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Muscle fiber type diversification during exercise and regeneration

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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.

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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

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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].

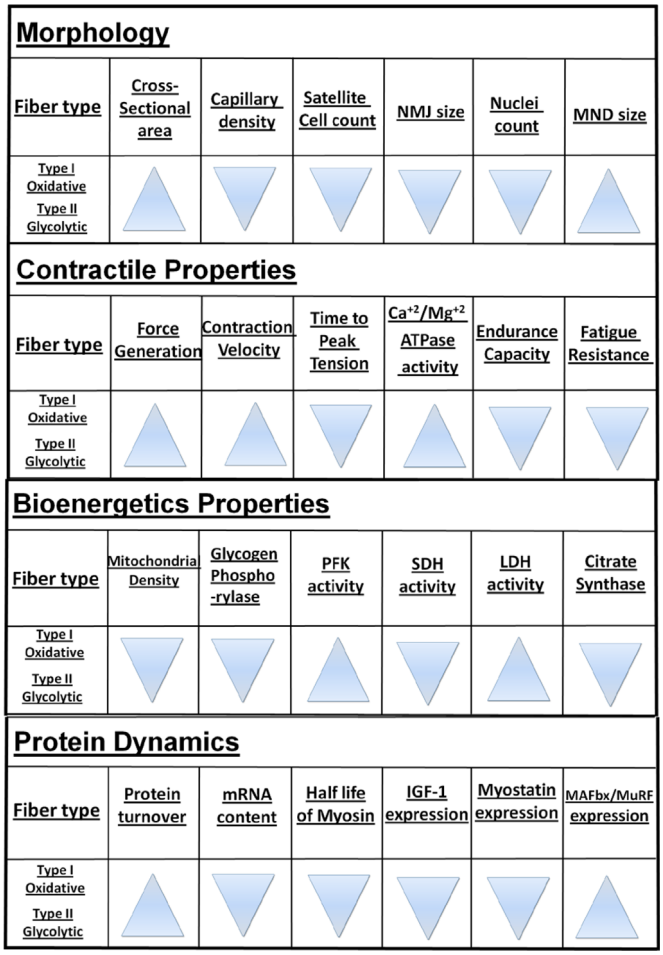

Fig. 1. Characteristics of individual fiber types in mammalian skeletal muscles. NMJ (Neuromuscular Junction); MND (Myonuclear Domain); PFK (Phosphofructo Kinase); SDH (Succinate Dehydrogenase); LDH (Lactate Dehydrogenase); IGF-1 (Insulin like Growth Factor-1).

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.