre damage is often caused by excessive strain in contracting fibre, not because of the absolute force developed in the muscle [2]. The anatomic site of myofibrillar injury is the attachment of myofibrils to the extrasarcolemic cytoskeleton [3].

Certain intracellular mechanisms are associated with muscle damage, such as calcium 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 [4]. 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 [5-7]. The ability to alter mitochondrial content and function is an important adaptive response of the skeletal muscle. It has been shown that skeletal muscle regeneration is accompanied by a marked stimulation of mitochondrial biogenesis concomitant with the onset of muscle fibre differentiation [8].

Muscle fibres regenerate via the activation of quiescent muscle precursor cells (**Figure 1**) and proceed with the formation of proliferating progenitors that fuse to generate differentiated myofibres [9]. These satellite cells (Sc) activated by muscle injury give rise to intermediate progenitor cells expressing the MyoD and myogenic transcription factor Pax3, which are asymmetrically divided and differentiated into Pax3, Myf-5 and desmin myoblasts [10]. Regeneration in exhausted skeletal muscle, caused by both endurance and strength training, is slow as the lack of insulin-like growth factor-I (IGF-I)

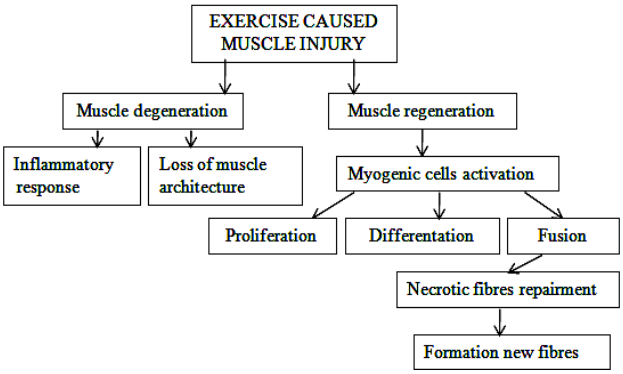

Figure 1. Skeletal muscle repair process after exercise caused muscle damage. Muscle fibres regenerate by activation of satellite cells. Satellite cells activated by muscle injury and express myogenic transcription factors. Regeneration in exercise caused exhausted muscle is slow as lack of several factors prevents the activation of satellite cells under the basal lamina of muscle fibres.

and mechano-growth factor (MGF) prevents the activation of Sc under the basal lamina of muscle fibres.

In this review, the current understandings of the changes in skeletal muscle regeneration capacity in response to resistance, endurance and overtraining and reasons thereof are presented. Morpho-functional characteristics of injured muscle and the role of Sc and different myogenic factors in the repair of myofibres after damage are discussed.

2. REGENERATION CAPACITY OF SKELETAL MUSCLE FIBRES

Under the basal lamina, skeletal muscle contains quiescent mononucleated cells 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 [11,12]. Sc, which develop further into myoblasts, contain a lot of ribosomes, branching granular sarcoplasmic reticulum with widened canals and a well-developed Golgi apparatus [13]. 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 [14].

Many growth factors are produced in injured skeletal muscle and influence its regeneration [11,15]. Leukaemia inhibitory factor (LIF) stimulates skeletal muscle Sc proliferation and is involved in muscle hypertrophy and regeneration during exercise [16]. Peroxisome proliferator-activated receptor isoform δ (Ppar δ) gene, which regulates skeletal muscle oxidative capacity via Sc proliferation [17] as well as injury induced myokine insulin-like 6 (Insl6) [18] also support 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 [19]. Oxidative muscle fibres contain a large number of myonuclei and Sc compared with glycolytic fibres [20, 21]. 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 [22,23]. The number of Sc in very different stages of development under the basal lamina of type I and type IIA muscle fibres increases during endurance training (ET) [14,19,24]. The fact that Sc play a direct role in fast-to-slow fibre transition shows that considerable adaptive capacity resides in myonuclei [25]. The location of Sc in the postsynaptic region is evidence of the plastic regenerative capacity of this region [13]. If necessary, this kind of cells can join the muscle fibres and increase the area of the synapse and the number of nuclei in the region (**Figure 2**). Slow-twitch (ST) oxidative muscle fibres contain a large number of Sc in comparison with fast-twitch (FT) glycolytic fibres [20]. 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 [13]. 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 [6,26].

3. RESPONSE TO RESISTANCE TRAINING

In resistance training (RT), the repetition regimen plays an important role in the development of muscle fibre hypertrophy as well as regeneration capacity [27, 28]. The increased number of Sc in power lifters shows that Sc make skeletal muscle more responsive to training and regeneration [29]. Sc are provided as additional myonuclei via the proliferation, differentiation and fusion with existing myofibres during muscle hypertrophy [31]. Sc number has shown to increase after RT. The paired box transcription factor Pax7 plays a critical role in regulating the specification of Sc and in maintaining the Sc population via self-renewal [31,32]. An increase in Sc is related to several factors expressing different genes and FT muscle hypertrophy [33,34]. IGF-I is involved in the hypertrophy of muscle fibres via stimulation of the protein synthesis rate. The MGF level increases with the increase in the number of Sc in mature muscle fibres [35].

RT causes muscle hypertrophy in two ways. First, damaged mature fibres regenerate as a result of the fusion with Sc [36]. It is proved by the incorporation of ^{3}H

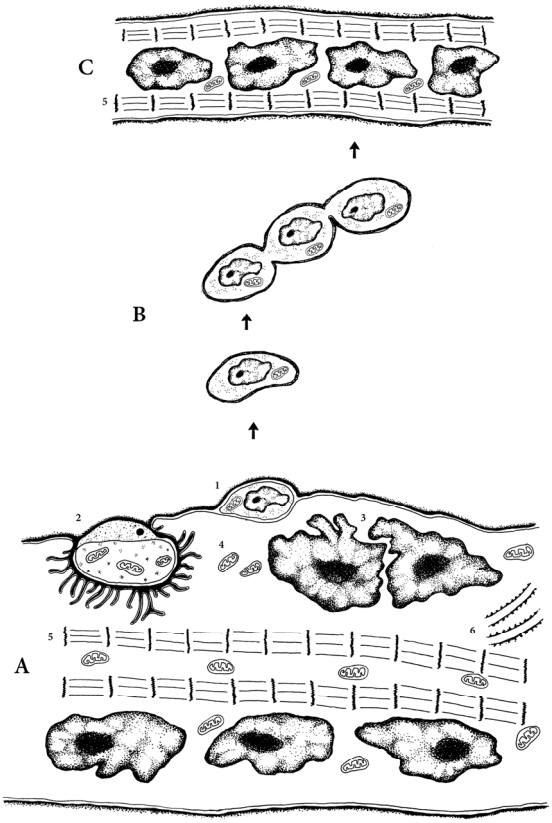

Figure 2. Schematic representation of the skeletal muscle repair process following strenuous exercise: A. Satellite cells (Sc) activation by muscle injury. Sc divide, proliferate, differentiate, mature (B) and form new muscle fibres (C) or fuse with damage mature fibres and gives impulse for regeneration of these fibres. 1—satellite cell under the based laminea; 2—neuromuscular junction; 3—myonuclei; 4—mitochondria; 5—myofibrils; 6—granular sarcoplasmic reticulum; B. Satellite cells devide, later myosymplasts fuse with each other and form myotubes; C. Myotube.

thymidine into the nucleus of the muscle fibre [37]. As ^{3}H thymidine is not incorporated into the nucleus of a mature muscle fibre, the only option for incorporation is via Sc (**Figure 2**). The second way is the activation of Sc under the basal lamina of muscle fibres during resistance training (**Figure 2**). Sc divide and later myosymplasts fuse with each other and form myotubes [36]. As noted, Sc are the source of forming new muscle fibres during RT. Hyperplasia plays a certain role in the process of muscle hypertrophy in RT, even in adults [38].

Skeletal muscle fibres are multinucleated cells, where each myonucleus controls the production of protein synthesis over a finite volume of cytoplasm—the DNA unit or myonuclear domain [39,40]. An increase in myonuclei is the source of muscle hypertrophy, but moderate changes in the skeletal muscle size are possible without new myonuclei [41].

4. RESPONSE TO ENDURANCE TRAINING

Endurance training (ET) increases the maximum rate of oxygen consumption, influences the enzyme system of the Krebs cycle, electron transport chain, capillary supply, changes in key metabolic enzymes involved in fatty acid activation and does not result in hypertrophy of skeletal muscle fibres [42-44]. Skeletal muscle cross sectional area (CSA) in ET stays on the same level or has a tendency to decrease, particularly in fibres with higher oxidative capacity [13]. This is important from the standpoint of oxygen diffusion distance, the decrease of which supports the increase in oxidative capacity of skeletal muscle during endurance exercise [45]. ET stimulates mitochondrial biogenesis and improves its functional parameters [46]. Increased mitochondrial biogenesis via adenosine monophosphate-activated protein kinase (AMPK) is accompanied by suppression of the myofibrillar protein synthesis through pathways mediated by mitogen-activated protein kinases (MAPK), nuclear factor kappa B (NF-kB) mammalian target of rapamycin (mTOR) and tuberous sklerosis coplex (TSC) [47,48]. Muscle fibres with higher oxidative capacity contain higher quantities of Sc, myonuclei, mitochondria, mRNA, and total ribosomal RNA content. IGF-I expression is also higher in ST fibres [49,50]. Myostatin, the expression inhibitor of muscle hypertrophy, is higher in FT fibres [51,52]. The proteasome-, lysosome- and Ca^{2+}-mediated protein degradation is more intensive in the fibres, where the oxidative capacity is higher [53]. The components of the degradation system of muscle protein, such as ubiquitin ligases muscle atrophy F-box (MAFbx) and muscle ring finger (MuRF), are about twofold higher in muscle fibres with higher oxidative capacity (ST type I and FT type IIA fibres) [47]. The number of Sc in rat skeletal muscle increased about 3.5 times during ET [54]. Both, oxidative capacity and Sc number in muscle fibres determine muscle regenerative capacity. In ET, muscle protein synthesis and degradation are balanced so that ST type I and FT type IIA fibre size does not increase. This process is supported by the turnover rate of muscle protein [45].

ET programs in a variety of forms improve the energetic potential of skeletal muscle and support the effective functioning of the myofibrillar apparatus [55,56]. Activation of AMPK in response to ET includes the induction of glucose transport, glycogen metabolism, fatty acid oxidation and transcriptional regulation of structural genes [57] and α1 isoform of AMPK, which regulates skeletal muscle growth [58].

Exercise training supports muscle regeneration capacity (**Figure 2** and **3**). It is important from the standpoint of top level endurance athletes and also recreational athletes who exercise regularly as regular exercise training

is the way for the relatively fast regeneration of muscle fibres.

5. REGENERATION OF MUSCLE CONTRACTILE APPARATUS IN RESISTANCE AND ENDURANCE TRAINING

5.1. Regeneration Capacity Changes in Response to Resistance Training

RT increases the CSA of the whole muscle and individual muscle fibres, and increases myofibrillar size and number [27]. The hypertrophy response to RT is related to the activation of Sc in the early stage of training [27]. RT also causes other morphological adaptations, such as hyperplasia, changes in muscle fine architecture, in myofilament density and in the structures of connective tissue [27]. RT mainly causes an increase in the CSA of IIX/IIB and IIA fibres. Structural changes in skeletal muscle during RT are fibre specific. FT fibres are more vulnerable to damage than ST [59]. In resistance training, type IIX/IIB fibres have twisted myofibrils in a relatively small area and they have lost connection with the neighbouring structures [13]. 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 [60]. 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 [48]. Structural changes with exercise-induced muscle damage are associated with the influence of gene expression strengthening the muscle, protecting the tissue against further injury [61], and an increased protein turnover rate [13]. Recovery from damaging RT is slower as a result of age, whereas there are no age-related differences in recovery from less damaging metabolic fatigue [62]. 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 (**Figure 2**) with damaged fibres or the formation of new muscle fibres as a result of myoblasts' fusion in order to maintain myonuclear domain size [37]. RT increases the level of IGF-I and MGF in skeletal muscle and these factors support faster recovery of muscle tissue [6].

5.2. Regeneration Capacity Changes in Response to Endurance Training

ET causes most changes in type I and IIA muscle fibres. The day following ET, significant destructive changes are visible in the myofibrils of these fibres. This damage includes the destruction of myosin and actin filaments and the disturbance of the regularity of Z-line in some sarcomeres [19]. 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 [19,45]. Small structural rearrangements take place in type IIB fibres during ET as these fibres are less recruited. The number of mitochondria in type IIB fibres during ET does not increase significantly; they are located in small groups near nuclei and between myofibrils on the level of Z-line, but not in each sarcomere [13].

AMPK is activated in response to ET [63] and related

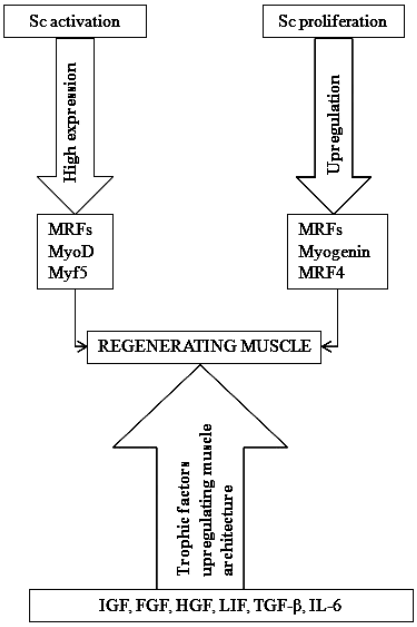

Figure 3. Molecular events regulating satellite cell activation in exercise damaged skeletal muscle regeneration process. Both resistance and endurance exercise stimulate muscle regeneration. Resistance exercise increase the level of insulin-like growth factor 1 and mechano-growth factor in skeletal muscle and these factors support faster recovery of muscle tissue. Endurance exercise increase the number of satellite cells under the basal lamina of type I and IIA fibres and increase the regeneration capacity, particularly metabolic adaptaion of muscle. MRFs—muscle regulatory factors; MyoD—myoblast determination protein; Myf5—myogenic factor 5; MRF4—muscle regulatory factor 4; IGF—insulin-like growth factor; FGF—fibroblasts growth factor; MGF—mechano-growth factor; HGF—hepatocyte growth factor; LIF—leukemia inhibitory factor; TGF—β-transforming growth factor-β family; IL-6—interleukin-6; Sc—satellite cell.

to the metabolic adaptation of skeletal muscle. AMPK function includes glucose transport, glycogen metabolism, fatty acid oxidation and transcriptional regulation of structural muscle genes [57]. α1 isoform of AMPK is the regulator of skeletal muscle growth and α2 isoform regulates metabolic adaptation [58]. Protein turnover in skeletal muscle is relatively slow, particularly contractile proteins and aerobic endurance exercise training stimulates protein turnover [45]. 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 [64]. ET mainly increases the number of Sc under the basal lamina of type I and IIA fibres and increases the regeneration capacity (**Figures 2** and **3**) of these fibres [13].

It is well known that different modes of mechanical activity result in the selective up- and down-regulation of myosin MyHC isoforms in FT skeletal muscle in humans and animals. Most studies have shown that the relative content of MyHC IIx and IIb isoforms decreases during RT. A low number of repetitions during the training session and a low volume of RT cause relatively small hypertrophy of muscle. However, the highest increase in muscle strength and a small increase in the relative content of MyHC IIb isoform were simultaneously registered in FT muscles [65]. It seems that both in case of RT and ET, an increase in the training volume decreases the relative content of MyHC IIb isoform in FT skeletal muscles.

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 [66]. The mechanisms involved in regulating changes in the myosin expression and in the muscle mass may have different sensitivities to mechanical load [67].

6. RESPONSE TO OVERTRAINING

An excessive volume of ET leads to exercise intolerance. Problems with recovery have been shown to occur in animal experiments when exercise training time reaches 10% within a 24 h period [6,68]. A significant decrease in physical work capacity during exhaustive exercise as compared to the recommended training protocol suggests that lack of recovery in the training protocol leads to overtraining syndrome. If the exercise session lasts too long and training sessions are so frequent that they interrupt the recovery phase, the necessary adaptation does not occur [69,70]. The importance of recovery is evident from the fact that a much longer recovery time is needed after symptoms of overtraining appear [68]. Deterioration of the capillary network decreases the exchange of oxygen between capillaries and muscle fibres. As a result, muscle oxidative and regeneration capacity decreases as well as the Sc number under the basal lamina of muscle fibres [71,72]. A decrease in the number of Sc means that new muscle fibres do not form as quickly as in intact muscle and damaged fibres do not regenerate appropriately since Sc do not fuse with damaged fibres [6].

Lack of Sc, a decreased differentiation of myosymplasts and level of transcription factors (MyD family), except for myostatin, decrease muscle regeneration capacity (**Figure 3**). Lack of MGF leads to apoptosis. If muscle fibres do not regenerate, muscle atrophy develops [6]. Only myostatin and heat shock protein (HSP-70) synthesis increases in atrophied muscle. A decrease in the synthesis rates of muscle proteins, particularly myofibrillar proteins, and increased protein degradation lead to the "wastage" of muscle. A decrease in myonuclei number and DNA damage lead to a decrease in DNA units in overtrained skeletal muscle [68]. Lack of myonuclei accompanied by decreased synthesis and an increased degradation rate of muscle proteins, particularly myofibrillar proteins [68], lead to a decrease in the muscle growth and regenerative capacity in overtraining caused myopathic skeletal muscle [6,71]. It has been shown that the inflammatory cytokines cycloo xy genase-2 (COX-2) and phosphatidic acid (PA) may play role in the inhibition of skeletal muscle growth induced by overtraining [73].

7. REGENERATION CAPACITY IN OVERTRAINING CAUSED MYOPATHIC MUSCLE

The DNA content in muscle, and the protein and DNA ratio in FT muscles decreases during exhaustion showing signs of myopathy as a result of muscular overload [68]. As far as is presently known, overtraining caused myopathy is characterized by slow turnover of MyHC in FT muscle fibres, depressed neuromuscular and depressed α-motoneuron excitability [6]. Pro-inflammatory cytokine profile changes also constitute a risk for overtraining syndrome [74,75]. Vitamin D insufficiency is the reason for the increased concentration of the inflammatory cytokine TNF-α [76].

The decreased synthesis and increased degradation rate of contractile proteins, which was observed in overtraining caused myopathic muscle, is in good agreement with the increased occurrence of destructive processes in FT fibres [6,68]. Contrary to the decreased turnover rate of contractile proteins, overtrained athletes show a persistent high synthesis rate and concentration of HSP, which might show an increased stress tolerance of affected cells and mediate the cellular repair process [77]. During migratory flight, which can last 50 - 100 h, mus-

cle damage occurs mainly in young, relatively unadapted (untrained) birds. Experienced migrants may avoid damage behaviourally, or have efficient biochemical and physiological defence systems against muscle injury [78]. Damaged muscle tissue releases cytokines (**Figure 3**), which act in the hypothalamus to re-set the regulatory mechanisms which, among other things, shut down functions that might promote further damage.

8. ROLE OF CYTOKINES IN REGENERATING SKELETAL 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 [79]. It is possible that HSP may act as a cytokine in reaction to exhaustive 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 [80]. 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 [81]. High concentration of pro-inflammatory cytokine TNF-α promotes damage and impairs skeletal muscle [82] and vitamin D supplementation improves the cytokine profile in patients with chronic diseases [84] but not in healthy individuals [85,86].

Muscle damage during exhaustive exercise increases athletes' energy and protein needs [87]. It has been shown that basal metabolic rate increases by 32% after skeletal muscle trauma [88] as the acquisition of new muscle mass is an energy-costly process in athletes and a 2300 - 3500 kcal surplus is required to build each pound of new muscle tissue [89].

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 [90]. Exhaustive exercise induces an anti-inflammatory effect in skeletal muscle, especially in FT muscle fibres and a pro-inflammatory effect in adipose tissue [91]. This effect contributes to increased lipolysis to provide energy for the exercising muscle.

Muscle fibre phenotype maintenance and transition depends on motoneuron-specific impulse patterns, neuromuscular activity and mechanical load. Depending on the type, intensity and duration of changes in any of these factors, muscle fibres adjust their phenotype to meet the altered functional demands [66].

9. CONCLUSION

Exercise-induced skeletal muscle damage follows unaccustomed training processes. Muscle damage is caused by excessive strain in contracting fibre. Systematic recovery periods in the training process are necessary for performance improvement. Growth factors play a certain role in injured skeletal muscle and influence its regeneration. LIF stimulates skeletal muscle Sc proliferation and is involved in muscle hypertrophy and regeneration during exercise (**Figure 1**). 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 increases during chronic RT. The paired box transcription factor Pax7 plays a critical role in regulating the specification of Sc and in maintaining the Sc population via self-renewal. 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. Increased mitochondrial biogenesis via AMP-activated AMPK is accompanied by suppression of the myofibrillar protein synthesis through pathways mediated by MAPK and NF-kB. 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 fibres. The proteasome-, lysosome- and Ca^{2+}-mediated protein degradation is more intensive in fibres with higher oxidative capacity. 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 (**Figure 2**). Muscle protein synthesis and degradation are balanced in ET so that fibre size does not increase. This process is supported by the turnover rate of muscle protein. 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 α1 isoform of AMPK, which regulates skeletal muscle growth. If the exercise session lasts too long, the training sessions are too frequent and interrupt the recovery phase, adaptation does not occur and overtraining syndrome develops. The decreased synthesis and increased degradation rate of contractile proteins are in accordance with the increase in destructive processes in muscle and lead to the decrease

in the regeneration capacity in overtrained skeletal muscle. Cytokines play an important role in the exercise-induced immune reaction, exercise-related metabolic and cellular signal transduction and the increase in HSP synthesis. HSP may act as a cytokine during exhaustive exercise, stimulate TNF-α, IL-β, and IL-8 in monocytes, and activate CD 14-dependent and Ca^{2+}-dependent pathways. LIF, the trauma factor for injured skeletal muscle due to its myotrophic action and in response to muscle injury together with IL-6 are upregulated in injured muscle fibres and mononuclear cells in case of muscle injury (**Figure 3**). High concentration of pro-inflammatory cytokine TNF-α promotes damage and impair of skeletal muscle and vitamin D supplementation improves the cytokine profile in patients with chronic diseases.

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