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Cells in focus

Skeletal muscle: Increasing the size of the locomotor cell

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ABSTRACT

Skeletal muscle is the most abundant tissue in the body comprising 40–50% of body mass in humans and playing a central role in maintaining metabolic health. Skeletal muscle protein undergoes rapid turnover, a process that is intricately regulated by the balance between the rates of protein synthesis and degradation. The process of skeletal muscle hypertrophy and regeneration is an important adaptive response to both contractile activity (i.e., exercise) and nutrient availability (i.e., protein ingestion). Ageing and physical inactivity are two conditions associated with a loss of skeletal muscle protein (sarcopenia). Sarcopenia is characterised by a deterioration of muscle quantity and quality, although the precise mechanism(s) underlying this condition remain to be elucidated. This review will (1) summarise our current understanding of the origin and plasticity of skeletal muscle, (2) discuss the major effectors of muscle growth, and (3) highlight the importance of skeletal muscle health in the prevention of several common pathologies.

Cell facts

- Approximately 50% of the body is comprised of skeletal muscle.
- There are two main types of skeletal muscle fibres: red, oxidative (slow) and white glycolytic (fast).
- Each skeletal muscle fibre contains several hundred to several thousand myofibrils which are comprised of large polymerized protein molecules (actin and myosin) responsible for contraction.
- Skeletal muscle cells show enormous plasticity adapting to a variety of external stimuli such as mechanical loading/unloading to either increase (hypertrophy) or decrease in size (atrophy).
- In healthy individuals ~80% of insulin-stimulated glucose uptake is taken up by skeletal muscle, highlighting the importance of this tissue in metabolic health.

1. Introduction

1.1. Morphology

In humans, skeletal muscle is the most abundant tissue in the body comprising 40–50% of body mass and playing vital roles in locomotion, heat production during periods of cold stress, and overall metabolism. Skeletal muscle is composed of bundles of muscle fibres called fascicles. The cell membrane surrounding the muscle cell is the sarcolemma, and beneath the sarcolemma lies the sarcoplasm, which contains the cellular proteins, organelles, and myofibrils. The myofibrils are composed of two major types of protein filaments: the thin actin filament and the thicker myosin filament. The arrangement of these two protein filaments gives skeletal muscle its striated appearance.

Human skeletal muscle fibres are classified in terms of contractile and metabolic properties (for review see Zierath and Hawley, 2004). Based upon histochemical staining, muscle fibres are commonly distinguished as slow-twitch (ST) oxidative (which stain dark or red), and fast-twitch (FT) glycolytic (which stain light or pale). In humans, a further subdivision of the FT fibres is made whereby the more aerobic (or oxidative) FT fibre is designated FT_a, and the more anaerobic (glycolytic) fibre is termed FT_b (Zierath and Hawley, 2004). There is a large degree of homogeneity within individual skeletal muscles in rodents, but this is not the case for humans. Indeed, the heterogeneity of fibre type composition between individuals helps explain, in part, the remarkable variation in metabolic potential and exercise capacity observed in

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humans. This brief review will (1) summarise our current understanding of the origin and plasticity of skeletal muscle, (2) discuss the major effectors of muscle growth, and (3) highlight the importance of skeletal muscle health in the prevention of several common pathologies.

2. Cell origin and plasticity

2.1. Cell origin

In 1961, two seminal studies demonstrated that the contractile unit of skeletal muscle, the myofibre, is formed by the fusion of large numbers of mononucleated myoblasts (Cooper and Konigsberg, 1961; Stockdale and Holtzer, 1961). Using electron microscopy techniques, it was observed that there was an apparently quiescent cell on the surface of the myofibre beneath its basement membrane. This cell was referred to as a 'satellite cell' in reference to its peripheral position (Mauro, 1961). Mammalian satellite cells originate from a group of transitory mesoderm-derived structures known as somites which differentiate into dermomyotome and sclerotome and the mesodermal cells become specified as skeletal muscle precursors within the nascent myotome (Zammit et al., 2006). Upon activation, satellite cells undergo a series of sequential events that lead ultimately to them fusing with existing myofibres and therefore increasing the size of the pre-existing muscle fibres. This process is carried out by a family of myogenic regulatory factors (MRF) including the myogenic differentiation factor (MyoD), myogenin, Myf5 and Myf6. Of these, MyoD is required to activate the satellite cell before being committed to differentiation by the second factor namely myogenin (see Fig. 1) (Arnold and Winter, 1998; Molkentin and Olson, 1996).

The MyoD family of basic helix–loop–helix transcription factors function as heterodimers with members of the E-protein family to induce myogenic gene activation by binding to the E1 E-box of the myogenin promoter leading to the activation of the transcriptional machinery (Parker et al., 2006). In the embryonic stage, MyoD is involved in the regulation of transcription defining myogenesis, whereas in adult skeletal muscle it plays an important role in muscle plasticity (discussed subsequently). An interaction between the phosphoinositide-3 kinase (PI3K) insulin signalling pathway and MyoD muscle cell differentiation has previously been demonstrated *in vitro*. In a yeast two-hybrid study, it was shown that protein kinase B (PKB/AKT) specifically interacted with prohibitin 2 (PHB2), a ubiquitously expressed regulator of cell proliferation (Sun et al., 2004). It is believed that PHB2 is able to inhibit muscle differentiation by repressing the transcriptional activity of MyoD. Phosphorylation and activation of AKT causes its partial translocation into the nucleus where by it competitively binds to PHB2 releasing its inhibitory effect on MyoD and therefore allowing the initiation of muscle differentiation.

2.2. Cell plasticity

Skeletal muscle is a highly heterogeneous tissue and demonstrates a remarkable plasticity, adapting to a variety of external stimuli including habitual level of contractile activity and loading state, substrate availability and the prevailing hormonal milieu. Within the basic functional unit of contraction, the sarcomere, there are a multitude of different structural, regulatory and contractile proteins, many of which exist as different isoforms, giving skeletal muscle a multiplicity of isoform expression (Schiaffino and Reggiani, 1996). Indeed, the inherent potential to increase the number of sarcomeres (i.e., hypertrophy), combined with an ability to alter protein isoform expression, gives muscle the unique ability to adapt to the many and varied challenges imposed upon it.

The introduction of invasive surgical procedures to exercise physiology in the mid-1970s (Bergstrom, 1975), permitted small biopsy samples (~100–150 mg) of human skeletal muscle to be excised, and by means of histological and biochemical analyses, the morphological, contractile, and metabolic properties were rapidly identified (Zierath and Hawley, 2004). Knowledge of the molecular and cellular events that regulate skeletal muscle plasticity is essential in order to define the capacity for adaptation in this tissue, as well as the potential for the discovery of novel genes and pathways in common clinical disease states (discussed subsequently).

3. Sending the signals for skeletal muscle growth

3.1. Effectors of muscle growth

Rates of human skeletal muscle protein synthesis can be determined by employing stable isotope techniques, in which labelled amino acid tracers (e.g., [$^2H_5$]phenylalanine) are infused intravenously for the duration of an intervention (i.e., exercise and/or nutrient challenge). Muscle protein synthesis is determined by measuring the incorporation of the tracer into small muscle samples obtained via single or multiple (time-course) biopsies (Rennie et al., 1982). These *in vivo* human techniques have the advantage of permitting the perfusion of the muscle by an intact circulatory system during a stable isotope infusion, coupled with the ability to combine direct measurements of protein turnover with simultaneous measures of protein and gene expression from the same muscle sample.

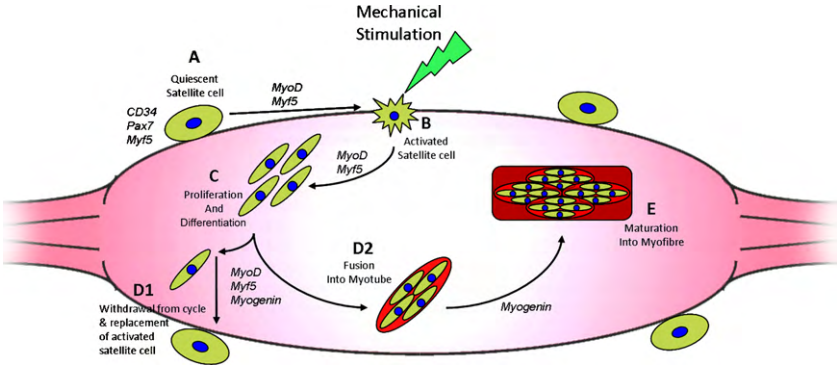

Fig. 1. Schematic of satellite cell activation in mature skeletal muscle. (A and B) Quiescent satellite cells are activated by external stimuli such as mechanical stimulation/contraction, (C) the activated satellite cell divides resulting in the formation of myoblasts that further proliferate and differentiate to form myotubes, (D1) at this stage, in a process of self renewal, some of the committed satellite cells withdraw from the cell cycle to replace the satellite cells that have been used up and therefore replenish the pool of quiescent satellite cells, and (D2 and E) the committed satellite cells which have fused to form myotubes then mature into myofibres. MyoD may act as a marker of satellite cell activation whereas myogenin is associated with the differentiation and formation of myofibres.