Free Radical Biology and Medicine 98 (2016) 56–67

Contents lists available at ScienceDirect

Free Radical Biology and Medicine

journal homepage: www.elsevier.com/locate/freeradbiomed

Muscle fiber type diversification during exercise and regeneration

Rizwan Qaisar, Shylesh Bhaskaran, Holly Van Remmen *

Aging and Metabolism Research Program, Oklahoma Medical Research Foundation, 825 NE 13th Street, Oklahoma City, OK 73104, USA

ARTICLE INFO

Article history:
Received 28 October 2015
Received in revised form
1 March 2016
Accepted 24 March 2016
Available online 29 March 2016

Keywords:
Exercise
Skeletal muscle
Fiber types
Injury
Regeneration
PGC-1 α

ABSTRACT

The plasticity of skeletal muscle can be traced down to extensive metabolic, structural and molecular remodeling at the single fiber level. Skeletal muscle is comprised of different fiber types that are the basis of muscle plasticity in response to various functional demands. Resistance and endurance exercises are two external stimuli that differ in their duration and intensity of contraction and elicit markedly different responses in muscles adaptation. Further, eccentric contractions that are associated with exercise-induced injuries, elicit varied muscle adaptation and regenerative responses. Most adaptive changes are fiber type-specific and are highly influenced by diverse structural, metabolic and functional characteristics of individual fiber types. Regulation of signaling pathways by reactive oxygen species (ROS) and oxidative stress also plays an important role in muscle fiber adaptation during exercise. This review focuses on cellular and molecular responses that regulate the adaptation of skeletal muscle to exercise and exercise-related injuries.

Published by Elsevier Inc.

1. Introduction

Skeletal muscle is a highly dynamic tissue that undergoes continuous remodeling in response to various metabolic and functional demands. The quantity and quality of muscle can be traced down to the structural and contractile proteins that respond to physiological and pathological conditions including exercise and injury [1]. Individual muscle fibers vary in their mechanical, biochemical and metabolic properties depending upon the fiber type. Various criteria have been used to classify fiber types including histochemical methods [2,3], speed of twitch contraction [4], fatigability, dominant enzymatic pathway and the myosin heavy chain (MyHC) isoform expression [5]. Of those, MyHC isoforms are the most frequently used classification criteria and are considered the molecular markers of fiber types. Myosin is the molecular motor and the prime driving protein in force generation. It is also the most abundant protein in the sarcomere comprising ≈25% of the total muscle proteins [6]. Due to its abundance and contractile significance, qualitative and quantitative changes in myosin and its isoforms have significant effects on muscle strength. Human limb muscles contain three isoforms of MyHC called type I, type IIa and type IIx, and a fiber can express a single MyHC isoform (i.e., pure fiber) or co-express multiple isoforms (i.e., hybrid fiber) [7]. Rodent muscles additionally contain type IIb and IIx fibers [8]. Type I fibers are called slow-twitch fibers because of their slow speed of contraction. They have a predominantly oxidative metabolism. Type IIb and IIx fibers are fast-twitch fibers because of their fast speed of contraction. They mainly metabolize glucose by glycolytic pathway. Type IIa fibers are intermediate fibers with fast speed of contraction but mixed (glycolytic/oxidative) metabolism [9]. The frequency of hybrid fibers increases under various stimuli and relates to high degree of muscle plasticity, with exercise and disuse being prime determinants of muscle fiber type transition [10,11]. Because fiber type diversity is associated with functional diversity, alterations in muscle fiber types affect contractile, metabolic and biochemical properties of the muscle.

Exercise training is one of the prime modulators of muscle plasticity as it triggers a series of intracellular signaling pathways which mediate muscle growth and adaptation [12]. These

Abbreviations: ATF, Activating Transcription Factor; CaMK, Ca^{2+}/Calmodulin-dependent protein kinase; CAT, Catalase; CREB, cAMP Response Element-binding Protein; EE, endurance exercise; ER α, Estrogen Receptor α; FOXO, Fork Head Box; GLUT-4, Glucose Transporter-4; GPX, glutathione peroxidase; GR, Glucocorticoids Receptor; HIF 1-α, hypoxia inducible factor 1-α; HNF4, Hepatocytes Nuclear Factor-4; IGF-1, Insulin like Growth Factor-1; LXR, Liver X Receptor; MAPK, Mitogen Activating Protein Kinase; MEF-2, Myocytes Enhance Factor-2; MND, myonuclear domain; LDH, Lactate Dehydrogenase; MRF, myogenic regulatory factor; MyHC, myosin heavy chain; NFAT, nuclear factor of activated T-cells; NFκB, nuclear factor κB; NMJ, Neuromuscular Junction; NRF, Nuclear Factor Eryhtoid-2 related factor; PFK, Phosphofructo Kinase; PGC-1, proliferator-activated receptor-ϒ coactivator-1α; PPAR α, Peroxisome Proliferator-activated Receptor α; RE, resistant exercise; Rheb, Ras homolog enriched in brain; RNS, reactive nitrogen species; ROS, reactive oxygen species; SDH, Succinate Dehydrogenase; SOD, superoxide dismutase; VEGF, Vascular Endothelial Growth Factor; TR, Thyroid Receptor

* Corresponding author.
E-mail address: Holly-VanRemmen@omrf.org (H. Van Remmen).

http://dx.doi.org/10.1016/j.freeradbiomed.2016.03.025
0891-5849/Published by Elsevier Inc.

adaptations include changes in contractile proteins structure and function [13], satellite cells and myonuclei [14], mitochondrial homeostasis [15], metabolic profile [16] and muscle capillary density [17]. Different modalities of exercise are possible depending upon the type, intensity and duration of contraction.

Contractile activity generates a complex set of reactive oxygen species (ROS) and reactive nitrogen species (RNS) in the skeletal muscle. These reactive species can positively or negatively modulate muscle force generation depending upon the concentration and temporal pattern on ROS generation [18], and play important role in contraction-induced muscle adaptation [19]. For the purpose of this review we will mainly focus on endurance (aerobic) exercise (EE) and resistance (strength) exercise (RE) which have become central issues in sports science and clinical settings. While these two types of exercises have many combined health benefits, they have been studied distinctly because of their divergent effects on various muscle parameters discussed later in this review. We will review the impact of muscle fiber type heterogeneity on exercise performance. We will also discuss various types of exercise affecting muscle fiber type diversity and the role of ROS production in this process. In the final section of this review we will highlight exercise-induced injuries and regeneration potential of skeletal muscle and individual fiber types.

2. Muscle fiber type diversification and exercise performance

2.1. Muscle fiber types

There are four major fiber types found in the skeletal muscles of limb and trunk in various proportions. The relative proportion of the fiber types in a given muscle may vary according to specie and the functional assignment of the muscle [8,20]. The diverse population of the muscle fibers in a given muscle allows for various types of tasks ranging from prolonged, low intensity contractions (e.g., to maintain posture) to fast and strong maximal contractions (e.g., kicking). This tremendous range of tasks is attributed to diversity in functional cell compartments in individual muscle fibers including membrane excitability, calcium transients, energy supply systems and the contractile machinery in the sarcomere (Fig. 1).

The diversity of muscle fibers allows them to perform specialized functional tasks. Thus the type I fibers with high oxidative capacity and capillary density are more suitable for endurance exercise [21] while type IIb fibers with low oxidative capacity and capillary density are suitable for short term RE [22]. Type IIa are the intermediate fiber types that allow high power generation at a considerable velocity with good endurance.

2.2. Muscle fiber type plasticity

The fiber type composition of a muscle, once thought to be genetically determined [23], is highly plastic and can be altered in response to functional demands including neuromuscular stimulation [24], mechanical loading [25], hormones [26] and aging [27]. Exercise induced changes in fiber type transition are determined by frequent nerve stimulation resulting in an increased duration of elevated cytosolic free Ca^{2+} [28]. It is believed that calcineurin, a calcium regulated serine/threonine phosphatase plays central role in fiber type specific gene regulation. Indeed, selective up regulation of calcineurin promotes type I fibers gene products while inhibition of calcineurin promotes type II fibers-specific gene activity [29]. This fiber type switching is controlled via calcineurin mediated activation of nuclear factor of activated T-cells (NFAT), which are a family of transcription factors involved in nerve activity sensing and calcium regulation [30]. A number of other transcription factors, co-activators and co-repressors have also been associated with fiber type switching and have been comprehensively reviewed elsewhere [31].

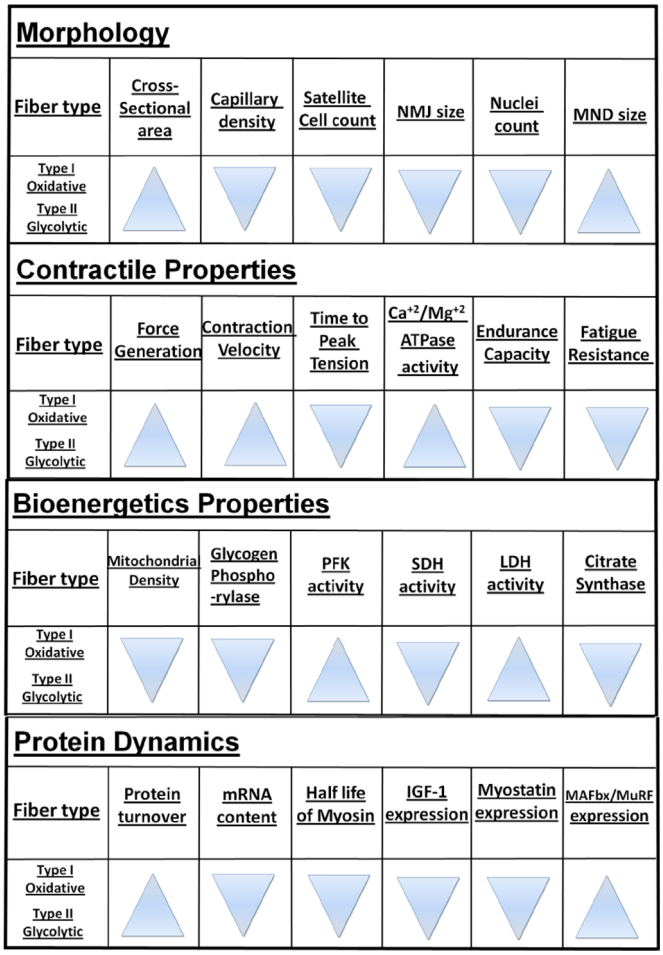

Fig. 1. Characteristics of individual fiber types in mammalian skeletal muscles. NMJ (Neuromuscular Junction); MND (Myonuclear Domain); PFK (Phosphofructo Kinase); SDH (Succinate Dehydrogenase); LDH (Lactate Dehydrogenase); IGF-1 (Insulin like Growth Factor-1).

2.3. ROS generation by muscle fibers

Marked differences exist between fast and slow twitch fibers with regard to production and metabolism of reactive oxygen species. Amplex red measurements of H_2O_2 from permeabilized muscle fibers [32] and isolated mitochondria [33] show up to three fold higher H_2O_2 release in fast-twitch gastrocnemius compared to slow-twitch soleus muscle in the presence of complex I or complex II substrate. This difference is attributed to fiber type-specific variations in endogenous H_2O_2 scavenging capacities. Indeed, direct measurements from isolated permeabilized fibers show that the mitochondria from slow-twitch fibers have an approximately two fold higher H_2O_2 scavenging capacity compared to mitochondria from fast-twitch fibers [34]. Further, the slow-twitch fibers also show higher activities of anti-oxidant enzymes superoxide dismutase (SOD) [35], glutathione peroxidase (GPX) [36] and Catalase (CAT) [37] compared to fast-twitch fibers. These differences are attributed to differential expression of proliferator-activated receptor-Υ coactivator-1α, PGC-1α and PGC-1β. This transcription coactivator, apart from inducing mitochondrial biogenesis also regulates the expression level of key antioxidant enzymes described above [38]. Taken together, these data highlight striking differences between H_2O_2 emitting capacity and buffering potential between two fiber types.

3. Endurance exercise

Endurance exercise (EE) is characterized by repeated, sustained, low intensity contractions for a prolong period of time without getting fatigue. The term generally refers to training the aerobic system (Krebs cycle, oxidative phosphorylation) versus the anaerobic system. The force production is relatively small (≈ 30%) relative to maximum force-generating capacity of the muscle [39]. Examples of this type of exercise include long distance running, cycling and swimming. EE involves maintaining a given power output for longest possible time and is characterized by numerous physiological benefits (Table 1).

Endurance training results in changes in muscle fiber type composition which are mainly restricted to type II fibers and involve a transformation from IIb to IIa fibers resulting in a more oxidative muscle [40]. Type I fibers are more economical in energy utilization during the cross-bridge cycle (i.e., lower adenosine triphosphatasae activity) compared to type II fibers, and are hence important in the energy efficiency of the muscle. The response in contractile properties of individual fibers is mainly limited to contractile speed where fast-twitch fibers become slower and slow-twitch fibers become faster. These changes in contractile speed are attributed to a shift in myosin light chain isoforms from fast to slow and slow to fast type, for the two isoforms respectively [40,41].

3.1. EE enhances mitochondrial biogenesis

A hallmark response of endurance training is mitochondrial biogenesis [42] coupled with improved functional parameters of mitochondria [43]. These responses might be linked to changes in concentrations of cellular metabolites which occur after chronic stimulation of skeletal muscle [44]. For instance, 6 weeks of exercise training increases the muscle mitochondrial content by ≈ 50–100% [45]. An increase in number and volume of mitochondria is attributed to but not limited to increased PGC-1α expression [46–48], the master regulator of mitochondrial biogenesis (Fig. 2). This is further supported by blunting of exercise-induced mitochondrial biogenesis in mice deficient for PGC-1α [49]. PGC-1α has four different isoforms (PGC-1α1, PGC-1α2, PGC-1α3, PGC-1α4) with alternate promoter usage and splicing of the primary transcript [50, 51]. Among them, PGC-1α1 which transcribes proximal promoter of PGC-1α gene, gets activated in response to EE and is mainly involved in oxidative phenotype (Fig. 2).

This phenotype is achieved via a group of nuclear and mitochondrial transcriptional factors summarized in Table 2.

To our knowledge the exercise-induced role(s) of PGC-1α isoforms are not studied in a fiber type-specific manner.

Among the human muscle fiber types, the mitochondrial content is highest in type I fibers followed by type IIa and type IIx fibers (Fig. 1) [62,63]. All three fiber types show an increase in PGC-1α expression after 6 weeks of exercise [21,64]. The response is intensity-specific whereas lower intensity exercise (≈ 50% VO_{2max}) predominantly increase the mitochondrial volume in type I fibers while much higher intensity exercise is required to recruit mitochondria in type II fibers [21,65]. These changes might delay the recruitment of type II fibers during the exercise helping the muscle energy efficiency in a positive manner [66]. In addition to

Table 1
Skeletal muscle adaptive response to endurance and resistant exercises. ↔, No change; ↔↑ no change or small effect; ↑, small effect; ↑↑, large effect.

	Endurance exercise	Resistance exercise
Muscle hypertrophy	↔	↑↑
Muscle strength	↔	↑↑
Muscle fiber size	↔↑	↑↑
Myofibriller protein synthesis	↑	↑↑
Satellite cells count	↑	↑↑
Myonuclei count	↔↑	↑↑
Lactate tolerance	↑↑	↔↑
Glycolytic function	↑	↑↑
Mitochondrial volume	↑↑	↑
Mitochondrial protein synthesis	↑↑	↔↑
Capillary density	↑↑	↔
Oxidative function	↑↑	↔↑
Endurance capacity	↑↑	↔↑

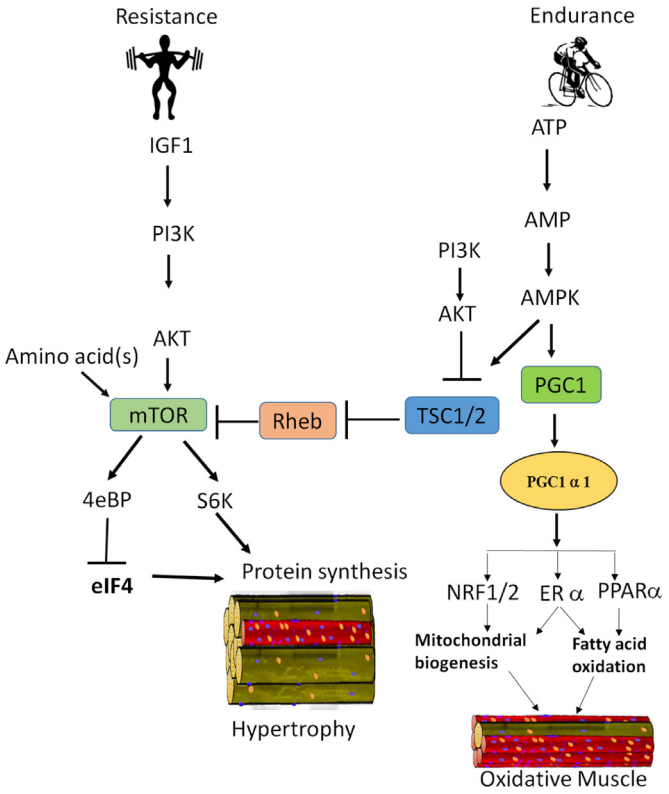

Fig. 2. Intracellular signaling pathways regulate different muscle phenotypes in response to resistant and endurance exercises.

Table 2
List of transcription factors interacting with PGC-1α to regulate genes involved in muscle adaptation process to exercise. NRF (Nuclear Respiratory Factor); PPAR (Proliferator Peroxisome-Activated Receptor); ERR (Estrogen Related Receptor); TR (Thyroid Receptor); LXR (Liver X Receptor); MEF2 (Myocytes Enhancer Factor 2); FOXO (Fork Head Box); ATF2 (Activating Transcription Factor 2); CREB (cAMP Response Element Binding Protein).

Transcription factors/nuclear receptors	Function	Reference
NRF1	Mitochondrial respiratory capacity and glucose transport	[52]
NRF2	Muscle regeneration and metabolic regulation	[53]
PPAR α, β/δ	Fatty acid oxidation	[54]
ERR α,β/δ	Homeostasis and regeneration	[55]
TR β	Homeostasis and repair	[56]
LXR α,β	Fatty acid oxidation	[57]
MEF2	Homeostasis and repair	[58]
FOXO1	Homeostasis and mitochondrial metabolism	[59]
ATF2	Metabolic adaptation	[60]
CREB	Muscle regeneration and homeostasis	[61]

mitochondrial content, the dynamic regulation of fission and fusion machinery is also considered integral part of muscle metabolic adaptation. Mitochondrial fusion is mainly controlled by mitofusion 1 and 2 (MFN 1 and MFN 2) in the outer mitochondrial membrane and optic atrophy type 1 (OPA 1) in the inner mitochondrial membrane. Fission is mainly controlled by dynamin-related protein 1 (Drp1) and its recruitment factors fission 1 (Fis1) and mitochondrial fission factor (MFF) in the outer membrane [67]. Chronic exercise triggers the expression of mitofusion 1 and 2 [68,69] which leads to increased mitochondrial volume. It is postulated that the elongated mitochondrial networks facilitate rapid transmission of membrane potential across greater distances in the cell [70]. Further, the fission machinery responds to EE by increasing the expression of DrP1 and Fis1 [68,71,72] although this effect is blunted in the presence of insulin resistance [73]. Hence, fission might be required to remodel the reticulum during proliferation and/or re-locate parts of it via fragmentation [70].

In addition to mitochondrial biogenesis and remodeling, EE-induced muscle adaptation likely requires effective removal of damaged and/or dysfunctional mitochondria. Mitophagy is an evolutionary conserved process for lysosome-dependent degradation of mitochondria. The regulatory effects of EE on skeletal muscle mitophagy are only beginning to emerge. EE along with mild caloric restriction prevents the age-related reduction in basal autophagy in the rat skeletal muscle [74] which is a beneficial effect as deficiency in basal autophagy is associated with muscle damage [75]. Recently, EE was shown to induce the expression of mitophagy protein Bnip3 along with basal autophagy markers in the mouse skeletal muscle [76]. Using the exercise-trained mice heterozygous for critical autophagy protein Atg6 the authors also showed that an attenuated increase of basal autophagy and mitophagy is associated with compromised endurance capacity. These findings demonstrate that EE-induced increase in basal autophagy and mitophagy is required for improved physical performance.

Together these findings elicit the complex interplay of the mitochondrial remodeling machinery involved in mitochondrial biogenesis, maintenance and clearance in the skeletal muscle. EE positively modulates each of these processes as part of muscle adaptation response towards enhanced metabolic and contractile capacity.

3.2. EE improves cellular aerobic fitness

In addition to enhancing mitochondrial biogenesis, EE also triggers an up-regulation of mitochondrial enzymes involved in the krebs cycle, electron transport chain and heme synthesis [77]. Additionally there is an up-regulation of enzymes involved in fatty acid oxidation and of the proteins mediating glucose entry (glucose transporter-4) into the cell [78,79]. Hence the relative contribution of fat to the muscle energy generation is greatly increased [80] along with a reduction in the rate of glycogen depletion [81] following EE. These adaptations improve the cellular capacity to generate ATP aerobically and the sensitivity of respiratory control in both type I and type II fibers during exercise [82]. EE alters many cellular properties resulting in enhanced aerobic capacity of the muscle fiber without changing the mean cross-sectional area. Both type I and type II muscle fibers show an increment in capillary density in response to EE [83,84]. An increase in myonuclear count per unit fiber length is reported in rats [85] and humans [86] in response to swimming and cycling, respectively. Since the fiber size is unaltered, the cytoplasmic volume per myonucleus (myonuclear domain) decreases optimizing the internuclear cooperation in metabolically active fibers. However, some studies report no increase in myonuclei content with EE [85,87]. In contrast, the amplification of muscle satellite cell pool is a consistent finding in mouse [88], rat [89] and humans (Table 1) [87]. Hence, the muscle mass regulation and the expansion of satellite cells pool appear to work independently (at least partly) in EE. These findings indicate that the EE increases the muscle oxidative and regenerative potential by increasing the proportion of slow myosin, mitochondria, capillaries, nuclei and the satellite cells pool. These adaptations allow the athlete to exercise long for a given intensity or increase the intensity for a given exercise time in an energy efficient way. This is reflected by an improvement in all four parameters of aerobic fitness with EE, the maximal oxygen uptake ($VO_{2\ max}$), exercise economy, the lactate/ventilatory threshold and the oxygen uptake kinetics [90–92].

4. Resistance exercise

Resistant exercise (RE) involves low-frequency, high intensity contractions against an external resistance with the aim of increasing the muscle bulk. Force production is high and in general $\approx$80% of maximum power output is considered optimal [93,94]. Typical activities under this module include body building and weight lifting.

4.1. RE induces muscle fiber hypertrophy

It is generally believed that the hypertrophy of existing muscle fibers following RE is predominantly, if not entirely due to muscle hypertrophy from the addition of new sarcomeres and myofibrils in parallel [95] alongside increases in the amount of contractile motor proteins actin and myosin [96]. Growth and proliferation of individual myofibrils has been reported in muscle fiber hypertrophy due to resistance training [97]. These authors reported no change in myofibrillar density indicating an addition of myofibrils to the periphery of the muscle fiber. This is consistent with the finding of incorporation of new proteins at the periphery of muscle fiber. The increase in contractile proteins is mirrored by an increase in number of myosin cross-bridges resulting in concomitant increase in muscle fiber diameter and force-generating capacity. In addition to contractile proteins, mixed, mitochondrial and cytosolic proteins synthesis rates also increase [98,99] in response to bouts of RE. These responses are dose dependent and increase with increasing exercise intensity [99]. Further, RE also induces an increase, albeit proportionally smaller one in muscle protein degradation rate [100]. The rate of protein synthesis should supersede degradation for an extended period of time before hypertrophic response is evident [101,102].

RE leads to the preferential hypertrophy of type II fibers [103,104]. Indeed, type II fibers show greater plasticity in size when compared to type I fibers, in response to various mechanical stimuli. They hypertrophy and atrophy more rapidly in response to exercise and detraining. This phenomenon is evident in short-term (6–10 weeks) RE which only lead to type II fibers hypertrophy [105–107]. The longer studies, on the other hand report an increase in both type I and type II fibers area [108,109]. In a given muscle, type II fibers have slightly larger cross-sectional area [110] and specific force [111] than type I fibers. Hence the proportion of type II fibers is positively correlated with hypertrophy [112] and strength [113] in response to 'RE'.

In contrast to EE, RE has smaller effect on mitochondrial volume and PGC-1α protein content. However, subcellular localization rather than total muscle PGC-1α content might be a better indicator of PGC-1α activity [114,115]. Immunofluourescence imaging shows that the PGC-1α is localized both in the nucleus and the cytoplasm. The subcellular distribution predominantly shifts to the nucleus during early response to the oxidative stress [114]. Indeed, nuclear PGC-1α protein is shown to preferentially

increase in response to low volume high intensity exercise [116] so that more PGC-1α is present in nucleus for the initial adoptive response to training. Further, PGC-1α4, an isoform of PGC-1α, is specifically expressed in response to RE in humans and regulates hypertrophic phenotype by inducing IGF-1 and repressing myostatin [51]. It is also shown to prevent skeletal muscle atrophy due to cancer-cachexia in mice [51]. However the precise role of PGC-1α4 in regulating skeletal muscle hypertrophy is controversial as it was not linked with chronic overload associated hypertrophy in synergistic-ablation mouse model [117]. The authors found no increase in p-Akt^{T308} in the synergistically ablated mice muscle and argue that this mode of hypertrophy is P13K-independent and hence might not involve PGC-1α4.

4.2. RE increases satellite cells and myonuclei count

A growing body of literature suggests that the number of satellite cells increases in response to short- [118–120] and long-term [121–123] resistance training (Table 1). This increase seems to occur in a fiber type-specific manner, and is mainly observed in type II fibers [124,125], despite the fact that the type I fibers contain a higher number of baseline satellite cells population [125,126] than type II fibers. The increment in satellite cells population of type II fibers is correlated with robust hypertrophy of these fibers in response to RE. Typically, a satellite cell undergoes mitosis and donates one of the daughter cells as a true myonucleus to the muscle fiber [127]. The new myonucleus, while in a post-mitotic stage, begins to produce muscle specific proteins that increase muscle size [128]. The increase in myonuclei counts, although a consistent finding in most hypertrophies [129,130] generally lags behind increase in fiber volume [131]. These findings support the notion of myonuclear 'ceiling' whereby existing myonuclei can support initially hypertrophy via enhancing protein synthesis [102,131] without the need for further myonuclear accretion. Once a certain 'threshold' for transcriptional activity is reached, further nuclei via satellite cells divisions are required to support hypertrophy [132–134]. Further, the ceiling limit differs for hypertrophy with and without functional competence where increase in size parallels or lags behind increase in force [135]. Despite these findings, the role of satellite cells in overload-induced muscle hypertrophy is still debated [136] and hypertrophy without satellite cells incorporation is reported in rodent models of satellite cells depletion [137,138]. For instance, ablation of $>90\%$ of satellite cells in mature mice skeletal muscle did not blunt the overload-induced hypertrophy in plantaris muscle [138]. However ≈ 2 fold increase in muscle weight within a short span of time may not adequately represent human adaptation [139]. Further, in humans a huge range of inter-subject variability is reported in hypertrophic response, and is attributed to variable sensitivity of mechanotransduction machinery to mobilize satellite cells [121,128,140].

4.3. RE enhances muscle net protein synthesis

Muscle hypertrophy is driven by net protein accretion with protein synthesis superseding degradation [102,141]. The acute response is intensity-dependent and is minimal at intensity $<40\%$ of one-repetition maximum (1-RM) but is 2–3 fold higher when muscle is activated at $>60\%$ of 1-RM intensity [99]. This suggests that the acute bouts of RE generate an anabolic response in a dose-dependent manner. The magnitude of response gets progressively smaller with time and is blunted by 3–6 weeks [142], reflecting desensitization of muscle anabolic machinery with repeated RE [143]. Not all the muscle proteins fractions respond to RE stimulus. Myofibriller proteins show a preferential increase in synthesis rate in the individuals trained for RE [144–146] along with smaller increase in protein breakdown [147]. However, this distinct response is blunted in untrained individuals where RE stimulus shows an additional increase in mitochondrial protein synthesis [146]. This is evident by an up regulation of mitochondrial enzymes involved in citric acid cycle (citrate synthase; [148,149]) and glucose phosphorylation in response to RE in untrained individuals. This is attributed to 'unfamiliarity' of exercise stimulus with larger disturbance of muscle homeostasis.

Muscle protein synthesis during hypertrophic response is induced through mechanical strain on the sarcolemma which induces signaling pathways through focal adhesion kinase (FAK), an attachment complex protein [150]. Activation of FAK induces mTOR which drives the mechanosensory pathways by activating P70^{S6K}, causing protein accretion (Fig. 2). This hypertrophic response is attenuated by the mTOR inhibitor, rapamycin [151] demonstrating the critical role of mTOR in muscle hypertrophy. mTOR enhances translational capacity and efficiency of muscle proteins leading to muscle fiber enlargement. These effects are primarily achieved via regulation of multiprotein complex mTORC1 [152] which relays signaling to P70^{S6K} and 4E-BP1. These effects are fiber-type specific and are more pronounced in muscles containing larger proportion of type II fibers [153,154] as against muscles primarily containing type I fibers [154]. Indeed, mTOR phosphorylation preferentially increases in type II fibers for up to several hours after a bout of RE [154]. Further, RE results in a greater phosphorylation of S6K1 in type II fibers compared to type I fibers [155] in alignment with preferential type II fibers hypertrophy. The subcellular localization of these two proteins also plays an important role in protein synthesis. Both the activation and phosphorylation of P70^{S6K} and 4E-BP1 have been correlated with nuclear mTOR, as nuclear import of mTOR enhances and export attenuates the phosphorylation/activation [156]. Similarly, using immunofluourescence staining p-S6K1 has primarily been found to localize in nucleus in pre-exercised status and in cytosol after the RE [155]. In accordance with the fiber type specific response these localizations are more pronounced in type II compared to type I fibers.

5. Eccentric exercise, injury and regeneration

Exercise induced injuries are common to the muscle and mostly involve eccentric or lengthening contraction. Such contractions, if not performed carefully, can cause excessive sarcomere strain leading to cellular membranes disruption and myofibrillar damage [157]. Type II fibers are more susceptible to such damage compared to type I fibers in humans [158], rabbit [159] and rodents [160]. This is attributed to ultrastructural and metabolic differences between two fiber types and is discussed in detail later in this review.

5.1. Ultrastructural changes in muscle fiber injury

Most of the eccentric-exercise induced damage at the sarcomere affects Z-disk which are the sarcomeric anchors for muscle structural integrity [161]. Thus in a mild form of injury, Z-disks appear wavy (i.e., Z-disk 'streaming') with slight myofibrillar disarray. In more severe cases, Z-disks disruption, thickening, focal losses and displacement into adjacent sarcomere are reported [162]. These changes are accompanied by disruption of other cytoskeletal elements especially desmin. Desmin is an intermediate filament that integrates the sarcolemma, Z-disk and nuclear membrane thus maintaining the longitudinal and transverse passive mechanical properties of the muscle fiber [163]. Eccentric contractions cause a segmental and rapid loss of desmin intermediate filaments that is not observed in inactivated muscle [164]. Further, the number of desmin-null fibers increases with repeated bouts of eccentric contractions, and the fibers lacking desmin

accumulate plasma fibronectin, indicating a loss of membrane integrity [164]. These changes are accompanied by disruption of the sarcomere [165], cytoskeleton elements [166] and sarcolemma [167], swollen mitochondria [158], displaced organelles [168] and impaired excitation–contraction coupling [169] resulting in reduced force generation [170].

5.2. ROS involvement in muscle injury

It is well established that the contracting skeletal muscle produces excess free radicals which are involved in regulating muscle adaption and function [171]. An augmented production of these free radicals during vigorous exercise produces oxidative stress.

ROS trigger pathways that regulate muscle adaptive changes to meet the physiological demand during exercise [172]. Indeed, moderate increase in ROS production in response to exercise stimulus is necessary for the remodeling of skeletal muscle [171]. However the effect of increased level of ROS on muscle structural integrity during strenuous exercise is still a subject of debate. Many studies report ROS involvement in exercise-mediated muscle injuries [173–175]. Increased level of ROS is detected following eccentric exercise using electron paramagnetic resonance spectroscopy [176] and indirect markers such as lipid peroxidation and protein oxidation [177]. It is postulated that the increased level of ROS may contribute to muscle injury as antioxidant supplements slightly attenuate the degree of delayed onset muscle soreness [174,178]. However, the ultrastructural damage due to eccentric exercise described above is not attenuated by anti-oxidants [179]. Further, ROS formation following eccentric exercise occurs after the maximal peak of muscle soreness has occurred [175]. Thus the precise relation between ROS and muscle structural damage following eccentric exercise remains unsubstantiated.

In contrast to the effects on muscle structure, the ROS mediated modulation of muscle force production is well characterized. Hence a modest increase in ROS in an unfatigued muscle positively modulates force production [180,181] as evident by antioxidants-mediated depression of force production [182,183]. However, when the ROS production crosses a certain threshold, a depression of force production and increased fatigue occur in skeletal muscle [184]. Conversely in such settings, antioxidant supplementation enhances the force production [185]. The modulation of force and fatigue properties by ROS and NO is achieved through numerous mechanisms including but not restricted to SR calcium regulation, myofilament structure and calcium sensitivity and mitochondrial ATP production [186,187]. Based on these findings a model was proposed where an optimal redox state is required for maximal isometric force production while a deviation from optimal redox state results in force depression [180].

Many signaling pathways are regulated by exercise-induced ROS generation leading to muscle remodeling. Among those, nuclear factor ƙB (NFƙB), mitogen activated protein kinase (MAPK) and PGC-1α play critical roles in the exercise physiology. Contractile activity triggers these pathways via increased H_2O_2 production. These pathways are involved in a wide variety of biological functions such as antioxidant defense, mitochondrial biogenesis, glucose transport and inflammation. A detailed description of these transcription factors is beyond the scope of this review and therefore, only a brief summary is presented. Readers are referred to several excellent reviews on this topic for detailed description [9,188–190].

NFƙB is a dimeric transcription factor in the sarcoplasm which is bound to its inhibitory subunit IƙB in its inactive form. Phosphorylation of IƙB releases P50/P65 subunits from NFƙB which then migrate to nucleus and bind to NFƙB binding sites of the promoter regions of a variety of target genes. NFƙB activation is redox sensitive and is blunted in response to reduced oxidative stress in exercising rats [191]. The peak DNA binding activity is reported 2 h after IƙB phosphorylation and acute exercise stimulus [192] and is mainly restricted to oxidative fibers with higher mitochondrial contents [193]. As a transcription factor, NFƙB regulates expression of over 150 genes including those encoding apoptosis, oxidative defense, disuse atrophy and redox status [194]. With regards to injury, NFƙB is tipped to facilitate post-exercise regenerative potential in the damaged tissues by inducing acute phase proteins and proinflammatory genes [190]. Indeed, increased inflammation and protein turnover are prerequisites for exercise-induced hypertrophic and regenerative response [195].

The MAPK constitute a family of serine/threonine kinases that control multitude of cellular processes including muscle repair and growth. The pathways are activated by both extracellular (inflammatory cytokines, growth factors) and intracellular (ROS) activators. MAPK pathways are activated during exercise and regulate various muscle responses to exercise including hypertrophy, upregulation of antioxidant enzymes and fiber type transitions. These effects are severely hampered by treatment with xanthine oxidase inhibitors eliciting redox sensitivity of MAPK [191]. The physiological relevance of MAPK cascades in tissue repair process is elicited by their activation in the immediate vicinity of injury site in the human skeletal muscle [196]. Indeed, dysfunctional MAPK signaling via deletion of its upstream regulators play an important role in regenerative myogenesis and in the pathogenesis of muscular dystrophies [197].

PGC-1α is considered a redox signaling pathway because ROS generated by exercise promote its expression along with its target genes [198]. Its role in exercise and muscle plasticity is discussed elsewhere in this review.

Many studies report ROS involvement in exercise-mediated muscle injuries [173–175]. Increased level of ROS is detected following eccentric exercise using electron paramagnetic resonance spectroscopy [176] and indirect markers such as lipid peroxidation and protein oxidation [177]. It is postulated that the increased level of ROS may contribute to muscle injury as antioxidant supplements slightly attenuate the degree of delayed onset muscle soreness [174,178]. However, the ultrastructural damage due to eccentric exercise described above is not attenuated by anti-oxidants [179].

Further, ROS formation following eccentric exercise occurs after the maximal peak of muscle soreness has occurred [175]. Thus the precise relation between ROS and muscle damage following eccentric exercise remains unsubstantiated.

5.3. Why are fast-twitch fibers more susceptible to eccentric exercise-induced damage?

Preferential damage to fast-twitch type II fibers due to eccentric exercise was first reported more than three decades ago [199] in human vastus lateralis muscles with a damage ratio of 3:1 between type II and type I fibers. These findings were subsequently confirmed in human gastrocnemius and biceps brachii muscles too [200]. Many animals and humans studies confirm these findings. For example, human quadriceps muscle show preferential type II fibers damage 72 h after plyometric exercise [158]. Similar findings have been reported in flexor muscles of elbow and foot [200]. Previously, this was attributed to early fatigue and prolongs rigor binding state of fast-twitch fibers causing mechanical damage when rigor fibers are stretched [201]. However subsequent studies found that the fatigued fibers are less susceptible to eccentric exercise induced damage [202,203].

It is now believed that the ultra-structural differences between the two fiber types account for higher vulnerability to damage of type II fibers (Fig. 3).

These cytoskeletal elements maintain structural integrity of muscle fiber during repeated mechanical stress and thus prevent it

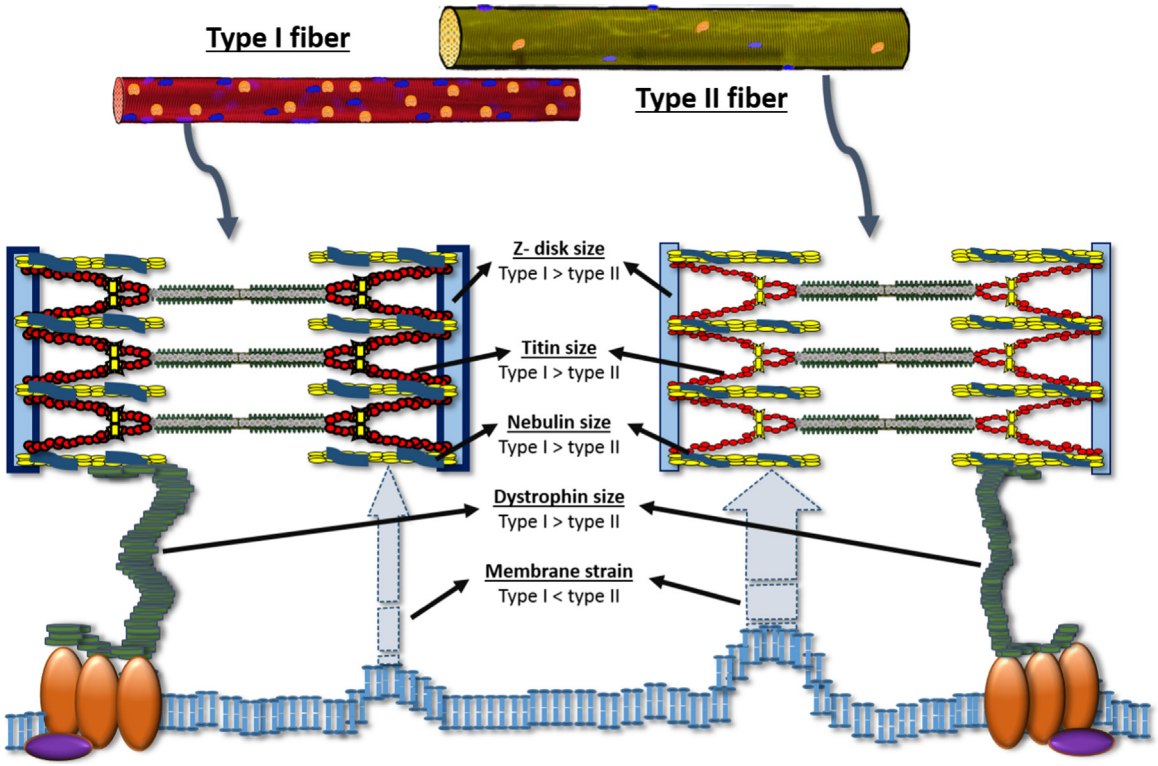

Fig. 3. Ultrastructural differences between type I and type II fibers related to exercise-induced damage. Type II fibers are more susceptible to injury due to smaller Z-disk, titin, nebulin and dystrophin as well as higher strain on the sarcolemma.

from injury. Type II fibers have narrow Z-disks [158] compared to type I fibers which reflect fewer attachments for sarcomeric filaments [204]. Type II fibers also express smaller isoforms of nebulin and myomesion which play important roles in sarcomeric assembly [205]. Further, adherent protein titin which spans half the sarcomere and regulates sarcomeric integrity is distinctly expressed in two fiber types. Type II fibers express low molecular weight, less elastic isoform than type I fibers [206] resulting in reduced resistance to strain. The structural vulnerability of cytoskeleton and sarcomere is compounded by the higher vulnerability to degradation of desmin and troponin T in type II fibers [207]. When the sarcomere contract, the longitudinal force vector is transmitted to the sarcolemma, hence sarcolemma integrity is pivotal to muscle fiber structural integrity. Dystrophin, a sarcolemma associated cytoskeletal protein has two fold higher content in type I compared to type II fibers [208]. Thus the type II fibers have less ability to absorb strain on the outer membrane. These fibers also have slightly higher specific force than type I fibers [111]. Thus, more force is exerted per unit surface area of sarcolemma in type II fibers. Compounded by structural weakness, this makes type II fibers inherently vulnerable to strain-induced damage. This vulnerability has been studied in a fiber type-specific manner where single fibers were subjected to standardized eccentric contractions and the force generating capacity was studied before and after contractions [209]. Force generation and force deficit before and after eccentric contractions were in harmony so that the stronger fibers showed greater force loss following eccentric contraction. In an isoform-specific manner, fibers expressing stronger and faster isoforms showed more damage.

In addition to structural proteins, type II fibers also express decreased level of ‘stress proteins’ including heat shock proteins that protect the fiber from mechanical stress during eccentric contractions and also accelerate recover after the stress stimulus is gone [210]. These fibers also have less regenerative capacity than type I fibers due to smaller number of nuclei and satellite cells.

6. Regeneration

The remarkable ability of skeletal muscle to induce repair and regeneration following injury is well documented [211,212]. Activation and proliferation of muscle satellite cells are key components of this process. This is evident by impaired regeneration after local depletion of satellite cells following exercise-induced muscle injury [213]. The muscle regenerative capacity is rescued by the transplantation of $Pax7^{+}$ satellite cells showing that the satellite cells are essential for acute injury related regeneration. Satellite cells are associated with all fiber types albeit with unequal distribution. For instance, slow-twitch muscles express two- to three-folds higher satellite cells density when compared to fast-twitch muscles [214,215]. These findings are reported in single muscle fibers too [216]. Further, phenotype of satellite cells from adult muscle fibers is similar to their fiber of origin and the fiber they tend to form [217,218]. This distinction also applies to various fiber types within the same muscles and points towards differential programming of different satellite cells.

Upon injury, quiescent satellite cells get activated and start proliferating, and are now referred to as adult myoblasts. The activation of adult myoblasts is characterized by up regulation of myogenic regulatory factors (MRFs), *Myf5* and *MyoD* while fusion is mediated by cell adhesion molecule M-cadherin although N-cadherin and R-cadherin can compensate for its deficiency. A detailed description of these molecular regulators of muscle regeneration can be found elsewhere [211]. Early stages of regeneration are characterized by expression of developmental myosin isoforms [219] followed by a switch to adult isoforms under the control of nerve activity. The type of default switch to adult myosin isoform type depends on the innervation status of the muscle. Thus the regenerating rat soleus muscle acquires adult slow-twitch profile when innervation is intact and fast-twitch profile when denervated [220,221]. Further, low frequency stimulations of the denervated soleus muscle capitulates the slow

twitch profile showing that the impulse frequency of the motor neurons dictates the muscle fiber type profile during regeneration [222].

7. Signaling pathways regulating fiber type switching

A sophisticated signaling network controls exercise-induced fiber type profiling within skeletal muscle. This network senses intracellular calcium concentration and metabolic stress to activate various transcription factors involved in fiber type transition. Indeed the type and activity of contraction determines intracellular calcium concentration [223] and different signaling pathways are activated by various intracellular calcium concentrations promoting fast or slow phenotype. The regulation is antithetical so that the promotion of fast phenotype causes repression of slow phenotype and vice versa. The slow-twitch phenotype is predominantly promoted by the activation of calcineurin-dependent nuclear factor of activated T-cells (NFAT) transcription factors [224] as blockage of this pathway blunts the slow phenotype promoting activity in the muscle [29]. Further, Ca^{2+}/Calmodulin-dependent protein kinase (CaMK) which decodes frequency dependent information [225] also induces exercise-induced slow phenotype by activating MEF2 transcription factors. Conversely, transgenic mice with a hyperactive form of MEF2 show an increased proportion of slow-twitch fibers and enhanced running endurance when compared to wild-type counterparts [226]. PGC-1α and PPARβ also participate in regulating slow oxidative phenotype [227] in response to EE, although PGC-1α is probably more involved in maintaining rather than inducing a slow-twitch phenotype [228].

Relatively less is known about the signaling pathways regulating switch from slow to fast phenotype during intense exercise. Skeletal muscle reprogramming from slow oxidative to fast glycolytic phenotype involves members of the Six1/Eya1 complex that are found in higher concentration in the nuclei of fast gastrocnemius compared to slow-switch soleus muscle. Moreover they induce the transition from oxidative to glycolytic phenotype when overexpressed in soleus muscle [229]. The muscle glycolytic enzymes activity during intense exercise is regulated by hypoxia inducible factor 1-α (HIF-1α) as shown by altered exercise endurance with deletion of HIF-1α [230]. The expression of myogenesis regulatory protein, MyoD is different in fast- and slow-twitch muscle fibers and thus influences the fiber type composition of muscle [231]. Indeed over-expression of MyoD is associated with increase number of fast-twitch glycolytic fibers in predominantly fast- [232] as well as slow-twitch muscles [233]. These findings are consistent with the hypothesis that the MyoD is required for fast glycolytic fibers formation.

8. Conclusion

Skeletal muscle is a very dynamic tissue which is composed of individual muscle fibers with a dynamic range of chemical, biomechanical and physiological properties. The presence of diverse fiber types with distinct ranges of adaptability reflects muscle plasticity to various external stimuli including exercise training. Endurance and resistant trainings on account of different intensity and duration reflect specific patterns of mechanical strain which prepare muscle to various functional tasks. This is achieved by modulating muscle fiber phenotype in a predetermined range of adaptation as well as fiber type switching to desired phenotype. Another area of attention in this review is exercise-induced injuries and the mechanisms of susceptibility of type II fibers to damage. Signaling pathways controlling fiber type diversification and maintenance during muscle adaptation process are briefly summarized. Promoting muscle fiber type switching and modulating specific fiber types can help to counter various muscle wasting conditions. This would help to build therapeutic strategies for targeted exercise interventions based on mode, duration and intensity of exercise.

Acknowledgment

This work was supported by a Merit Review Award # 1I01BX002595-01 from the United States (U.S.) Department of Veterans Affairs.

References

[1] B. Blaauw, S. Schiaffino, C. Reggiani, Mechanisms modulating skeletal muscle phenotype, Comp. Physiol. 3 (2013) 1645–1687.
[2] L. Guth, F.J. Samaha, Qualitative differences between actomyosin ATPase of slow and fast mammalian muscle, Exp. Neurol. 25 (1969) 138–152.
[3] H.J. Green, H. Reichmann, D. Pette, A comparison of two ATPase based schemes for histochemical muscle fibre typing in various mammals, Histochemistry 76 (1982) 21–31.
[4] R.E. Burke, D.N. Levine, P. Tsairis, F.E. Zajac III, Physiological types and histochemical profiles in motor units of the cat gastrocnemius, J. Physiol. 234 (1973) 723–748.
[5] L. Larsson, R.L. Moss, Maximum velocity of shortening in relation to myosin isoform composition in single fibres from human skeletal muscles, J. Physiol. 472 (1993) 595–614.
[6] P. Balagopal, O. Ljungqvist, K.S. Nair, Skeletal muscle myosin heavy-chain synthesis rate in healthy humans, Am. J. Physiol. 272 (1997) E45–E50.
[7] R. Qaisar, G. Renaud, Y. Hedstrom, E. Pollanen, P. Ronkainen, J. Kaprio, M. Alen, S. Sipila, K. Artemenko, J. Bergquist, V. Kovanen, L. Larsson, Hormone replacement therapy improves contractile function and myonuclear organization of single muscle fibres from postmenopausal monozygotic female twin pairs, J. Physiol. 591 (2013) 2333–2344.
[8] J.X. Liu, A.S. Hoglund, P. Karlsson, J. Lindblad, R. Qaisar, S. Aare, E. Bengtsson, L. Larsson, Myonuclear domain size and myosin isoform expression in muscle fibres from mammals representing a 100,000-fold difference in body size, Exp. Physiol. 94 (2009) 117–129.
[9] E. Ferraro, A.M. Giammarioli, S. Chiandotto, I. Spoletini, G. Rosano, Exercise-induced skeletal muscle remodeling and metabolic adaptation: redox signaling and role of autophagy, Antioxid. Redox Signal. 21 (2014) 154–176.
[10] T.I. Metaxas, A. Mandroukas, E. Vamvakoudis, K. Kotoglou, B. Ekblom, K. Mandroukas, Muscle fiber characteristics, satellite cells and soccer performance in young athletes, J. Sports Sci. Med. 13 (2014) 493–501.
[11] M.J. Castro, D.F. Apple Jr., E.A. Hillegass, G.A. Dudley, Influence of complete spinal cord injury on skeletal muscle cross-sectional area within the first 6 months of injury, Eur. J. Appl. Physiol. Occup. Physiol. 80 (1999) 373–378.
[12] G.A. Nader, K.A. Esser, Intracellular signaling specificity in skeletal muscle in response to different modes of exercise, J. Appl. Physiol. (1985) 90 (2001) 1936–1942.
[13] H. Gur, L. Gransberg, D. vanDyke, E. Knutsson, L. Larsson, Relationship between in vivo muscle force at different speeds of isokinetic movements and myosin isoform expression in men and women, Eur. J. Appl. Physiol. 88 (2003) 487–496.
[14] A.L. Mackey, A. Karlsen, C. Couppe, U.R. Mikkelsen, R.H. Nielsen, S. P. Magnusson, M. Kjaer, Differential satellite cell density of type I and II fibres with lifelong endurance running in old men, Acta Physiol. (Oxford) 210 (2014) 612–627.
[15] J.N. Cobley, P.R. Moult, J.G. Burniston, J.P. Morton, G.L. Close, Exercise improves mitochondrial and redox-regulated stress responses in the elderly: better late than never! Biogerontology 16 (2015) 249–264.
[16] M.J. Laye, M.B. Nielsen, L.S. Hansen, T. Knudsen, B.K. Pedersen, Physical activity enhances metabolic fitness independently of cardiorespiratory fitness in marathon runners, Dis. Markers (2015) 806418.
[17] M. Cocks, A.J. Wagenmakers, The effect of different training modes on skeletal muscle microvascular density and endothelial enzymes controlling NO availability, J. Physiol (2015).
[18] F. Derbre, B. Ferrando, M.C. Gomez-Cabrera, F. Sanchis-Gomar, V.E. Martinez-Bello, G. Olaso-Gonzalez, A. Diaz, A. Gratas-Delamarche, M. Cerda, J. Vina, Inhibition of xanthine oxidase by allopurinol prevents skeletal muscle atrophy: role of p38 MAPKinase and E3 ubiquitin ligases, PLoS ONE 7 (2012) e46668.
[19] C. Kang, K.M. O'Moore, J.R. Dickman, L.L. Ji, Exercise activation of muscle peroxisome proliferator-activated receptor-gamma coactivator-1alpha signaling is redox sensitive, Free Radic. Biol. Med. 47 (2009) 1394–1400.
[20] J.O. Marx, M.C. Olsson, L. Larsson, Scaling of skeletal muscle shortening velocity in mammals representing a 100,000-fold difference in body size,

Pflugers Arch. 452 (2006) 222–230.
[21] A.P. Russell, J. Feilchenfeldt, S. Schreiber, M. Praz, A. Crettenand, C. Gobelet, C. A. Meier, D.R. Bell, A. Kralli, J.P. Giacobino, O. Deriaz, Endurance training in humans leads to fiber type-specific increases in levels of peroxisome proliferator-activated receptor-gamma coactivator-1 and peroxisome proliferator-activated receptor-alpha in skeletal muscle, Diabetes 52 (2003) 2874–2881.
[22] A.C. Fry, The role of resistance exercise intensity on muscle fibre adaptations, Sports Med. 34 (2004) 663–679.
[23] P.V. Komi, J.H. Viitasalo, M. Havu, A. Thorstensson, B. Sjodin, J. Karlsson, Skeletal muscle fibres and muscle enzyme activities in monozygous and dizygous twins of both sexes, Acta Physiol. Scand. 100 (1977) 385–392.
[24] B.M. Doucet, A. Lam, L. Griffin, Neuromuscular electrical stimulation for skeletal muscle function, Yale J. Biol. Med. 85 (2012) 201–215.
[25] M. Maffei, E. Longa, R. Qaisar, V. Agoni, J.F. Desaphy, D.C. Camerino, R. Bottinelli, M. Canepari, Actin sliding velocity on pure myosin isoforms from hindlimb unloaded mice, Acta Physiol. (Oxford) 212 (2014) 316–329.
[26] D. Zhang, X. Wang, Y. Li, L. Zhao, M. Lu, X. Yao, H. Xia, Y.C. Wang, M.F. Liu, J. Jiang, X. Li, H. Ying, Thyroid hormone regulates muscle fiber type conversion via miR-133a1, J. Cell Biol. 207 (2014) 753–766.
[27] A. Cristea, R. Qaisar, P.K. Edlund, J. Lindblad, E. Bengtsson, L. Larsson, Effects of aging and gender on the spatial organization of nuclei in single human skeletal muscle cells, Aging Cell 9 (2010) 685–697.
[28] S. Salmons, F.A. Sreter, Significance of impulse activity in the transformation of skeletal muscle type, Nature 263 (1976) 30–34.
[29] K.J. McCullagh, E. Calabria, G. Pallafacchina, S. Ciciliot, S.L. Serrano, C. Argentini, J.M. Kalhovde, T. Lomo, S. Schiaffino, NFAT is a nerve activity sensor in skeletal muscle and controls activity-dependent myosin switching, Proc. Natl. Acad. Sci. USA 101 (2004) 10590–10595.
[30] Z.A. Rana, K. Gundersen, A. Buonanno, Activity-dependent repression of muscle genes by NFAT, Proc. Natl. Acad. Sci. USA 105 (2008) 5921–5926.
[31] R. Bassel-Duby, E.N. Olson, Signaling pathways in skeletal muscle remodeling, Annu. Rev. Biochem. 75 (2006) 19–37.
[32] M. Picard, R. Godin, M. Sinnreich, J. Baril, J. Bourbeau, H. Perrault, T. Taivassalo, Y. Burelle, The mitochondrial phenotype of peripheral muscle in chronic obstructive pulmonary disease: disuse or dysfunction? Am. J. Respir. Crit. Care Med. 178 (2008) 1040–1047.
[33] M. Picard, K. Csukly, M.E. Robillard, R. Godin, A. Ascah, C. Bourcier-Lucas, Y. Burelle, Resistance to Ca^{2+}-induced opening of the permeability transition pore differs in mitochondria from glycolytic and oxidative muscles, Am. J. Physiol. Regul. Integr. Comp. Physiol. 295 (2008) R659–R668.
[34] E.J. Anderson, P.D. Neufer, Type II skeletal myofibers possess unique properties that potentiate mitochondrial H(2)O(2) generation, Am. J. Physiol. Cell Physiol. 290 (2006) C844–C851.
[35] D. Criswell, S. Powers, S. Dodd, J. Lawler, W. Edwards, K. Renshler, S. Grinton, High intensity training-induced changes in skeletal muscle antioxidant enzyme activity, Med. Sci. Sports Exerc. 25 (1993) 1135–1140.
[36] J.M. Lawler, S.K. Powers, H. Van Dijk, T. Visser, M.J. Kordus, L.L. Ji, Metabolic and antioxidant enzyme activities in the diaphragm: effects of acute exercise, Respir. Physiol. 96 (1994) 139–149.
[37] S.K. Powers, D. Criswell, J. Lawler, L.L. Ji, D. Martin, R.A. Herb, G. Dudley, Influence of exercise and fiber type on antioxidant enzyme activity in rat skeletal muscle, Am. J. Physiol. 266 (1994) R375–R380.
[38] J. St-Pierre, S. Drori, M. Uldry, J.M. Silvaggi, J. Rhee, S. Jager, C. Handschin, K. Zheng, J. Lin, W. Yang, D.K. Simon, R. Bachoo, B.M. Spiegelman, Suppression of reactive oxygen species and neurodegeneration by the PGC-1 transcriptional coactivators, Cell 127 (2006) 397–408.
[39] K.M. Baldwin, F. Haddad, Skeletal muscle plasticity: cellular and molecular responses to altered physical activity paradigms, Am. J. Phys. Med. Rehabil. 81 (2002) S40–S51.
[40] Z. Yan, M. Okutsu, Y.N. Akhtar, V.A. Lira, Regulation of exercise-induced fiber type transformation, mitochondrial biogenesis, and angiogenesis in skeletal muscle, J. Appl. Physiol. (1985) 110 (2011) 264–274.
[41] J.J. Widrick, S.W. Trappe, C.A. Blaser, D.L. Costill, R.H. Fitts, Isometric force and maximal shortening velocity of single muscle fibers from elite master runners, Am. J. Physiol. 271 (1996) C666–C675.
[42] D.A. Hood, Mechanisms of exercise-induced mitochondrial biogenesis in skeletal muscle, Appl. Physiol. Nutr. Metab. 34 (2009) 465–472.
[43] V. Ljubicic, A.M. Joseph, A. Saleem, G. Uguccioni, M. Collu-Marchese, R.Y. Lai, L.M. Nguyen, D.A. Hood, Transcriptional and post-transcriptional regulation of mitochondrial biogenesis in skeletal muscle: effects of exercise and aging, Biochim. Biophys. Acta 1800 (2010) 223–234.
[44] J. Henriksson, S. Salmons, M.Y. Chi, C.S. Hintz, O.H. Lowry, Chronic stimulation of mammalian muscle: changes in metabolite concentrations in individual fibers, Am. J. Physiol. 255 (1988) C543–C551.
[45] D.A. Hood, Invited Review: contractile activity-induced mitochondrial biogenesis in skeletal muscle, J. Appl. Physiol. (1985) 90 (2001) 1137–1157.
[46] K. Baar, A.R. Wende, T.E. Jones, M. Marison, L.A. Nolte, M. Chen, D.P. Kelly, J. O. Holloszy, Adaptations of skeletal muscle to exercise: rapid increase in the transcriptional coactivator PGC-1, FASEB J. 16 (2002) 1879–1886.
[47] L. Deldicque, P. Atherton, R. Patel, D. Theisen, H. Nielens, M.J. Rennie, M. Francaux, Effects of resistance exercise with and without creatine supplementation on gene expression and cell signaling in human skeletal muscle, J. Appl. Physiol. (1985) 104 (2008) 371–378.
[48] P.M. Garcia-Roves, J. Huss, J.O. Holloszy, Role of calcineurin in exercise-induced mitochondrial biogenesis, Am. J. Physiol. Endocrinol. Metab. 290 (2006) E1172–E1179.
[49] T. Geng, P. Li, M. Okutsu, X. Yin, J. Kwek, M. Zhang, Z. Yan, PGC-1alpha plays a functional role in exercise-induced mitochondrial biogenesis and angiogenesis but not fiber-type transformation in mouse skeletal muscle, Am. J. Physiol. Cell Physiol. 298 (2010) C572–C579.
[50] M. Tadaishi, S. Miura, Y. Kai, Y. Kano, Y. Oishi, O. Ezaki, Skeletal muscle-specific expression of PGC-1alpha-b, an exercise-responsive isoform, increases exercise capacity and peak oxygen uptake, PLoS ONE 6 (2011) e28290.
[51] J.L. Ruas, J.P. White, R.R. Rao, S. Kleiner, K.T. Brannan, B.C. Harrison, N. P. Greene, J. Wu, J.L. Estall, B.A. Irving, I.R. Lanza, K.A. Rasbach, M. Okutsu, K. S. Nair, Z. Yan, L.A. Leinwand, B.M. Spiegelman, A PGC-1alpha isoform induced by resistance training regulates skeletal muscle hypertrophy, Cell 151 (2012) 1319–1331.
[52] K. Baar, Z. Song, C.F. Semenkovich, T.E. Jones, D.H. Han, L.A. Nolte, E.O. Ojuka, M. Chen, J.O. Holloszy, Skeletal muscle overexpression of nuclear respiratory factor 1 increases glucose transport capacity, FASEB J. 17 (2003) 1666–1673.
[53] O. Al-Sawaf, A. Fragoulis, C. Rosen, N. Keimes, E.A. Liehn, F. Holzle, Y.W. Kan, T. Pufe, T.T. Sonmez, C.J. Wruck, Nrf2 augments skeletal muscle regeneration after ischaemia-reperfusion injury, J. Pathol. 234 (2014) 538–547.
[54] T. Varga, Z. Czimmerer, L. Nagy, PPARs are a unique set of fatty acid regulated transcription factors controlling both lipid metabolism and inflammation, Biochim. Biophys. Acta 1812 (2011) 1007–1022.
[55] P. Diel, The role of the estrogen receptor in skeletal muscle mass homeostasis and regeneration, Acta Physiol. (Oxford) 212 (2014) 14–16.
[56] J.W. Lee, N.H. Kim, A. Milanesi, Thyroid hormone signaling in muscle development, repair and metabolism, J. Endocrinol. Diabetes Obes. 2 (2014) 1046.
[57] M. Baranowski, A.U. Blachnio-Zabielska, P. Zabielski, E. Harasim, D. Harasiuk, A. Chabowski, J. Gorski, Liver X receptor agonist T0901317 enhanced peroxisome proliferator-activated receptor-delta expression and fatty acid oxidation in rat skeletal muscle, J. Physiol. Pharmacol. 64 (2013) 289–297.
[58] S. Wales, S. Hashemi, A. Blais, J.C. McDermott, Global MEF2 target gene analysis in cardiac and skeletal muscle reveals novel regulation of DUSP6 by p38MAPK-MEF2 signaling, Nucleic Acids Res. 42 (2014) 11349–11362.
[59] A.M. Sanchez, R.B. Candau, H. Bernardi, FoxO transcription factors: their roles in the maintenance of skeletal muscle homeostasis, Cell. Mol. Life Sci. 71 (2014) 1657–1671.
[60] Z. Yan, Exercise, PGC-1alpha, and metabolic adaptation in skeletal muscle, Appl. Physiol. Nutr. Metab. 34 (2009) 424–427.
[61] R. Stewart, L. Flechner, M. Montminy, R. Berdeaux, CREB is activated by muscle injury and promotes muscle regeneration, PLoS ONE 6 (2011) e24714.
[62] G. Gouspillou, N. Sgarioto, B. Norris, S. Barbat-Artigas, M. Aubertin-Leheudre, J.A. Morais, Y. Burelle, T. Taivassalo, R.T. Hepple, The relationship between muscle fiber type-specific PGC-1alpha content and mitochondrial content varies between rodent models and humans, PLoS ONE 9 (2014) e103044.
[63] R.C. Wust, S.L. Gibbings, H. Degens, Fiber capillary supply related to fiber size and oxidative capacity in human and rat skeletal muscle, Adv. Exp. Med. Biol. 645 (2009) 75–80.
[64] H. Howald, H. Hoppeler, H. Claassen, O. Mathieu, R. Straub, Influences of endurance training on the ultrastructural composition of the different muscle fiber types in humans, Pflugers Arch. 403 (1985) 369–376.
[65] G.A. Dudley, P.C. Tullson, R.L. Terjung, Influence of mitochondrial content on the sensitivity of respiratory control, J. Biol. Chem. 262 (1987) 9109–9114.
[66] T. Moritani, T. Takaishi, T. Matsumoto, Determination of maximal power output at neuromuscular fatigue threshold, J. Appl. Physiol. (1985) 74 (1993) 1729–1734.
[67] B. Westermann, Mitochondrial fusion and fission in cell life and death, Nat. Rev. Mol. Cell Biol. 11 (2010) 872–884.
[68] H. Ding, N. Jiang, H. Liu, X. Liu, D. Liu, F. Zhao, L. Wen, S. Liu, L.L. Ji, Y. Zhang, Response of mitochondrial fusion and fission protein gene expression to exercise in rat skeletal muscle, Biochim. Biophys. Acta 1800 (2010) 250–256.
[69] R. Cartoni, B. Leger, M.B. Hock, M. Praz, A. Crettenand, S. Pich, J.L. Ziltener, F. Luthi, O. Deriaz, A. Zorzano, C. Gobelet, A. Kralli, A.P. Russell, Mitofusins 1/2 and ERRalpha expression are increased in human skeletal muscle after physical exercise, J. Physiol. 567 (2005) 349–358.
[70] V.P. Skulachev, Mitochondrial filaments and clusters as intracellular power-transmitting cables, Trends Biochem. Sci. 26 (2001) 23–29.
[71] Z. Yan, V.A. Lira, N.P. Greene, Exercise training-induced regulation of mitochondrial quality, Exerc. Sport Sci. Rev. 40 (2012) 159–164.
[72] A.R. Konopka, M.K. Suer, C.A. Wolff, M.P. Harber, Markers of human skeletal muscle mitochondrial biogenesis and quality control: effects of age and aerobic exercise training, J. Gerontol. A Biol. Sci. Med. Sci. 69 (2014) 371–378.
[73] C.E. Fealy, A. Mulya, N. Lai, J.P. Kirwan, Exercise training decreases activation of the mitochondrial fission protein dynamin-related protein-1 in insulin-resistant human skeletal muscle, J. Appl. Physiol. (1985) 117 (2014) 239–245.
[74] S.E. Wohlgemuth, A.Y. Seo, E. Marzetti, H.A. Lees, C. Leeuwenburgh, Skeletal muscle autophagy and apoptosis during aging: effects of calorie restriction and life-long exercise, Exp. Gerontol. 45 (2010) 138–148.
[75] E. Masiero, M. Sandri, Autophagy inhibition induces atrophy and myopathy in adult skeletal muscles, Autophagy 6 (2010) 307–309.
[76] V.A. Lira, M. Okutsu, M. Zhang, N.P. Greene, R.C. Laker, D.S. Breen, K.L. Hoehn, Z. Yan, Autophagy is required for exercise training-induced skeletal muscle adaptation and improvement of physical performance, FASEB J. 27 (2013) 4184–4193.
[77] E. Gnaiger, Capacity of oxidative phosphorylation in human skeletal muscle:

new perspectives of mitochondrial physiology, Int. J. Biochem. Cell Biol. 41 (2009) 1837–1845.
[78] E.A. Richter, M. Hargreaves, Exercise, GLUT4, and skeletal muscle glucose uptake, Physiol. Rev. 93 (2013) 993–1017.
[79] P. Nordby, P.L. Auerbach, M. Rosenkilde, L. Kristiansen, J.R. Thomasen, L. Rygaard, R. Groth, N. Brandt, J.W. Helge, E.A. Richter, T. Ploug, B. Stallknecht, Endurance training per se increases metabolic health in young, moderately overweight men, Obesity (Silver Spring) 20 (2012) 2202–2212.
[80] A.E. Jeukendrup, Regulation of fat metabolism in skeletal muscle, Ann. N. Y. Acad. Sci. 967 (2002) 217–235.
[81] N. Ortenblad, H. Westerblad, J. Nielsen, Muscle glycogen stores and fatigue, J. Physiol. 591 (2013) 4405–4413.
[82] B. Egan, J.R. Zierath, Exercise metabolism and the molecular regulation of skeletal muscle adaptation, Cell Metab. 17 (2013) 162–184.
[83] N. Tamaki, Effect of endurance training on muscle fiber type composition and capillary supply in rat diaphragm, Eur. J. Appl. Physiol. Occup. Physiol. 56 (1987) 127–131.
[84] M.I. Lewis, M. Fournier, H. Wang, T.W. Storer, R. Casaburi, J.D. Kopple, Effect of endurance and/or strength training on muscle fiber size, oxidative capacity and capillarity in hemodialysis patients, J Appl Physiol (1985) (2015) 01084–02014.
[85] M. Kurosaka, H. Naito, Y. Ogura, S. Machida, S. Katamoto, Satellite cell pool enhancement in rat plantaris muscle by endurance training depends on intensity rather than duration, Acta Physiol. (Oxford) 205 (2012) 159–166.
[86] S. Frese, M. Ruebner, F. Suhr, T.M. Konou, K.A. Tappe, M. Toigo, H.H. Jung, C. Henke, R. Steigleder, P.L. Strissel, H. Huebner, M.W. Beckmann, P. van der Keylen, B. Schoser, T. Schiffer, L. Frese, W. Bloch, R. Strick, Long-term endurance exercise in humans stimulates cell fusion of myoblasts along with fusogenic endogenous retroviral genes in vivo, PLoS ONE 10 (2015) e0132099.
[87] J. Verney, F. Kadi, N. Charifi, L. Feasson, M.A. Saafi, J. Castells, K. Piehl-Aulin, C. Denis, Effects of combined lower body endurance and upper body resistance training on the satellite cell pool in elderly subjects, Muscle Nerve 38 (2008) 1147–1154.
[88] G. Parise, I.W. McKinnell, M.A. Rudnicki, Muscle satellite cell and atypical myogenic progenitor response following exercise, Muscle Nerve 37 (2008) 611–619.
[89] G. Shefer, G. Rauner, Z. Yablonka-Reuveni, D. Benayahu, Reduced satellite cell numbers and myogenic capacity in aging can be alleviated by endurance exercise, PLoS One 5 (2010) e13307.
[90] A.M. Jones, H. Carter, The effect of endurance training on parameters of aerobic fitness, Sports Med. 29 (2000) 373–386.
[91] J. Helgerud, K. Hoydal, E. Wang, T. Karlsen, P. Berg, M. Bjerkaas, T. Simonsen, C. Helgesen, N. Hjorth, R. Bach, J. Hoff, Aerobic high-intensity intervals improve VO2max more than moderate training, Med. Sci. Sports Exerc. 39 (2007) 665–671.
[92] A.E. Tjonna, I.M. Leinan, A.T. Bartnes, B.M. Jenssen, M.J. Gibala, R.A. Winett, U. Wisloff, Low- and high-volume of intensive endurance training significantly improves maximal oxygen uptake after 10-weeks of training in healthy men, PLoS One **8** (2013) e65382.
[93] M.J. McDonagh, C.T. Davies, Adaptive response of mammalian skeletal muscle to exercise with high loads, Eur. J. Appl. Physiol. Occup. Physiol. 52 (1984) 139–155.
[94] P. Cormie, G.O. McCaulley, N.T. Triplett, J.M. McBride, Optimal loading for maximal power output during lower-body resistance exercises, Med. Sci. Sports Exerc. 39 (2007) 340–349.
[95] A.C. Paul, N. Rosenthal, Different modes of hypertrophy in skeletal muscle fibers, J. Cell Biol. 156 (2002) 751–760.
[96] D.W. West, N.A. Burd, A.W. Staples, S.M. Phillips, Human exercise-mediated skeletal muscle hypertrophy is an intrinsic process, Int. J. Biochem. Cell Biol. 42 (2010) 1371–1375.
[97] M.J. Toth, M.S. Miller, P. VanBuren, N.G. Bedrin, M.M. LeWinter, P.A. Ades, B. M. Palmer, Resistance training alters skeletal muscle structure and function in human heart failure: effects at the tissue, cellular and molecular levels, J. Physiol. 590 (2012) 1243–1259.
[98] D.L. Hasten, J. Pak-Loduca, K.A. Obert, K.E. Yarasheski, Resistance exercise acutely increases MHC and mixed muscle protein synthesis rates in 78–84 and 23–32 yr olds, Am. J. Physiol. Endocrinol. Metab. 278 (2000) E620–E626.
[99] V. Kumar, A. Selby, D. Rankin, R. Patel, P. Atherton, W. Hildebrandt, J. Williams, K. Smith, O. Seynnes, N. Hiscock, M.J. Rennie, Age-related differences in the dose-response relationship of muscle protein synthesis to resistance exercise in young and old men, J. Physiol. 587 (2009) 211–217.
[100] D.S. Willoughby, J.R. Stout, C.D. Wilborn, Effects of resistance training and protein plus amino acid supplementation on muscle anabolism, mass, and strength, Amino Acids 32 (2007) 467–477.
[101] T.S. Wong, F.W. Booth, Protein metabolism in rat gastrocnemius muscle after stimulated chronic concentric exercise, J. Appl. Physiol. (1985) 69 (1990) 1709–1717.
[102] M.J. Rennie, H. Wackerhage, E.E. Spangenburg, F.W. Booth, Control of the size of the human muscle mass, Annu. Rev. Physiol. 66 (2004) 799–828.
[103] A.P. Palstra, M. Rovira, D. Rizo-Roca, J.R. Torrella, H.P. Spaink, J.V. Planas, Swimming-induced exercise promotes hypertrophy and vascularization of fast skeletal muscle fibres and activation of myogenic and angiogenic transcriptional programs in adult zebrafish, BMC Genom. 15 (2014) 1136.
[104] A.A. Mero, J.J. Hulmi, H. Salmijarvi, M. Katajavuori, M. Haverinen, J. Holviala, T. Ridanpaa, K. Hakkinen, V. Kovanen, J.P. Ahtiainen, H. Selanne, Resistance training induced increase in muscle fiber size in young and older men, Eur. J. Appl. Physiol. 113 (2013) 641–650.
[105] P. Aagaard, J.L. Andersen, P. Dyhre-Poulsen, A.M. Leffers, A. Wagner, S. P. Magnusson, J. Halkjaer-Kristensen, E.B. Simonsen, A mechanism for increased contractile strength of human pennate muscle in response to strength training: changes in muscle architecture, J. Physiol. 534 (2001) 613–623.
[106] S.M. Phillips, Physiologic and molecular bases of muscle hypertrophy and atrophy: impact of resistance exercise on human skeletal muscle (protein and exercise dose effects), Appl. Physiol. Nutr. Metab. 34 (2009) 403–410.
[107] D.R. Claflin, L.M. Larkin, P.S. Cederna, J.F. Horowitz, N.B. Alexander, N.M. Cole, A.T. Galecki, S. Chen, L.V. Nyquist, B.M. Carlson, J.A. Faulkner, J.A. Ashton-Miller, Effects of high- and low-velocity resistance training on the contractile properties of skeletal muscle fibers from young and older humans, J. Appl. Physiol. (1985) 111 (2011) 1021–1030.
[108] J.D. MacDougall, G.C. Elder, D.G. Sale, J.R. Moroz, J.R. Sutton, Effects of strength training and immobilization on human muscle fibres, Eur. J. Appl. Physiol. Occup. Physiol. 43 (1980) 25–34.
[109] R.S. Hikida, R.S. Staron, F.C. Hagerman, S. Walsh, E. Kaiser, S. Shell, S. Hervey, Effects of high-intensity resistance training on untrained older men. II. Muscle fiber characteristics and nucleo-cytoplasmic relationships, J. Gerontol. A Biol. Sci. Med. Sci. 55 (2000) B347–B354.
[110] J.L. Rivero, R.J. Talmadge, V.R. Edgerton, Fibre size and metabolic properties of myosin heavy chain-based fibre types in rat skeletal muscle, J. Muscle Res. Cell Motil. 19 (1998) 733–742.
[111] S. Medler, Comparative trends in shortening velocity and force production in skeletal muscles, Am. J. Physiol. Regul. Integr. Comp. Physiol. 283 (2002) R368–R378.
[112] K. Hakkinen, R.U. Newton, S.E. Gordon, M. McCormick, J.S. Volek, B.C. Nindl, L. A. Gotshalk, W.W. Campbell, W.J. Evans, A. Hakkinen, B.J. Humphries, W. J. Kraemer, Changes in muscle morphology, electromyographic activity, and force production characteristics during progressive strength training in young and older men, J. Gerontol. A Biol. Sci. Med. Sci. 53 (1998) B415–B423.
[113] P. Aagaard, J.L. Andersen, Correlation between contractile strength and myosin heavy chain isoform composition in human skeletal muscle, Med. Sci. Sports Exerc. 30 (1998) 1217–1222.
[114] R.M. Anderson, J.L. Barger, M.G. Edwards, K.H. Braun, C.E. O'Connor, T. A. Prolla, R. Weindruch, Dynamic regulation of PGC-1alpha localization and turnover implicates mitochondrial adaptation in calorie restriction and the stress response, Aging Cell 7 (2008) 101–111.
[115] B.L. Olson, M.B. Hock, S. Ekholm-Reed, J.A. Wohlschlegel, K.K. Dev, A. Kralli, S. I. Reed, SCFCdc4 acts antagonistically to the PGC-1alpha transcriptional coactivator by targeting it for ubiquitin-mediated proteolysis, Genes Dev. 22 (2008) 252–264.
[116] J.P. Little, A. Safdar, G.P. Wilkin, M.A. Tarnopolsky, M.J. Gibala, A practical model of low-volume high-intensity interval training induces mitochondrial biogenesis in human skeletal muscle: potential mechanisms, J. Physiol. 588 (2010) 1011–1022.
[117] J. Perez-Schindler, S. Summermatter, G. Santos, F. Zorzato, C. Handschin, The transcriptional coactivator PGC-1alpha is dispensable for chronic overload-induced skeletal muscle hypertrophy and metabolic remodeling, Proc. Natl. Acad. Sci. USA 110 (2013) 20314–20319.
[118] R.M. Crameri, H. Langberg, P. Magnusson, C.H. Jensen, H.D. Schroder, J. L. Olesen, C. Suetta, B. Teisner, M. Kjaer, Changes in satellite cells in human skeletal muscle after a single bout of high intensity exercise, J. Physiol. 558 (2004) 333–340.
[119] C. O'Reilly, B. McKay, S. Phillips, M. Tarnopolsky, G. Parise, Hepatocyte growth factor (HGF) and the satellite cell response following muscle lengthening contractions in humans, Muscle Nerve 38 (2008) 1434–1442.
[120] B.R. McKay, M. De Lisio, A.P. Johnston, C.E. O'Reilly, S.M. Phillips, M. A. Tarnopolsky, G. Parise, Association of interleukin-6 signalling with the muscle stem cell response following muscle-lengthening contractions in humans, PLoS ONE 4 (2009) e6027.
[121] J.K. Petrella, J.S. Kim, D.L, Mayhew, J.M. Cross, M.M. Bamman, Potent myofiber hypertrophy during resistance training in humans is associated with satellite cell-mediated myonuclear addition: a cluster analysis, J. Appl. Physiol. (1985) 104 (2008) 1736–1742.
[122] A.L. Mackey, L. Holm, S. Reitelseder, T.G. Pedersen, S. Doessing, F. Kadi, M. Kjaer, Myogenic response of human skeletal muscle to 12 weeks of resistance training at light loading intensity, Scand. J. Med. Sci. Sports 21 (2011) 773–782.
[123] S.M. Roth, G.F. Martel, F.M. Ivey, J.T. Lemmer, B.L. Tracy, E.J. Metter, B. F. Hurley, M.A. Rogers, Skeletal muscle satellite cell characteristics in young and older men and women after heavy resistance strength training, J. Gerontol. A Biol. Sci. Med. Sci. 56 (2001) B240–B247.
[124] L.B. Verdijk, B.G. Gleeson, R.A. Jonkers, K. Meijer, H.H. Savelberg, P. Dendale, L. J. van Loon, Skeletal muscle hypertrophy following resistance training is accompanied by a fiber type-specific increase in satellite cell content in elderly men, J. Gerontol. A Biol. Sci. Med. Sci. 64 (2009) 332–339.
[125] H.K. Smith, T.L. Merry, Voluntary resistance wheel exercise during post-natal growth in rats enhances skeletal muscle satellite cell and myonuclear content at adulthood, Acta Physiol. (Oxford) 204 (2012) 393–402.
[126] G. Shefer, D.P. Van de Mark, J.B. Richardson, Z. Yablonka-Reuveni, Satellite-cell pool size does matter: defining the myogenic potency of aging skeletal muscle, Dev. Biol. 294 (2006) 50–66.

[127] H. Yin, F. Price, M.A. Rudnicki, Satellite cells and the muscle stem cell niche, Physiol. Rev. 93 (2013) 23–67.
[128] J.K. Petrella, J.S. Kim, J.M. Cross, D.J. Kosek, M.M. Bamman, Efficacy of myonuclear addition may explain differential myofiber growth among resistance-trained young and older men and women, Am. J. Physiol. Endocrinol. Metab. 291 (2006) E937–E946.
[129] L.M. Bellamy, S. Joanisse, A. Grubb, C.J. Mitchell, B.R. McKay, S.M. Phillips, S. Baker, G. Parise, The acute satellite cell response and skeletal muscle hypertrophy following resistance training, PLoS ONE 9 (2014) e109739.
[130] J.C. Bruusgaard, I.B. Johansen, I.M. Egner, Z.A. Rana, K. Gundersen, Myonuclei acquired by overload exercise precede hypertrophy and are not lost on detraining, Proc Natl Acad Sci USA 107 (2010) 15111–15116.
[131] Y.W. Chen, G.A. Nader, K.R. Baar, M.J. Fedele, E.P. Hoffman, K.A. Esser, Response of rat muscle to acute resistance exercise defined by transcriptional and translational profiling, J. Physiol. 545 (2002) 27–41.
[132] J.D. Rosenblatt, D. Yong, D.J. Parry, Satellite cell activity is required for hypertrophy of overloaded adult rat muscle, Muscle Nerve 17 (1994) 608–613.
[133] R.R. Roy, S.R. Monke, D.L. Allen, V.R. Edgerton, Modulation of myonuclear number in functionally overloaded and exercised rat plantaris fibers, J. Appl. Physiol. (1985) 87 (1999) 634–642.
[134] R. Qaisar, L. Larsson, What determines myonuclear domain size? Indian J. Physiol. Pharmacol. 58 (2014) 1–12.
[135] R. Qaisar, G. Renaud, K. Morine, E.R. Barton, H.L. Sweeney, L. Larsson, Is functional hypertrophy and specific force coupled with the addition of myonuclei at the single muscle fiber level? FASEB J. 26 (2012) 1077–1085.
[136] R.S. O'Connor, G.K. Pavlath, J.J. McCarthy, K.A. Esser, Last Word on Point: Counterpoint: Satellite cell addition is/is not obligatory for skeletal muscle hypertrophy, J. Appl. Physiol. (1985) 103 (2007) 1107.
[137] Q. Wang, A.C. McPherron, Myostatin inhibition induces muscle fibre hypertrophy prior to satellite cell activation, J. Physiol. 590 (2012) 2151–2165.
[138] J.J. McCarthy, J. Mula, M. Miyazaki, R. Erfani, K. Garrison, A.B. Farooqui, R. Srikuea, B.A. Lawson, B. Grimes, C. Keller, G. Van Zant, K.S. Campbell, K. A. Esser, E.E. Dupont-Versteegden, C.A. Peterson, Effective fiber hypertrophy in satellite cell-depleted skeletal muscle, Development 138 (2011) 3657–3666.
[139] F.W. Booth, D.B. Thomason, Molecular and cellular adaptation of muscle in response to exercise: perspectives of various models, Physiol. Rev. 71 (1991) 541–585.
[140] M.J. Hubal, H. Gordish-Dressman, P.D. Thompson, T.B. Price, E.P. Hoffman, T. J. Angelopoulos, P.M. Gordon, N.M. Moyna, L.S. Pescatello, P.S. Visich, R. F. Zoeller, R.L. Seip, P.M. Clarkson, Variability in muscle size and strength gain after unilateral resistance training, Med. Sci. Sports Exerc. 37 (2005) 964–972.
[141] V. Sartorelli, M. Fulco, Molecular and cellular determinants of skeletal muscle atrophy and hypertrophy, Sci STKE (2004) re11.
[142] M.S. Brook, D.J. Wilkinson, W.K. Mitchell, J.N. Lund, N.J. Szewczyk, P. L. Greenhaff, K. Smith, P.J. Atherton, Skeletal muscle hypertrophy adaptations predominate in the early stages of resistance exercise training, matching deuterium oxide-derived measures of muscle protein synthesis and mechanistic target of rapamycin complex 1 signaling, FASEB J. (2015).
[143] R. Ogasawara, T. Yasuda, N. Ishii, T. Abe, Comparison of muscle hypertrophy following 6-month of continuous and periodic strength training, Eur. J. Appl. Physiol. 113 (2013) 975–985.
[144] F. Damas, S. Phillips, F.C. Vechin, C. Ugrinowitsch, A review of resistance training-induced changes in skeletal muscle protein synthesis and their contribution to hypertrophy, Sports Med. 45 (2015) 801–807.
[145] S.B. Wilkinson, S.M. Phillips, P.J. Atherton, R. Patel, K.E. Yarasheski, M. A. Tarnopolsky, M.J. Rennie, Differential effects of resistance and endurance exercise in the fed state on signalling molecule phosphorylation and protein synthesis in human muscle, J. Physiol. 586 (2008) 3701–3717.
[146] P.L. Kim, R.S. Staron, S.M. Phillips, Fasted-state skeletal muscle protein synthesis after resistance exercise is altered with training, J. Physiol. 568 (2005) 283–290.
[147] G. Biolo, S.P. Maggi, B.D. Williams, K.D. Tipton, R.R. Wolfe, Increased rates of muscle protein turnover and amino acid transport after resistance exercise in humans, Am. J. Physiol. 268 (1995) E514–E520.
[148] W.R. Frontera, C.N. Meredith, K.P. O'Reilly, W.J. Evans, Strength training and determinants of VO2max in older men, J. Appl. Physiol. (1985) 68 (1990) 329–333.
[149] J.E. Tang, J.W. Hartman, S.M. Phillips, Increased muscle oxidative potential following resistance training induced fibre hypertrophy in young men, Appl. Physiol. Nutr. Metab. 31 (2006) 495–501.
[150] H. Crossland, A.A. Kazi, C.H. Lang, J.A. Timmons, P. Pierre, D.J. Wilkinson, K. Smith, N.J. Szewczyk, P.J. Atherton, Focal adhesion kinase is required for IGF-I-mediated growth of skeletal muscle cells via a TSC2/mTOR/S6K1-associated pathway, Am. J. Physiol. Endocrinol. Metab. 305 (2013) E183–E193.
[151] S.C. Bodine, T.N. Stitt, M. Gonzalez, W.O. Kline, G.L. Stover, R. Bauerlein, E. Zlotchenko, A. Scrimgeour, J.C. Lawrence, D.J. Glass, G.D. Yancopoulos, Akt/mTOR pathway is a crucial regulator of skeletal muscle hypertrophy and can prevent muscle atrophy in vivo, Nat. Cell Biol. 3 (2001) 1014–1019.
[152] A. Philp, D.L. Hamilton, K. Baar, Signals mediating skeletal muscle remodeling by resistance exercise: PI3-kinase independent activation of mTORC1, J. Appl. Physiol. (1985) 110 (2011) 561–568.
[153] K. Sakamoto, W.G. Aschenbach, M.F. Hirshman, L.J. Goodyear, Akt signaling in skeletal muscle: regulation by exercise and passive stretch, Am. J. Physiol. Endocrinol. Metab. 285 (2003) E1081–E1088.
[154] J.D. Parkington, A.P. Siebert, N.K. LeBrasseur, R.A. Fielding, Differential activation of mTOR signaling by contractile activity in skeletal muscle, Am. J. Physiol. Regul. Integr. Comp. Physiol. 285 (2003) R1086–R1090.
[155] R. Koopman, A.H. Zorenc, R.J. Gransier, D. Cameron-Smith, L.J. van Loon, Increase in S6K1 phosphorylation in human skeletal muscle following resistance exercise occurs mainly in type II muscle fibers, Am. J. Physiol. Endocrinol. Metab. 290 (2006) E1245–E1252.
[156] J.E. Kim, J. Chen, Cytoplasmic-nuclear shuttling of FKBP12-rapamycin-associated protein is involved in rapamycin-sensitive signaling and translation initiation, Proc. Natl. Acad. Sci. USA 97 (2000) 14340–14345.
[157] R.L. Lieber, J. Friden, Mechanisms of muscle injury after eccentric contraction, J. Sci. Med. Sport 2 (1999) 253–265.
[158] F. Macaluso, A.W. Isaacs, K.H. Myburgh, Preferential type II muscle fiber damage from plyometric exercise, J. Athl. Train 47 (2012) 414–420.
[159] C.S. Lieber, Carbohydrate deficient transferrin in alcoholic liver disease: mechanisms and clinical implications, Alcohol 19 (1999) 249–254.
[160] K. Vijayan, J.L. Thompson, K.M. Norenberg, R.H. Fitts, D.A. Riley, Fiber-type susceptibility to eccentric contraction-induced damage of hindlimb-unloaded rat AL muscles, J. Appl. Physiol. (1985) 90 (2001) 770–776.
[161] P.K. Luther, The vertebrate muscle Z-disc: sarcomere anchor for structure and signalling, J. Muscle Res. Cell Motil. 30 (2009) 171–185.
[162] J. Friden, R.L. Lieber, Eccentric exercise-induced injuries to contractile and cytoskeletal muscle fibre components, Acta Physiol. Scand. 171 (2001) 321–326.
[163] A.M. Boriek, Y. Capetanaki, W. Hwang, T. Officer, M. Badshah, J. Rodarte, J. G. Tidball, Desmin integrates the three-dimensional mechanical properties of muscles, Am. J. Physiol. Cell Physiol. 280 (2001) C46–C52.
[164] R.M. Lovering, A. O'Neill, J.M. Muriel, B.L. Prosser, J. Strong, R.J. Bloch, Physiology, structure, and susceptibility to injury of skeletal muscle in mice lacking keratin 19-based and desmin-based intermediate filaments, Am. J. Physiol. Cell Physiol. 300 (2011) C803–C813.
[165] D.A. Opar, M.D. Williams, A.J. Shield, Hamstring strain injuries: factors that lead to injury and re-injury, Sports Med. 42 (2012) 209–226.
[166] T.J. Koh, J. Escobedo, Cytoskeletal disruption and small heat shock protein translocation immediately after lengthening contractions, Am. J. Physiol. Cell Physiol. 286 (2004) C713–C722.
[167] R.M. Lovering, P.G. De Deyne, Contractile function, sarcolemma integrity, and the loss of dystrophin after skeletal muscle eccentric contraction-induced injury, Am. J. Physiol. Cell Physiol. 286 (2004) C230–C238.
[168] C. Jamart, N. Benoit, J.M. Raymackers, H.J. Kim, C.K. Kim, M. Francaux, Autophagy-related and autophagy-regulatory genes are induced in human muscle after ultraendurance exercise, Eur. J. Appl. Physiol. 112 (2012) 3173–3177.
[169] E.W. Yeung, C.D. Balnave, H.J. Ballard, J.P. Bourreau, D.G. Allen, Development of T-tubular vacuoles in eccentrically damaged mouse muscle fibres, J. Physiol. 540 (2002) 581–592.
[170] M.E. Isner-Horobeti, S.P. Dufour, P. Vautravers, B. Geny, E. Coudeyre, R. Richard, Eccentric exercise training: modalities, applications and perspectives, Sports Med. 43 (2013) 483–512.
[171] N.B. Vollaard, J.P. Shearman, C.E. Cooper, Exercise-induced oxidative stress: myths, realities and physiological relevance, Sports Med 35 (2005) 1045–1062.
[172] E. Barbieri, P. Sestili, Reactive oxygen species in skeletal muscle signaling, J. Signal Transduct. (2012) 982794.
[173] G.L. Close, T. Ashton, T. Cable, D. Doran, D.P. MacLaren, Eccentric exercise, isokinetic muscle torque and delayed onset muscle soreness: the role of reactive oxygen species, Eur. J. Appl. Physiol. 91 (2004) 615–621.
[174] M.J. Jackson, M. Khassaf, A. Vasilaki, F. McArdle, A. McArdle, Vitamin E and the oxidative stress of exercise, Ann. N. Y. Acad. Sci. 1031 (2004) 158–168.
[175] G.L. Close, T. Ashton, A. McArdle, D.P. Maclaren, The emerging role of free radicals in delayed onset muscle soreness and contraction-induced muscle injury, Comp. Biochem. Physiol. A Mol. Integr. Physiol. 142 (2005) 257–266.
[176] S. Mrakic-Sposta, M. Gussoni, S. Porcelli, L. Pugliese, G. Pavei, G. Bellistri, M. Montorsi, P. Tacchini, A. Vezzoli, Training effects on ROS production determined by electron paramagnetic resonance in master swimmers, Oxid. Med. Cell Longev. (2015) 804794.
[177] A.L. Spirlandeli, R. Deminice, A.A. Jordao, Plasma malondialdehyde as biomarker of lipid peroxidation: effects of acute exercise, Int J Sports Med **35** (2014) 14–18.
[178] G.L. Close, T. Ashton, T. Cable, D. Doran, C. Holloway, F. McArdle, D. P. MacLaren, Ascorbic acid supplementation does not attenuate post-exercise muscle soreness following muscle-damaging exercise but may delay the recovery process, Br. J. Nutr. 95 (2006) 976–981.
[179] M.L. Urso, Anti-inflammatory interventions and skeletal muscle injury: benefit or detriment? J. Appl. Physiol. (1985) 115 (2013) 920–928.
[180] M.B. Reid, Invited Review: redox modulation of skeletal muscle contraction: what we know and what we don't, J. Appl. Physiol. (1985) 90 (2001) 724–731.
[181] G.S. Supinski, L.A. Callahan, Free radical-mediated skeletal muscle dysfunction in inflammatory conditions, J. Appl. Physiol. (1985) 102 (2007) 2056–2063.
[182] M.B. Reid, F.A. Khawli, M.R. Moody, Reactive oxygen in skeletal muscle. III. Contractility of unfatigued muscle, J. Appl. Physiol. (1985) (1993) 1081–1087.
[183] C. Coirault, A. Guellich, T. Barbry, J.L. Samuel, B. Riou, Y. Lecarpentier, Oxidative stress of myosin contributes to skeletal muscle dysfunction in rats with chronic heart failure, Am. J. Physiol. Heart Circ. Physiol. 292 (2007) H1009–H1017.
[184] M.A. Smith, M.B. Reid, Redox modulation of contractile function in

respiratory and limb skeletal muscle, Respir. Physiol. Neurobiol. 151 (2006) 229–241.
[185] M.B. Reid, D.S. Stokic, S.M. Koch, F.A. Khawli, A.A. Leis, N-acetylcysteine inhibits muscle fatigue in humans, J. Clin. Invest. 94 (1994) 2468–2474.
[186] S.K. Powers, L.L. Ji, A.N. Kavazis, M.J. Jackson, Reactive oxygen species: impact on skeletal muscle, Comp. Physiol. 1 (2011) 941–969.
[187] A.M. Niess, P. Simon, Response and adaptation of skeletal muscle to exercise–the role of reactive oxygen species, Front. Biosci. 12 (2007) 4826–4838.
[188] L.L. Ji, Redox signaling in skeletal muscle: role of aging and exercise, Adv. Physiol. Educ. 39 (2015) 352–359.
[189] S.K. Powers, M.J. Jackson, Exercise-induced oxidative stress: cellular mechanisms and impact on muscle force production, Physiol. Rev. 88 (2008) 1243–1276.
[190] H.F. Kramer, L.J. Goodyear, Exercise, MAPK, and NF-kappaB signaling in skeletal muscle, J. Appl. Physiol. (1985) 103 (2007) 388–395.
[191] M.C. Gomez-Cabrera, C. Borras, F.V. Pallardo, J. Sastre, L.L. Ji, J. Vina, Decreasing xanthine oxidase-mediated oxidative stress prevents useful cellular adaptations to exercise in rats, J. Physiol. 567 (2005) 113–120.
[192] J. Hollander, R. Fiebig, M. Gore, T. Ookawara, H. Ohno, L.L. Ji, Superoxide dismutase gene expression is activated by a single bout of exercise in rat skeletal muscle, Pflugers Arch. 442 (2001) 426–434.
[193] L.L. Ji, M.C. Gomez-Cabrera, N. Steinhafel, J. Vina, Acute exercise activates nuclear factor (NF)-kappaB signaling pathway in rat skeletal muscle, FASEB J. 18 (2004) 1499–1506.
[194] H.L. Pahl, Activators and target genes of Rel/NF-kappaB transcription factors, Oncogene 18 (1999) 6853–6866.
[195] W.J. Evans, J.G. Cannon, The metabolic effects of exercise-induced muscle damage, Exerc. Sport Sci. Rev. 19 (1991) 99–125.
[196] D. Aronson, J.F. Wojtaszewski, A. Thorell, J. Nygren, D. Zangen, E.A. Richter, O. Ljungqvist, R.A. Fielding, L.J. Goodyear, Extracellular-regulated protein kinase cascades are activated in response to injury in human skeletal muscle, Am. J. Physiol. 275 (1998) C555–C561.
[197] H. Shi, E. Boadu, F. Mercan, A.M. Le, R.J. Flach, L. Zhang, K.J. Tyner, B.B. Olwin, A.M. Bennett, MAP kinase phosphatase-1 deficiency impairs skeletal muscle regeneration and exacerbates muscular dystrophy, FASEB J. 24 (2010) 2985–2997.
[198] C. Handschin, B.M. Spiegelman, The role of exercise and PGC1alpha in inflammation and chronic disease, Nature 454 (2008) 463–469.
[199] J. Friden, M. Sjostrom, B. Ekblom, Myofibrillar damage following intense eccentric exercise in man, Int. J. Sports Med. 4 (1983) 170–176.
[200] D.A. Jones, D.J. Newham, J.M. Round, S.E. Tolfree, Experimental human muscle damage: morphological changes in relation to other indices of damage, J. Physiol. 375 (1986) 435–448.
[201] J. Friden, R.L. Lieber, Structural and mechanical basis of exercise-induced muscle injury, Med. Sci. Sports Exerc. 24 (1992) 521–530.
[202] D.L. Morgan, J.E. Gregory, U. Proske, The influence of fatigue on damage from eccentric contractions in the gastrocnemius muscle of the cat, J. Physiol. 561 (2004) 841–850.
[203] S.J. Choi, J.J. Widrick, Combined effects of fatigue and eccentric damage on muscle power, J. Appl. Physiol. (1985) 107 (2009) 1156–1164.
[204] M. Yamaguchi, M. Izumimoto, R.M. Robson, M.H. Stromer, Fine structure of wide and narrow vertebrate muscle Z-lines. A proposed model and computer simulation of Z-line architecture, J. Mol. Biol. 184 (1985) 621–643.
[205] I. Agarkova, R. Schoenauer, E. Ehler, L. Carlsson, E. Carlsson, L.E. Thornell, J. C. Perriard, The molecular composition of the sarcomeric M-band correlates with muscle fiber type, Eur. J. Cell Biol. 83 (2004) 193–204.
[206] L.G. Prado, I. Makarenko, C. Andresen, M. Kruger, C.A. Opitz, W.A. Linke, Isoform diversity of giant proteins in relation to passive and active contractile properties of rabbit skeletal muscles, J. Gen. Physiol. 126 (2005) 461–480.
[207] S. Muroya, P. Ertbjerg, L. Pomponio, M. Christensen, Desmin and troponin T are degraded faster in type IIb muscle fibers than in type I fibers during postmortem aging of porcine muscle, Meat Sci. 86 (2010) 764–769.
[208] M.A. Ho-Kim, P.A. Rogers, Quantitative analysis of dystrophin in fast- and slow-twitch mammalian skeletal muscle, FEBS Lett. 304 (1992) 187–191.
[209] S.J. Choi, J.J. Widrick, Calcium-activated force of human muscle fibers following a standardized eccentric contraction, Am. J. Physiol. Cell Physiol. 299 (2010) C1409–C1417.
[210] T.J. Koh, Do small heat shock proteins protect skeletal muscle from injury? Exerc. Sport Sci. Rev. 30 (2002) 117–121.
[211] S.B. Charge, M.A. Rudnicki, Cellular and molecular regulation of muscle regeneration, Physiol. Rev. 84 (2004) 209–238.
[212] L.C. Ceafalan, B.O. Popescu, M.E. Hinescu, Cellular players in skeletal muscle regeneration, Biomed. Res. Int. (2014) 957014.
[213] R. Sambasivan, R. Yao, A. Kissenpfennig, L. Van Wittenberghe, A. Paldi, B. Gayraud-Morel, H. Guenou, B. Malissen, S. Tajbakhsh, A. Galy, Pax7-expressing satellite cells are indispensable for adult skeletal muscle regeneration, Development 138 (2011) 3647–3656.
[214] H. Schmalbruch, U. Hellhammer, The number of nuclei in adult rat muscles with special reference to satellite cells, Anat. Rec. 189 (1977) 169–175.
[215] J.D. Rosenblatt, A.I. Lunt, D.J. Parry, T.A. Partridge, Culturing satellite cells from living single muscle fiber explants, In Vitro Cell Dev. Biol. Anim. 31 (1995) 773–779.
[216] M.C. Gibson, E. Schultz, The distribution of satellite cells and their relationship to specific fiber types in soleus and extensor digitorum longus muscles, Anat. Rec. 202 (1982) 329–337.
[217] C. Barjot, M.L. Cotten, C. Goblet, R.G. Whalen, F. Bacou, Expression of myosin heavy chain and of myogenic regulatory factor genes in fast or slow rabbit muscle satellite cell cultures, J. Muscle Res. Cell Motil. 16 (1995) 619–628.
[218] Y.C. Huang, R.G. Dennis, K. Baar, Cultured slow vs. fast skeletal muscle cells differ in physiology and responsiveness to stimulation, Am. J. Physiol. Cell Physiol. 291 (2006) C11–C17.
[219] N. Zanou, P. Gailly, Skeletal muscle hypertrophy and regeneration: interplay between the myogenic regulatory factors (MRFs) and insulin-like growth factors (IGFs) pathways, Cell. Mol. Life Sci. 70 (2013) 4117–4130.
[220] K. Esser, P. Gunning, E. Hardeman, Nerve-dependent and -independent patterns of mRNA expression in regenerating skeletal muscle, Dev. Biol. 159 (1993) 173–183.
[221] R.G. Whalen, J.B. Harris, G.S. Butler-Browne, S. Sesodia, Expression of myosin isoforms during notexin-induced regeneration of rat soleus muscles, Dev. Biol. 141 (1990) 24–40.
[222] J.M. Kalhovde, R. Jerkovic, I. Sefland, C. Cordonnier, E. Calabria, S. Schiaffino, T. Lomo, "Fast" and "slow" muscle fibres in hindlimb muscles of adult rats regenerate from intrinsically different satellite cells, J. Physiol. 562 (2005) 847–857.
[223] M.W. Berchtold, H. Brinkmeier, M. Muntener, Calcium ion in skeletal muscle: its crucial role for muscle function, plasticity, and disease, Physiol. Rev. 80 (2000) 1215–1265.
[224] J. Tothova, B. Blaauw, G. Pallafacchina, R. Rudolf, C. Argentini, C. Reggiani, S. Schiaffino, NFATc1 nucleocytoplasmic shuttling is controlled by nerve activity in skeletal muscle, J. Cell Sci. 119 (2006) 1604–1611.
[225] A.J. Rose, M. Hargreaves, Exercise increases Ca2+-calmodulin-dependent protein kinase II activity in human skeletal muscle, J. Physiol. 553 (2003) 303–309.
[226] M.J. Potthoff, H. Wu, M.A. Arnold, J.M. Shelton, J. Backs, J. McAnally, J. A. Richardson, R. Bassel-Duby, E.N. Olson, Histone deacetylase degradation and MEF2 activation promote the formation of slow-twitch myofibers, J. Clin. Invest. **117** (2007) 2459–2467.
[227] M. Schuler, F. Ali, C. Chambon, D. Duteil, J.M. Bornert, A. Tardivel, B. Desvergne, W. Wahli, P. Chambon, D. Metzger, PGC1alpha expression is controlled in skeletal muscles by PPARbeta, whose ablation results in fiber-type switching, obesity, and type 2 diabetes, Cell Metab. 4 (2006) 407–414.
[228] C. Zechner, L. Lai, J.F. Zechner, T. Geng, Z. Yan, J.W. Rumsey, D. Collia, Z. Chen, D.F. Wozniak, T.C. Leone, D.P. Kelly, Total skeletal muscle PGC-1 deficiency uncouples mitochondrial derangements from fiber type determination and insulin sensitivity, Cell Metab. 12 (2010) 633–642.
[229] R. Grifone, C. Laclef, F. Spitz, S. Lopez, J. Demignon, J.E. Guidotti, K. Kawakami, P.X. Xu, R. Kelly, B.J. Petrof, D. Daegelen, J.P. Concordet, P. Maire, Six1 and Eya1 expression can reprogram adult muscle from the slow-twitch phenotype into the fast-twitch phenotype, Mol. Cell. Biol. 24 (2004) 6253–6267.
[230] S.D. Mason, R.A. Howlett, M.J. Kim, I.M. Olfert, M.C. Hogan, W. McNulty, R. P. Hickey, P.D. Wagner, C.R. Kahn, F.J. Giordano, R.S. Johnson, Loss of skeletal muscle HIF-1alpha results in altered exercise endurance, PLoS Biol. 2 (2004) e288.
[231] S.M. Hughes, K. Koishi, M. Rudnicki, A.M. Maggs, MyoD protein is differentially accumulated in fast and slow skeletal muscle fibres and required for normal fibre type balance in rodents, Mech Dev 61 (1997) 151–163.
[232] A. Hennebry, C. Berry, V. Siriett, P. O'Callaghan, L. Chau, T. Watson, M. Sharma, R. Kambadur, Myostatin regulates fiber-type composition of skeletal muscle by regulating MEF2 and MyoD gene expression, Am. J. Physiol. Cell Physiol. 296 (2009) C525–C534.
[233] T. Kitamura, Y.I. Kitamura, Y. Funahashi, C.J. Shawber, D.H. Castrillon, R. Kollipara, R.A. DePinho, J. Kitajewski, D. Accili, A Foxo/Notch pathway controls myogenic differentiation and fiber type specification, J. Clin. Invest. 117 (2007) 2477–2485.