Metabolic plasticity in sarcopenia

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Abstract Epidemiological findings suggest that the pathogenesis and mortality rates of many age-related diseases are associated with sarcopenia, a condition defined as age-associated muscle weakening and atrophy. Skeletal muscle plays important roles beyond bodily movement, including modulating metabolic homeostasis in response to environmental changes. Skeletal muscle has great metabolic plasticity that enables it to modify its fiber-type composition to suit nutritional, state, and environmental changes. Aging brings a gradual decline in the metabolic plasticity of muscle. Deciphering the mechanisms of muscular metabolic adaptation can enable us to develop a better understanding of sarcopenia and assist in the development of early diagnostic tools as well as effective dietary and exercise intervention programs.

Keywords : sarcopenia, metabolic plasticity, fiber type, neuromuscular junctions (NMJs)

Introduction

Age-related disorders often diminish the quality of life in people fortunate enough to live a long life. Epidemiological studies in humans and experimental studies with rodents have indicated that skeletal muscle aging is a risk factor of mortality and age-related diseases, including metabolic syndrome, cancer, and dementia, as well as other neurological diseases¹⁻⁷. Although sarcopenia - that is, an age-related decline in muscle strength, mass, and performance^{8,9} - is a well-known geriatric syndrome¹⁰, there isn't a clear understanding of its effects or how to best mitigate it. In particular, the physiological roles of skeletal muscle beyond bodily mobility are underappreciated in sarcopenia.

Muscle is an important player in metabolism. Muscle tissue has a catabolic physiological response to fasting and cold conditions, during which it liberates metabolic energy stores and produces heat, respectively¹¹⁻¹⁴. Although the total amount of ATP in the adult human body is only about 100 g, the body cycles through approximately 40 kg of ATP in a 24-hour period at rest, and can cycle through 60 kg of ATP in 2 h of running¹⁵. Hence, a remarkably rapid turnover of ATP enables the body to be responsive to our dynamic environments. Moreover, several recent studies have indicated that the skeletal musculature functions as a key organ of metabolic adaptation^{7,16,17}.

The mechanisms and consequences of metabolic changes in sarcopenic muscles are poorly understood. The aim of this short review is to discuss the roles of metabolic adaptation of muscle and the implications of muscle fiber-type switching in sarcopenia.

Skeletal muscle and metabolism

In 2014, a new fossil discovery provided the earliest evidence of a muscled animal on Earth. The fossil, dubbed *Haoootia quadriformis*, dates from the Ediacaran Period, an interval spanning 635 to 541 million years ago¹⁸. *H. quadriformis* was identified as a cnidarian with bundles of fibrous ridges (Fig. 1). The finding of *H. quadriformis* fosters contemplation of the evolutionary advantages of muscular development, such as movement to enhance

Fig. 1 Creative illustration of the cnidarian *H. quadriformis*. *H. quadriformis* is the earliest known muscle bearing-animal to have lived on Earth, with the age of its recently discovered fossil dating to ca. 560 million years ago. (Reproduced from Liu et al. (2014) with permission¹⁸)

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feeding, storage of energy that could be harvested in starvation, and general adaptability.

In modern vertebrates, the skeletal musculature is physiologically vital and represents an immense portion of body mass. Indeed, approximately 40% of the weight of a healthy adult human is comprised of muscle. In addition to carrying out motor actions, our muscles provide an avenue of metabolic plasticity that enables us to adapt to changes in nutrient availability, environmental conditions, and internal state conditions^{19,20}. Although skeletal muscle accounts for only ~30% of the body's energy metabolism at rest, muscle cells can mediate 85% of the body's glucose disposal needs when they are stimulated by insulin. The remarkable metabolic upregulation achieved during intense physical activity (up to 20 times basal metabolic rate) is due overwhelmingly (~90%) to muscle activity²¹. During intense contraction, the energy use of skeletal muscle can increase by more than 100-fold nearly instantaneously²². In evolutionary terms, the remarkable dynamics of muscular metabolic plasticity have become critical to survival, especially in regards to avoiding natural enemies and hunting. Moreover, the metabolic plasticity of skeletal muscle can assist survival in harsh environments, including acting as a reservoir of potential energy that can be tapped in times of hunger and acting as a producer of body heat in cold environments.

Hence, given the multifaceted roles of muscle in adaptive responses, it is important to consider the physiological consequences of muscle atrophy beyond weakness and a decline in mobility. In particular, the potential loss of metabolic plasticity that may accompany sarcopenia should be examined and clarified.

Metabolic plasticity of muscles

The functional properties of particular muscles - of which there are more than 300 in the human body - are determined largely by the muscle's composition of muscle fiber types, namely type I (slow-oxidative), type IIa (fast-oxidative, a.k.a. intermediate), and type IIb (fast-glycolytic) muscle fibers. Each fiber type has characteristic contractile and metabolic traits, including a characteristic efficiency and capacity for energy production by oxidative/glycolytic metabolism.

ATP regeneration via the glycolytic pathway is approximately two times more active in type IIb fibers than in type I fibers; conversely, regeneration of creatine phosphate (source of phosphate for ADP→ATP reaction) by creatine kinase is also more active in type IIb fibers than in type I fibers^{19,23,24}. These features enable muscle fibers to generate a rapid and powerful contraction, providing the capacity for sudden high-intensity work.

On the other hand, mitochondrial oxidative ATP regeneration is more effective in slow type I fibers, which are highly enriched with mitochondria, than in fast type IIb fibers. The oxidative pathway in slow type I fibers has

the advantage of being able to utilize a variety of fuel sources, including both fatty acids and sugars. Thus, although ATP regeneration occurs at a slower rate in type I fibers relative to that in type IIb fibers, type I fibers are able to sustain ongoing activity. The metabolic properties of intermediate type IIa fibers appear to be a combination of those of type IIb and type I fibers, but the pathway dynamics for ATP regeneration in type IIa fibers are still not fully understood.

Contractile performance is dependent on the expression of myosin heavy chain (MyHC) isoforms²³. ATP hydrolysis rates differ among the MyHC isoforms, with the kinetic parameters increasing in the order 1-2A-(2X)-2B (MyHC 2B isoform is expressed in rodent muscles, but not human muscles; human IIb fibers express MyHC 2X isoform)²³. Hence, the highly glycolytically-active type IIb fibers expressing MyHC 2B can generate more power than type I fibers expressing MyHC 1, but they also consume ATP much more rapidly.

The relative make-up of fiber types within muscles, together with the expression of their characteristic myosin isoforms, can be altered in response to physiological demands, such as athletic training, even in adulthood^{17,24,25}. Shifts in muscle fiber composition can also be induced by pathophysiological conditions, including neuromuscular diseases, sarcopenia, hormonal changes, and drug abuse^{24,25} (Fig. 2). Furthermore, fiber-type composition has been shown to be altered in metabolic diseases^{24,25}. For example, type-1 diabetics exhibit a slow-to-fast shift with muscle wasting, whereas type-2 diabetics and obese individuals exhibit a fast-to-slow shift with muscle wasting. The causal relationship between muscle wasting and these fiber-type shifts is unknown. Interestingly, in aging muscles, fiber size and/or number reduction appears to occur mainly in type II (intermediate IIa and fast IIb) fibers, leading to a progressive decrease in the type II-to-type I fiber area ratio^{24,25}.

Fiber type shift in sarcopenia

Fast-to-slow fiber shifts in sarcopenia have been thought to be consequent to neurogenic adaptation rather than local metabolic cues. According to this view, loss of motor neurons and the neuromuscular junctions (NMJs) may remove stimulation for maintenance of the fast-fiber phenotype²⁶, and lead to compensatory reinnervation of originally fast fibers by axons innervating adjacent slow fibers. The observation that motor units (i.e. motor axons and their innervated muscle fibers) in young muscle are composed of all or nearly all the same fiber type support this supposition²⁷. Indeed, transient elevation of calcineurin, as is characteristic of endurance muscle activities, promotes fiber switching toward the slow type I phenotype¹⁷. Transgenic expression of constitutively active calcium/calmodulin-dependent protein kinase II (CaMKII) also promotes the formation of type I fibers in mice,

Fig. 2 Summary of conditions to induce muscle fiber-type switching.

whereas decreased CAMKII activity reduces the expression of type I-fiber genes¹⁷⁾. However, in cross-reinnervation experiments, electrical stimulation of muscle with patterns normally evoked by motoneurons innervating the intended “switch-to” fiber phenotype does not convert muscle fiber types as completely as would be expected if switching were neurogenically driven^{28,29)}.

In recent immunohistological experiments conducted in aged mice, structural changes in NMJs could not be consistently associated with a particular muscle fiber type³⁰⁾. In the soleus muscle, a higher incidence of age-related NMJ structural defects was observed in type I fibers than in type IIa fibers, whereas in the extensor digitorum longus, the incidence of NMJ defects in type I and type II fibers was similar. Furthermore, it has been shown that the determination of muscle fiber types and the homogeneity of a motor unit are influenced by the mutual interactions between motor neurons and muscle fibers³¹⁾.

Conclusions

Future research should examine whether sarcopenia involves an impairment of the metabolic flexibility of muscles, and if so, whether that impairment is due to a disruption of motoneuron-fiber interactions. Technological innovations, such as the development of mice with fiber-specific labeling that can demonstrate fiber type-shifts clearly³²⁾, can be used to resolve mechanistic questions about sarcopenia pathogenesis.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this article.

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