Primer

Skeletal Muscle Fiber Type: Influence on Contractile and Metabolic Properties

Juleen R. Zierath*, John A. Hawley

Skeletal muscle demonstrates a remarkable plasticity, adapting to a variety of external stimuli (Booth and Thomason 1991; Chibalin et al. 2000; Hawley 2002; Flück and Hoppeler 2003), including habitual level of contractile activity (e.g., endurance exercise training), loading state (e.g., resistance exercise training), substrate availability (e.g., macronutrient supply), and the prevailing environmental conditions (e.g., thermal stress). This phenomenon of plasticity is common to all vertebrates (Schiaffino and Reggiani 1996). However, there exists a large variation in the magnitude of adaptability among species, and between individuals within a species. Such variability partly explains the marked differences in aspects of physical performance, such as endurance or strength, between individuals, as well as the relationship of skeletal muscle fiber type composition to certain chronic disease states, including obesity and insulin resistance.

In most mammals, skeletal muscle comprises about 55% of individual body mass and plays vital roles in locomotion, heat production during periods of cold stress, and overall metabolism (Figure 1). Thus, knowledge of the molecular and cellular events that regulate skeletal muscle plasticity can define the potential for adaptation in performance and metabolism, as well as lead to the discovery of novel genes and pathways in common clinical disease states.

How Is Skeletal Muscle Fiber Type Classified?

Much of our early understanding of the plasticity of skeletal muscle has been derived from studies undertaken by exercise physiologists (e.g., Holloszy 1967). With the application of surgical techniques to exercise physiology in the late 1960s (Bergstrom and Hultman 1966), it became possible to obtain biopsy samples (~150 mg) of human skeletal muscle, and by means of histological and biochemical analyses, specific morphological, contractile, and metabolic properties were identified. In 1873, the French anatomist Louis Antoine Ranvier had already observed that some muscles of the rabbit were redder in color, and contracted in a slower, more sustained manner, than paler muscles of the same animal. These early observations formed the basis of the classical terminology of red and white muscle fibers, which was subsequently found to be related to myoglobin (an iron-containing oxygen-transport protein in the red cells of the blood) content (Needham 1926). Based upon histochemical staining (Engel 1962), muscle fibers are now commonly distinguished as slow-twitch (ST), which stain dark or red, and fast-twitch (FT), which stain light or pale. In humans, a further subdivision of the FT fibers is made (Brooke and Kasier 1970), whereby the more aerobic (or oxidative) FT fiber is designated FT_{a}, and the more anaerobic (glycolytic) fiber is termed FT_{b}. Under aerobic conditions (sufficient oxygen supply to the working muscles), energy is produced without the production of lactate. Under anaerobic conditions (insufficient oxygen supply to the working muscles), energy is produced primarily through the production of lactate.

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Abbreviations: FT, fast-twitch; FT_{a}, aerobic FT fiber; FT_{b}, anaerobic FT fiber; HIF-1α, Hypoxia Inducible Factor-1α; MAPK, mitogen-activated protein kinase; MEF2, myocyte enhancer factor 2; PGC-1, peroxisome proliferator-activated receptor γ coactivator 1; PPARγ, peroxisome proliferator-activated receptor γ; ST, slow-twitch; VO_{2max}, maximal O_{2} uptake

Juleen R. Zierath is with the Department of Surgical Sciences, Section of Integrative Physiology, Karolinska Institutet, in Stockholm, Sweden. John A. Hawley is with the Exercise Metabolism Group, School of Medical Sciences, Faculty of Life Sciences at RMIT University in Bundoora, Australia.

*To whom correspondence should be addressed. E-mail: Juleen.Zierath@fyfa.ki.se

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working muscles), energy is produced via the glycolytic pathway, which results in lactate accumulation and in turn limits anaerobic exercise. Thus, muscle fibers can be classified in terms of contractile and metabolic properties (Table 1).

All individuals have different capacities to perform aerobic or anaerobic exercise, partly depending on their muscle fiber composition. In untrained individuals, the proportion of ST fibers in the vastus lateralis muscle (the largest of the quadriceps muscles and the most commonly studied muscle in humans), is typically around 55%, with FT fibers being twice as common as FT fibers (Saltin et al. 1977). While marked differences in the metabolic potentials between FT and FT fibers are observed in untrained humans, the absolute level for the activities of oxidative and glycolytic enzymes in all fiber types is large enough to accommodate substantial aerobic and anaerobic metabolism (Saltin et al. 1977). The dramatic heterogeneity of fiber type composition between people may explain their remarkable variation in exercise performance.

Does Muscle Fiber Type Composition Influence Athletic Performance?

During the 1970s and 1980s, it was popular to determine the muscle fiber composition of athletes from different sports events. These studies revealed that successful endurance athletes have relatively more ST than FT fibers in the trained musculature (Costill et al. 1976; Fink et al. 1977; Saltin et al. 1977). In contrast, sprinters have muscles that are composed predominantly of FT fibers (Costill et al. 1976). Accordingly, the belief that muscle fiber type can predict athletic success gained credibility. In particular, the notion that the proportion of ST fibers might be a factor governing success in endurance events was proposed (Gollnick et al. 1972; Costill et al. 1976).

In this regard, the results of Fink et al. (1977) are important. These researchers determined the fiber composition from the gastrocnemius muscle (the muscle of the calf of the leg) of 14 elite male long distance runners, 18 good (but not world-class) male long distance runners, and 19 untrained men. The elite group included Olympic medal winners (Figure 2) and American record holders at the time. Muscle from the elite runners contained a larger proportion of ST fibers than either the good runners or the untrained men (79.0% ± 3.5% versus 61.8% ± 2.9%.

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**Table 1. Contractile Characteristics, Selected Enzyme Activities, and Morphological and Metabolic Properties of Human Skeletal Muscle Fiber Types**

| Characteristic                  | ST Oxidative | FT Oxidative | FT Glycolytic |
|--------------------------------|--------------|--------------|---------------|
| **Contractile characteristics**|              |              |               |
| Time to peak tension           | 1.0          | 0.4          | 0.4           |
| Ca\(^{2+}\) myosin ATPase       | 1.0          | 3.0          | 3.0           |
| Mg\(^{2+}\) actomyosin ATPase   | 1.0          | 2.8          | 2.8           |
| **Enzyme activities**          |              |              |               |
| Creatine phosphokinase         | 1.0          | 1.3          | 1.3           |
| Phosphofructokinase            | 1.0          | 1.5          | 2.1           |
| Glycogen phosphorylase         | 1.0          | 2.1          | 3.1           |
| Citrate synthase               | 1.0          | 0.8          | 0.6           |
| **Morphological properties**   |              |              |               |
| Capillary density              | 1.0          | 0.8          | 0.6           |
| Mitochondrial density          | 1.0          | 0.7          | 0.4           |
| **Metabolic properties**       |              |              |               |
| Oxidative potential            | 1.0          | 0.7          | 0.2           |
| Glycolytic potential           | 1.0          | 1.5          | 2.0           |
| [Phosphocreatine]              | 1.0          | 1.2          | 1.2           |
| [Glycogen]                     | 1.0          | 1.3          | 1.5           |
| [Triacylglycerol]              | 1.0          | 0.4          | 0.2           |

This table highlights the relationship between skeletal muscle fiber-type composition and the indicated contractile and metabolic properties that are consistent with differences in speed and endurance. All values are expressed as a fold-change relative to ST oxidative fibers. DOI: 10.1371/journal.pbio.0020348.t001
metabolic properties (see Table 1), and is related to several contractile and functional properties is not confined to athletic ability. Insulin sensitivity also correlates with the proportion of ST oxidative fibers (Lilljoh et al. 1987). Specifically, insulin-stimulated glucose transport is greater in skeletal muscle enriched with ST muscle fibers (Henriksen et al. 1990; Song et al. 1999; Daugard et al. 2000), thus priming ST muscle for accelerated glucose uptake and metabolism. A shift in fiber distribution from ST to FT fibers gives rise to altered activities of key oxidative and glycolytic enzymes (Pette and Hofer 1980). Indeed, the ratio between glycolytic and oxidative enzyme activities in the skeletal muscle of non-insulin-dependent diabetic or obese individuals is related to insulin resistance (Simoneau et al. 1995; Simoneau and Kelley 1997). Similarly, with ageing and physical inactivity, two other conditions associated with ST-to-FT fiber-type transformation, oxidative capacity and insulin sensitivity, are diminished (Papa 1996).

Genes That Define Skeletal Muscle Phenotype

Skeletal muscle fiber-type phenotype is regulated by several independent signaling pathways (Figure 3). These include pathways involved with the Ras/mitogen-activated protein kinase (MAPK) (Murgia et al. 2000), calcineurin (Chin et al. 1998; Naya et al. 2000), calcium/calmodulin-dependent protein kinase IV (Wu et al. 2002), and the peroxisome proliferator-activated receptor δ (PPARδ) signaling pathway. Mice that harbor an activated form of PPARδ display a “endurance” phenotype, with a coordinated increase in oxidative enzymes that promote the nerve-dependent induction of the slow program in regenerating muscle (Murgia et al. 2000). Calcineurin, a Ca²⁺/calmodulin-activated phosphatase implicated in nerve activity-dependent fiber-type specification in skeletal muscle, directly controls the phosphorylation state of the transcription factor NFAT, allowing for its translocation to the nucleus and leading to the activation of slow-type muscle proteins in cooperation with myocyte enhancer factor 2 (MEF2) proteins and other regulatory proteins (Chin et al. 1998; Serrano et al. 2001). Calcium-dependent Ca²⁺/calmodulin kinase activity is also upregulated by slow motor neuron activity, possibly because it amplifies the slow-type calcineurin-generated effects on promoting MEF2 transactivator functions and enhancing oxidative capacity through stimulation of mitochondrial biogenesis (Wu et al. 2002).

Do Alterations in Skeletal Muscle Fiber Type Contribute to Metabolic Disease?

The close coupling between muscle fiber type and associated morphological, metabolic, and functional properties is not confined to athletic ability. Insulin sensitivity also correlates with the proportion of ST oxidative fibers (Lilljoh et al. 1987). Specifically, insulin-stimulated glucose transport is greater in skeletal muscle enriched with ST muscle fibers (Henriksen et al. 1990; Song et al. 1999; Daugard et al. 2000), thus priming ST muscle for accelerated glucose uptake and metabolism. A shift in fiber distribution from ST to FT fibers gives rise to altered activities of key oxidative and glycolytic enzymes (Pette and Hofer 1980). Indeed, the ratio between glycolytic and oxidative enzyme activities in the skeletal muscle of non-insulin-dependent diabetic or obese individuals is related to insulin resistance (Simoneau et al. 1995; Simoneau and Kelley 1997). Similarly, with ageing and physical inactivity, two other conditions associated with ST-to-FT fiber-type transformation, oxidative capacity and insulin sensitivity, are diminished (Papa 1996).
Can You Become a Slow-Twitcher?

With the 2004 Olympics still fresh on our minds, many will ask: Who has the right stuff to go the distance? Athletes like Olympic champion Frank Shorter are clearly exceptional and represent an extreme in human skeletal muscle phenotype. Realistically, few of us can ever hope to run a marathon in world-class time. However, there may be cause for some optimism for the average mortal, since endurance exercise training in healthy humans leads to fiber-type specific increases in the abundance of PGC-1 and PPAR-α protein in skeletal muscle (Russell et al. 2003). Moreover, functional genomics support the concept that skeletal muscle remodeling to a ST phenotype, either through activated calcineurin or PPARδ, can protect against the development of dietary-induced insulin resistance (Ryder et al. 2003) and obesity (Wang et al. 2004). The results of these studies have clinical relevance since insulin-resistant elderly subjects or PPARδ, can protect against the development of dietary-induced insulin resistance (Ryder et al. 2003) and obesity (Wang et al. 2004). The results of these studies have clinical relevance since insulin-resistant elderly subjects or PPARδ, can protect against the development of dietary-induced insulin resistance (Ryder et al. 2003) and obesity (Wang et al. 2004). The results of these studies have clinical relevance since insulin-resistant elderly subjects or PPARδ, can protect against the development of dietary-induced insulin resistance (Ryder et al. 2003) and obesity (Wang et al. 2004). The results of these studies have clinical relevance since insulin-resistant elderly subjects or PPARδ, can protect against the development of dietary-induced insulin resistance (Ryder et al. 2003) and obesity (Wang et al. 2004). The results of these studies have clinical relevance since insulin-resistant elderly subjects or PPARδ, can protect against the development of dietary-induced insulin resistance (Ryder et al. 2003) and obesity (Wang et al. 2004). The results of these studies have clinical relevance since insulin-resistant elderly subjects or PPARδ, can protect against the development of dietary-induced insulin resistance (Ryder et al. 2003) and obesity (Wang et al. 2004). The results of these studies have clinical relevance since insulin-resistant elderly subjects or PPARδ, can protect against the development of dietary-induced insulin resistance (Ryder et al. 2003) and obesity (Wang et al. 2004). The results of these studies have clinical relevance since insulin-resistant elderly subjects or PPARδ, can protect against the development of dietary-induced insulin resistance (Ryder et al. 2003) and obesity (Wang et al. 2004). The results of these studies have clinical relevance since insulin-resistant elderly subjects or PPARδ, can protect against the development of dietary-induced insulin resistance (Ryder et al. 2003) and obesity (Wang et al. 2004).

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