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Review

Development

Muscle fibre types: their role in health, disease and as therapeutic targets

N Hagiwara*

Abstract

Introduction

Accounting for approximately half of the body weight, the skeletal muscle is the largest organ in the human body. The functional significance of the muscle is seen in the two-fold purpose it serves–as a source of force production for locomotion and as a major regulatory organ for glucose and fatty acid metabolism. This short review will focus on muscle fibre types, starting with a brief historical overview of fibre types, their physiological and metabolic significance, how fibre type plasticity affects both contractile and metabolic properties of muscle and how these properties relate to human diseases known to exhibit muscle fibre type (slow-twitch vs. fast-twitch) disproportion. Also, based on recent animal model experiments, this paper discusses the efficacy of using fibre type manipulation for therapeutic purposes.

Conclusion

Because of its adaptability to external stimuli and easy accessibility, skeletal muscle remodeling could be a viable therapeutic approach for various diseases manifesting fibre type shifts. Reduced ratios of slow-oxidative muscle are significantly associated with obesity and type 2 diabetes. Recent information obtained from animal model studies for metabolic syndrome and muscle atrophy present multiple candidate genes and signaling pathways for use as therapeutic targets. As more detailed molecular mechanisms of fibre type specification and plasticity are revealed, manipulating physiological properties of skeletal muscle holds a promise for treatment of obesity-induced clinical conditions as well as muscle atrophy.

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Introduction

Heterogeneity is the foundation for the functional plasticity of the skeletal muscle. Muscle fibres contain a bundle of myofibrils, which consist of tandem repeats of sarcomeres, the contractile unit of skeletal muscle (Figure 1). The defining physiological properties of each muscle fibre–its contraction speed (slow/fast) and metabolic capacity (oxidative/glycolytic)–are a functional culmination of the coordinated expression of numerous sarcomeric contractile protein isoforms and metabolic enzymes. Therefore, the functionality of each muscle fibre is a summation of these properties and the resultant combination is termed 'fibre type'. Visual recognition of muscle fibre type–red versus white–has been reported for centuries[1]; however, only in the past 50 years has the extent of heterogeneity of muscle been fully appreciated. As an organ, human muscle is a checker board of these heterogeneous fibre types, allowing remarkable adaptation to various tasks requiring different degrees of intensity and duration.

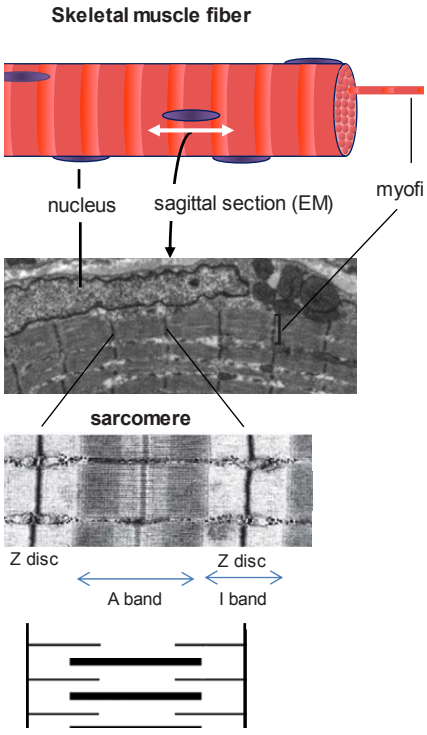

Figure 1: Skeletal muscle fibre.

Although muscle fibre type specification occurs during development[2], fibre type is not static in adult life. In addition to the activity-induced functional plasticity seen in normal adult muscle, disuse of muscle and disease-induced pathologies can selectively influence muscle fibre types, inducing different responses between fibre types. One common response associated with pathologic conditions is the predominance of one fibre type over the others. This phenomenon has been recognized as a significant clinical feature for human neuromuscular diseases over 40 years[3]. In spite of this decades old observation, three major unknowns still remain for any given disease: (1) what determines the differential responses between muscle fibre types, (2) whether predominance of one fibre type is causal or secondary to the pathological condition and (3) whether manipulating muscle fibre type can improve pathological

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conditions associated with fibre type predominance. Answers to the first two questions remain elusive; however, promising data have been obtained in recent years through the use of genetically engineered animal models to address the third issue, which in turn gives clues to answer the first two questions. The aim of this review is to discuss muscle fibre types and their role in health, disease and as therapeutic targets.

Discussion

The author has referenced some of his own studies in this review. These referenced studies have been conducted in accordance with the Declaration of Helsinki (1964) and the protocols of these studies have been approved by the relevant ethics committees related to the institution in which they were performed. All human subjects, in these referenced studies, gave informed consent to participate in these studies. Animal care was also in accordance with the institution guidelines.

Fibre type classification

Historically muscle fibre classification was performed visually, resulting in the classic 'red' and 'white' muscle terminology[1]. In the 1970s, histochemical analysis of myosin ATPase activity (still in use today) expanded the red/white distinction into three distinct fibre types, type 1, 2A and 2B (slow to fast respectively)[4]. It was not until the late 1980s that the development of isoform-specific myosin heavy chain (MyHC) monoclonal antibodies and single fibre analysis revealed that there are actually more than three fibre types in mammalian skeletal muscle[5,6]. While interpreting cross-species data, it is important to bear in mind species differences in histochemical ATPase classification to avoid confusion. It is now known that there are major species differences in the nature of classically defined type 2B fibres–particularly between small mammals such as rodents and large mammals such as humans[7,8] (Figure 2). Good historical overviews covering the evolution of fibre types[7,8] and the importance of hybrid fibres (expressing more than one MyHC isoform)[9,10] can be found in the literature.

Another important fibre type trait is metabolic capacity (i.e. oxidative and glycolytic metabolism). In adult skeletal muscle, contractile speed dictated by the MyHC ATPase activity is correlated with the spectrum of metabolic capacity; simply put, slow type I is high in mitochondrial content thus in oxidative enzymes (slow-oxidative), type2A–oxidative and glycolytic (fast oxidative-glycolytic), and type 2B–high in glycolytic enzymes and lowest in mitochondrial content (fast-glycolytic). Recently, functional specialization in mitochondria between oxidative and glycolytic fibres has been reported[11], adding yet more differential parameters for fibre type diversity.

Muscle fibre type in healthy and disease conditions

Muscle fibre type properties are modulated and maintained by electronic stimulations from motoneurons. Like skeletal muscle fibres, motoneurons are not made equal; different subsets of motoneurons stimulate muscle with distinctive frequencies[12,13], maintaining muscle fibre types in accordance with firing frequencies–higher frequencies of stimulation induce and maintain faster contracting and lower frequencies, slower contracting fibre type[14–16]. Therefore, specialized exercise regimens (aerobic or anaerobic) can induce a significant change towards slow oxidative or fast glycolytic transition[17–19]. Disuse of muscle also induces fibre type shift, in this case, from slow towards fast. In a microgravity environment (space flight) or bed rest, both of which largely release muscle from its weight bearing function, a measurable shift occurs from slow-oxidative towards fast-glycolytic[20–22]. In the muscle-disuse conditions, atrophy was also prominent in the muscle rich in slow-oxidative fibres[20,23].

In daily life, though our living situation is not as extreme as microgravity, a sedentary life style resulting in decreased muscle activity is becoming more common. A recent report portends worsening health conditions in the Unites States by revealing

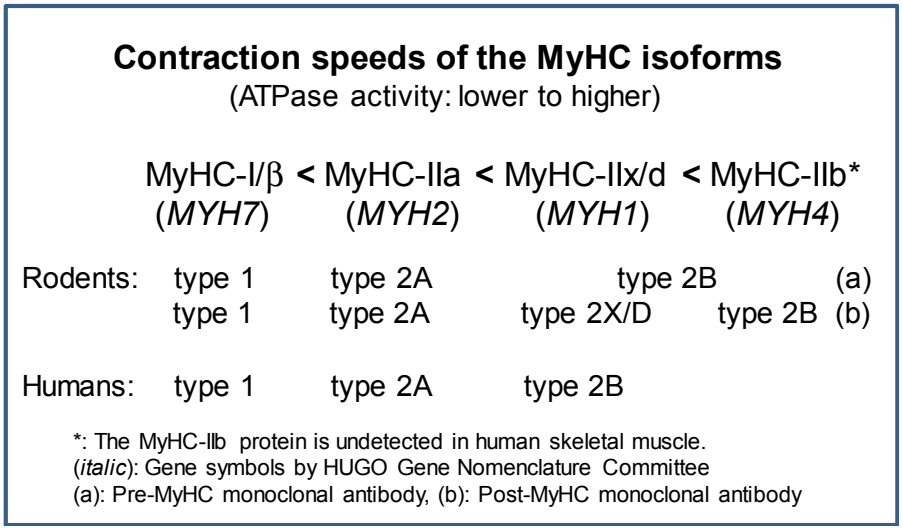

Figure 2: Contractions speeds of the MyHC isoforms (ATPase activity: lower to higher).

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significant increases in obesity, hypertension, hypercholesterolemia and diabetes in baby boomers, attributable to declining physical activity in American adults[24]. One might predict that in lifestyle-induced pathological conditions, skeletal muscle properties would exhibit similar changes to those seen in un-weighted muscle. Indeed, it has been reported that high-BMI (body mass index) individuals with insulin resistance and patients of type 2 diabetes exhibit decreased slow-oxidative fibres concurrent with increased fast-glycolytic fibres[25–27].

Gene expression profiling supports these observations at the molecular level; expression of the genes involved in oxidative metabolism is significantly decreased in pre-diabetic and type 2 diabetic individuals[28–30]. These reports collectively establish that insulin resistance and type 2 diabetes are strongly linked with reduced slow-oxidative fibre content and oxidative metabolic capacity.

Oxygen accessibility is also a significant factor affecting muscle fibre type proportion. Because of their heavy reliance on oxygen for ATP synthesis, hypoxic conditions are inhospitable for slow-oxidative fibres. Fibre type proportion in the limb muscle of chronic obstructive pulmonary disease (COPD)[31–34] and chronic heart failure (CHF)[35–38] patients show significant shifts from slow-oxidative towards fast-glycolytic. Together, the significant decrease in slow-oxidative fibres and reduction in oxidative metabolic capacity leads to exercise intolerance in COPD and CHF patients, substantially affecting their quality of life[39].

To begin addressing the topic of fibre types and congenital muscle disease, I would like to quote the opening sentence from Engle's prescient review written in 1970[3]: 'During the past few years, our studies of the histochemical changes of skeletal muscle in human neuromuscular diseases and experimental animal models have gradually led to the development of an analytical approach which places major emphasis upon determining whether there is selective or non-selective involvement of muscle fibre types in each human and animal condition studied'. Historically, at this point, only two types of fibres (I and II) were identified; however, even with this limitation it was clear that in many muscle diseases, there was a shift in the normally observed fibre type ratios or morphologies. With the advent of increased molecular diagnostics, many of the underlying mutations are coming to light, thinning out what has historically been a nosological minefield[40]. For example, a group of congenital myopathies with heterogeneous aetiologies known as congenital fibre type disproportion show morphological variance; type I fibres are consistently smaller than type II. According to this, mutations in at least four genes are known to lead to this disease[40,41]. Another common observation is variation of fibre type ratios, as seen in the monogenic disease Duchenne muscular dystrophy (DMD) which is caused by the loss of a functional dystrophin gene[42]. Dystrophin is expressed in all fibre types, and as the disease progresses, all muscle fibres in the proximal muscle of DMD patients succumb to degeneration; however, in the progression of the disease, it is the fast-glycolytic fibres that are the first to degenerate[43,44]. In the limb muscle of mdx mutant mice, a mouse model for DMD, fast fibres are more susceptible to degeneration–regeneration cycles, though the muscle pathology is far less severe than DMD[45]. The biological basis for this preferential degeneration of fast fibres in DMD muscle is not known. One hypothesis is that type 2B fibres are more susceptible to damage because of the mechanical stress caused by the rapid and forceful contraction of fast muscle[43,44]. This proposal was corroborated by the observation that in the mdx mice limb, fast muscles are more susceptible to contraction-induced injuries than the slow fibre-rich muscle[46].

Regulatory factors for fibre type specification

Mouse models have been instrumental in identifying genes involved in fibre type specification of mammalian skeletal muscle. I will discuss three categories of regulatory molecules reported to direct coordinate expression of fibre type specific genes. The goal here is not to present a complete list, but rather to present ideas of the nature of regulatory pathways involved in muscle fibre type specification.

Transcription factors regulating development

In recent years, transcription factors orchestrating expression of muscle fibre type-specific genes have been identified. Initially, the main focus was how fast and slow motoneuron-specific stimulation is converted into intracellular signals to initiate necessary transcriptional events for fibre type specification. When the skeletal muscle is electrically stimulated, Ca^{2+} is released from sarcoplasmic reticulum to initiate contraction. In slow fibre specification, this Ca^{2+} burst leads to activation of the NFAT[47–49] and Mef2 transcription factor families[50,51]. Together, these transcription factors play significant roles in slow fibre-specific gene transcription in response to motoneuron stimulation.

More recently, the transcription factors regulating muscle fibre type differentiation during development have started to be identified. Our laboratory showed that inactivation of the Sox6 transcription factor in muscle leads to a major shift in fibre type from fast to slow[52–54]. Using ChIP-seq, we have shown that Sox6 suppresses transcription of slow fibre-specific genes by directly binding to their regulatory sequences *in vivo*[52]. Sox6-null skeletal muscle also shows increased tolerance against fatigue[55], an

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oxidative fibre characteristic, indicating that Sox6 may be involved in the regulation of metabolic adaptation in the skeletal muscle. In line with these observations, the human SOX6 gene has been shown to be associated with obesity risk[56,57], suggesting the likelihood that Sox6 is involved in orchestrating the overall fibre type properties by repressing genes involved in the slow fibre phenotype.

In addition to transcriptional suppressors, activators of fibre type-specific genes have also been identified. For example, Tead1 and Six1/Six4 transcription factors have been shown to be necessary for activation of slow and fast fibre-specific genes, respectively[58,59]. It has been shown that muscle-specific Tead1 transgenic mice exhibit an increase of slow-oxidative fibres at the expense of fast-glycolytic fibres[60] and Six1/Six4 knockout mice show decrease in fast fibre differentiation in embryonic muscle[61].

Nuclear receptors and cofactor for energy metabolism

As the largest metabolic organ in the body, skeletal muscle is heavily influenced by, and in turn, highly influential on the metabolic state of the body. The dynamic status of glucose and fatty acids in the body has a significant influence on muscle fibre type regulation by altering the balance of oxidative (slow) and glycolytic (fast) fibres. One of the conduits for this influence is through ligands (fatty acids and their derivatives) interacting with nuclear receptors.

The peroxisome proliferator-activated receptors (PPARs) (α, β/δ, γ) are ligand-activated nuclear receptors[62]. Among them, PPARs α and β/δ have been shown to stimulate expression of genes for fatty acid oxidation in muscle[63,64]. Indeed, muscle-specific PPAR δ transgenic mice displayed a significant increase in both oxidative metabolic enzyme expression and type 1 fibres[65]. More recently, another family of nuclear receptors, the oestrogen receptor-related receptors (specifically, ERRγ), have been reported to stimulate the formation of not only slow-oxidative fibres but also vascularization[66,67], further expanding the involvement of nuclear receptors in metabolism-induced skeletal muscle remodelling.

Nuclear receptor functions are modulated by co-activators and/or co-repressors. PGC-1α, a co-activator of multiple lipid-activated nuclear receptors, plays a major role in mitochondrial biogenesis and regulation of oxidative phosphorylation[68]. Muscle-specific PGC-1α overexpression in mice leads to a significant increase in slow-oxidative fibres[69]. Conversely, nuclear receptor co-repressors suppress slow-oxidative fibre formation. Nuclear receptor corepressor 1 (NCoR1) antagonizes PGC-1a, thus suppressing oxidative metabolism in muscle[70,71].

MicroRNA

Muscle-specific microRNA plays a significant role in muscle fibre type regulation by addition of post-transcriptional regulation[72,73]. miR-499 has been shown to target Sox6[74,75]. Muscle-specific miR-499 overexpression in mice significantly increases expression of slow fibre-specific contractile protein genes, presumably by suppressing Sox6 activity[75]. In addition, microRNAs, whose expression is altered by physical activity have been reported[76,77], predicting the expanding role of miRNAs in skeletal muscle plasticity.

Therapeutic potential of muscle fibre remodelling for ameliorating muscle pathology

Recently researchers have shown that it is possible to manipulate muscle fibre type *in vivo*. Coordinated changes in muscle fibre type-specific genes shaping contractile and metabolic capacities observed in the genetically engineered mouse models discussed above have begun to reveal the therapeutic possibilities of muscle fibre type remodelling.

To date, multiple mouse models have been created that genetically increase type 1 fibres. These have been used to test the hypothesis that muscle enriched with slow-oxidative fibres can improve pathophysiology and force production in mdx mice (the mouse model for DMD). The results have shown promise. The higher content of type 1 fibres in mdx mice, induced by a PGC-1α transgene[78], transfection of the Wnt7a gene[79], or activation of calcineurin[80–82], all displayed decreased mechanical injury and improved force production. Of note, utrophin, a structurally and functionally similar protein to dystrophin, which is more abundantly expressed in type 1 slow fibres[83] is likely the basis for this improvement. Despite the physiological differences in human and mouse skeletal muscles, these emerging data point to the use of fibre type remodelling for amelioration of muscle degenerative pathology.

How can we take advantage of these discoveries? Pharmacological activation of some of the regulatory pathways discussed above has shown promise. For example, selective activation of PPARδ or AMP-activated protein kinase (a target of ERRγ[66]) had beneficial effects on mdx muscle pathology and significantly improved exercise capacity[84,85]. Therefore, with the ever increasing understanding of fibre type regulation, coupled with the growing ability to manipulate fibre type in vivo, the ability to remodel our skeletal muscle fibre types to alleviate muscle pathology or to expedite weight loss[86] to improve our overall health appears on the horizon.

Conclusion

Skeletal muscle is highly adaptive to external stimulations even in adult. Because of its easy accessibility, identifying targets for effective muscle remodeling could provide new approaches to treat various disease conditions manifesting fibre

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type shifts, such as type 2 diabetes and COPD. Animal model studies for metabolic syndrome and muscle atrophy have identified multiple genes whose expression can be manipulated to reduce weight gain and muscle wasting, providing new therapeutic target candidates. As more detailed molecular mechanisms of fibre type specification and plasticity are revealed, manipulating physiological properties of skeletal muscle holds a promise for treatment of obesity-induced clinical conditions as well as muscle atrophy.

Abbreviations list

BMI, body mass index; CHF, chronic heart failure; COPD, chronic obstructive pulmonary disease; DMD, Duchenne muscular dystrophy; MyHC, myosin heavy chain; NCoR1, nuclear receptor corepressor 1; PPARs, peroxisome proliferator-activated receptors.

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