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Cells in focus

# Human exercise-mediated skeletal muscle hypertrophy is an intrinsic process

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ABSTRACT

Muscle cells (fibres) are post-mitotic and thus undergo changes in phenotype by modifying their existing structure. Hypertrophy is a hallmark change that occurs in response to increased loading and can be achieved in humans through repeated bouts of resistance exercise (i.e., training). In resistance exercise, contractions are initiated by neural drive leading to immediate perturbations such as calcium influx, cross-bridge cycling and tension/stress on the cytoskeleton, sarcolemma and extracellular matrix, as well as more delayed cellular events such as the production/release of potential local growth factors (e.g., IGF-1). Resistance exercise can also elevate the systemic concentration of certain hormones (growth hormone, testosterone, IGF-1) that are hypothesized to drive hypertrophy. However, while these hormones are clearly anabolic during childhood and puberty, or when given at supraphysiological exogenous doses, the transient post-exercise elevations in hormone concentration are of little consequence to the either the acute protein synthetic response or to a hypertrophic phenotype after resistance training. Thus, the acute post-exercise increases in systemic hormones are in no way a proxy marker for anabolism since they do not underpin the capacity of the muscle to hypertrophy in any measurable way. In contrast, the acute activation of intrinsically located signalling proteins such as $p70^{S6K}$ and the acute elevation of muscle protein synthesis are more reflective of the potential to increase in muscle mass with resistance training. Ultimately, local mechanisms are activated by the stress imposed by muscle loading and prime the muscle for protein accretion. Membrane-derived molecules and tension-sensing pathways are two intrinsic mechanisms implicated in upregulating the synthesis and incorporation of muscle proteins into the myofibre in response to mechanical stress derived from loaded contractions.



**Cell facts**

- Myocytes grow out of a developing myotome that arises from the somite.
- Muscle cells hypertrophy in response to locally mediated signals induced by chronic overload (e.g., resistance training).
- Exercise-induced changes in growth hormone and testosterone are *not* proxy markers of muscle cell hypertrophy.
- Muscular dystrophy affects ~1 in 3 500 male births leading to cardiac or respiratory failure and early death.

## 1. Introduction

Skeletal muscle hypertrophy describes an increase in the cross-sectional area of muscle cells (fibres). This process is primarily driven by the accretion of myofibrillar proteins which are predominantly composed of actin and myosin. Myofibrillar proteins are arranged into sarcomeres which are highly organized structures that form the basic contractile units of the muscle and which are assembled in series and in parallel to form the core of a multinucleated skeletal muscle fibre. Resistance exercise can elevate muscle protein synthesis (MPS) for ≥2 days (Phillips et al., 1997) and ingesting dietary protein during that post-exercise time period further potentiates the rise in MPS such that it exceeds the rate of protein breakdown resulting in a net positive protein balance and protein accretion (Biolo et al., 1997). Newly synthesized proteins are incorporated into the contractile apparatus which expands the mass of the existing protein pool and summates to measurably expand the myofibre. Resistance exercise activates a number of anabolic intracellular signalling pathways that increase MPS; this review will not focus on these intracellular signals per se but rather will outline several potential upstream mechanisms that initiate them. One exception is $p70^{S6K}$ which will be discussed in the context of a potential proxy marker for anabolism and hypertrophy.

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Proxy markers of muscle fibre hypertrophy can predict the anabolic response and are likely mediating crucial steps in the sequence of events that precede hypertrophy.

There has been confusion surrounding the influence of exercise-induced changes in systemic ostensibly 'anabolic' hormones such as growth hormone (GH), insulin-like growth factor-1 (IGF-1), and testosterone on muscle hypertrophy. Despite little empirical evidence, it has been hypothesized that the post-exercise rise in concentration of these hormones is important for inducing hypertrophy and thus has been used as a surrogate measure of hypertrophy potential. We contend that there is a complete lack of merit for purportedly anabolic exercise-induced elevations in systemic hormones to be used as proxy markers of hypertrophy. Instead, we will focus on local mechanisms that are intrinsically tied to contraction and which are far better candidates for increasing the activity of the cellular anabolic machinery leading to protein accretion.

Resistance exercise places a unique stress on muscle fibres that activates a variety of local mechanisms which prime the muscle for protein accretion in advance of measurable hypertrophy. Readers are referred to the following reviews for detailed descriptions of sarcomerogenesis (Kontrogianni-Konstantopoulos et al., 2009) and remodelling (Bassel-Duby and Olson, 2006), two processes that are integral to the assembly of newly synthesized proteins into a functional hypertrophied muscle fibre.

## 2. Cell origin and plasticity

### 2.1. Cell origin

Muscles cells grow out of the developing myotome that arises from the somite. The myotome forms epixial (back muscles) and hypaxial (abdominal, respiratory and limb muscles) regions. Continued development gives rise to a fully formed musculoskeletal system that continues to grow until shortly after puberty.

### 2.2. Plasticity and hormonal influences

Overt increases in muscle mass that occur during puberty in boys or following exogenous testosterone administration have led to the assumption that exercise-induced elevations in systemic hormones such as testosterone can be optimized to enhance hypertrophy (e.g., Gotshalk et al., 1997). Recently our work has focused on determining the relevance of the acute post-resistance exercise elevation of purportedly anabolic systemic hormones to the acute and chronic anabolic responses of skeletal muscle. Using a within-subject model, in one condition, participants performed exercise with a small muscle mass (elbow flexors) that resulted in no change in basal hormone levels. In the other condition, the participants perform the exact same arm exercise followed immediately by a bout of intense leg resistance exercise (i.e., exercised a large muscle mass) that elicited a large rise in endogenous hormone availability. We report that exercised-induced increases in testosterone, growth hormone and IGF-1 are neither necessary for nor do they enhance the acute synthesis of myofibrillar proteins (West et al., 2009b). Furthermore, exercise-induced increases in availability of these hormones did not enhance muscle strength or hypertrophy with training (West et al., 2009a). It should be noted that this transient elevation in systemic hormones such as testosterone is in contrast to the chronic supraphysiological levels of circulating testosterone that are induced by exogenous testosterone administration and which result in obvious muscle hypertrophy (Bhasin et al., 1996). Thus, the same anabolic mechanisms, such as increased MPS and gene expression and/or satellite cell addition, that are active when testosterone is at supraphysiological levels are not activated when testosterone is transiently elevated to level that is similar to the peak of the normal diurnal range. It is recognized that a normal physiological concentration of testosterone is required for a normal adaptive response to resistance exercise (Kvorning et al., 2006); our data (West et al., 2009a,b) suggests, however, that local mechanisms that are intrinsic to muscle contraction under load are of primary importance to protein accretion (Fig. 1).

### 2.3. Membrane mechanisms

Resistance exercise leads to deformation of the sarcolemma, the lipid bilayer encompassing the skeletal muscle cell, which alters the spatial relationship of enzymes and components of the membrane. These alterations are sensed by the muscle cell and conveyed to the translational machinery which regulates muscle protein turnover. It has become increasingly apparent that phosphatidic acid (PA), a membrane phospholipid released by phospholipase D (PLD) activation, is important for activating protein kinases/phosphatases that are involved in mediating muscle protein synthesis (Wang et al., 2006). For example, O'Neil et al. (2009) recently demonstrated in an *ex vivo* electrical stimulation model that PA concentration and mTOR activation, a key regulatory protein involved in protein synthesis, increase in response to eccentric contractions. Furthermore, blocking the synthesis of PA with L-butanol, a PLD inhibitor, completely abolished the increase in $p70^{S6K}$ following eccentric contractions and therefore may also inhibit MPS. Mechanistically, it appears that PA may be modulating mTOR via the FKBP12-rapamycin binding (FRB) domain of mTOR (Hornberger et al., 2006; Vilella-Bach et al., 1999) by binding to FRB which may elicit a conformational change that promotes autophosphorylation (Vilella-Bach et al., 1999). In contrast, rapamycin, an immunosuppressant drug with anti-proliferative effect, binds to the FKBP12 receptor protein and the FKBP12-rapamycin complex binds to the FRB domain on mTOR preventing the interaction of mTOR with target proteins involved in initiating MPS (Fang et al., 2001). Drummond et al. (2009) recently demonstrated that rapamycin administration blocks the normal obligatory rise in MPS following an acute bout of resistance exercise in humans. Collectively, these data (Drummond et al., 2009; O'Neil et al., 2009) point to the role of PA as an upstream regulator of mTOR which, in turn, regulates MPS. Overall, the control of MPS is a complex process with numerous regulatory points, but these studies (Hornberger et al., 2006; O'Neil et al., 2009), combined with others (Trappe et al., 2001) that demonstrate the role prostaglandin-derived pathways, provide compelling evidence that membrane-derived molecules play important roles in the regulation of MPS in humans and highlight an intrinsic pathway responsible for the ability of skeletal muscle to respond to a loading stimulus (Fig. 2).

### 2.4. Tension sensors

Intramuscular tension has long been identified as a key regulator of muscle mass on the basis of pioneering work in the areas of muscle hypertrophy and atrophy (Goldberg et al., 1975). Force produced by the myosin cross-bridge must be transferred through an extensive cytoskeletal and extracellular matrix in order to produce tension in the whole muscle and movement of the skeleton. There are many sites both in the force-generating apparatus and/or the force-transferring apparatus that may provide mechanosensory feedback to regulate muscle protein synthesis. These sites include: the myosin and elastic filaments, the costamere and extracellular matrix and the myotendinous junction.

The mechanosensory regulation of muscle protein synthesis has been widely studied at the level of the costamere (adhesion complexes that connect the Z-disk to the extracellular matrix) and the myotendinous junction (the connection of the ends of

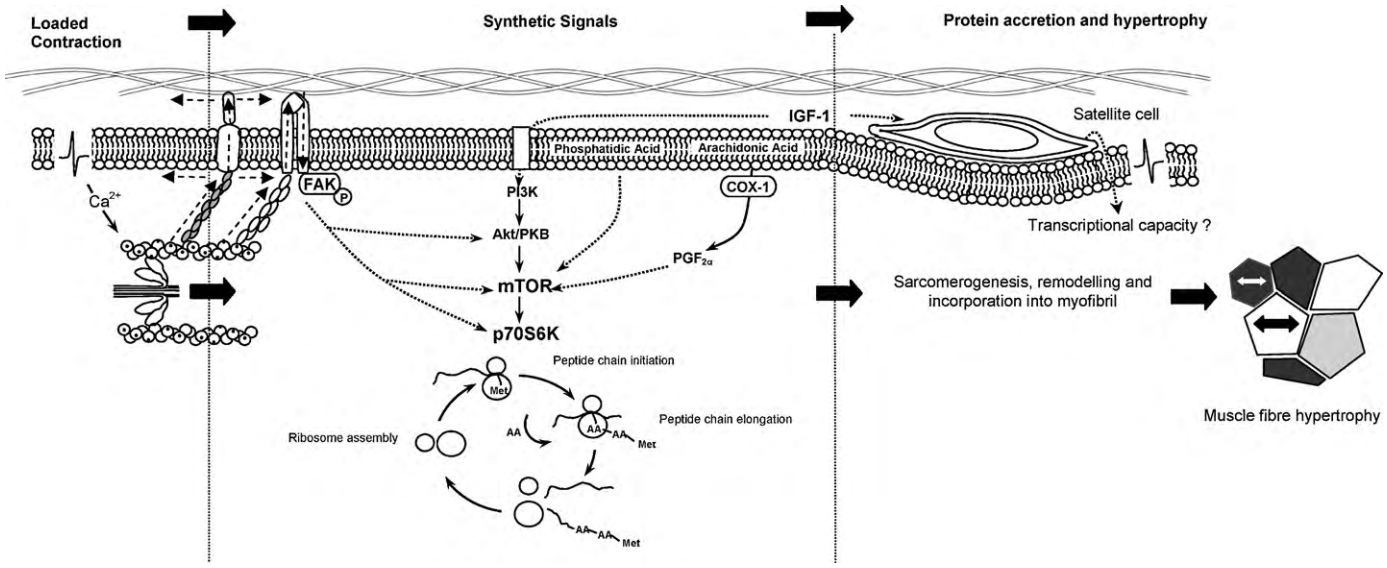


**Fig. 1.** Cellular events contributing to muscle protein synthesis, protein accretion and hypertrophy. Dashed arrows with solid heads on left hand side depict broad hypothesized patterns of force transmission. Tracings of IGF-1 and the satellite cell pathways rely primarily on animal data.

the myofibrils to the extracellular matrix). The costamere and the myotendinous junction each permit the transmission of force from the force-generating myofibrillar apparatus to the extracellular matrix and the mechanical deformation of transmembrane receptors (integrins) at these sites produce conformational changes in many of the receptor-associated multimodular proteins (Jani and Schock, 2009). In particular, mechanically induced conformational changes of focal adhesion kinase (FAK) proteins can elicit a phosphotransferase activity that may activate $p70^{S6K}$ via PI3K-Akt-mTOR-dependent (Zanchi and Lancha, 2008) and/or independent (Klossner et al., 2009) pathways. In addition to the reported role of integrins in upregulating muscle translational efficiency, deformation of the integrin molecule has been proposed to: promote the formation, expansion and development of adhesions, and to establish a scaffold matrix to guide the incorporation of actin and myosin during sarcomerogenesis (Jani and Schock, 2009). Interestingly, the phosphorylation of FAK has consistently been shown to be modulated by the activation history of a muscle, whether it is reduced activation of FAK in animal and human (Glover et al., 2008b) muscle following a period of unloading, or increased activation of FAK following increased muscle loading (Fluck et al., 1999). Thus, in response to mechanical stress, integrins may serve as a regulatory node for the coordinated up-regulation of the synthesis and incorporation of muscle proteins into the functional myofibre (Fig. 3).

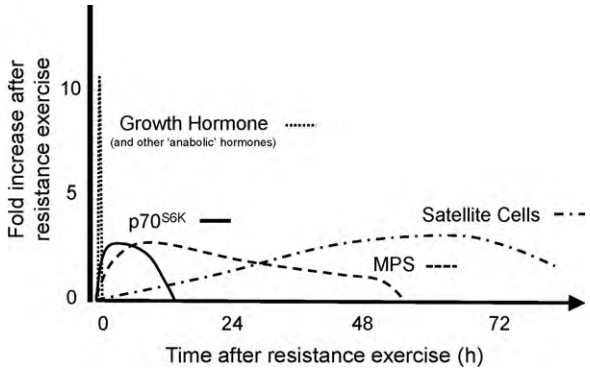


**Fig. 2.** Approximate time courses of selected intrinsic ($p70^{S6K}$, satellite cells, muscle protein synthesis (MPS)) and extrinsic (growth hormone) elements after an acute bout of resistance exercise in humans. Time courses approximate findings from West et al. (2009a) (growth hormone), Glover et al. (2008a) (p70S6K1), Phillips et al. (1997) (MPS) and McKay et al. (2009) (satellite cells). *Note*: Elevated phosphorylation of the p70S6K1 auto-inhibitory domain (T421/S424) but not the T389 site is reported 24 h post-exercise (Mayhew et al., 2009) although increased phosphorylation of the latter site is elevated 24 h following 12 min of stepping exercise (Cuthbertson et al., 2006).

### 2.5. Proxy markers of hypertrophy

The common observation that type II fibres tend to hypertrophy to a greater extent than type I fibres (e.g., Staron et al., 1990) provides the opportunity to examine differences in their anabolic signalling profile in response to loading. For example, it has been demonstrated that $p70^{S6K}$ is activated to a greater degree in type II fibres (Koopman et al., 2006), which may lead to a greater amplitude or duration of translation initiation and a subsequent rise in protein synthesis and account, at least in part, for the greater hypertrophy found in type II fibres. This observation is in agreement with a number of studies (e.g., Kumar et al., 2009; Terzis et al., 2008) that demonstrate that the acute activation of $p70^{S6K}$ can be indicative of the anabolic response. The phosphorylation sequence and kinetics of multiple serine and threonine residues on $p70^{S6K}$ by PI3-kinase-dependent and -independent regulatory protein kinases continue to be elucidated. It is thought that the $p70^{S6K}$ carboxy-terminal tail is auto-inhibitory in its unphosphorylated state, restricting phosphorylation by PDK1, preventing phosphorylation of a Thr252 residue and decreasing $p70^{S6K}$ activity (Alessi et al., 1998). Phosphorylation of multiple sites on the non-catalytic tail exposes key Ser/Thr residues to be phosphorylated which increases $p70^{S6K}$ catalytic activity. Interestingly, it appears that amino acids extend initial exercise-induced phosphorylation changes leading to phosphorylation of the Thr389 residue and full $p70^{S6K}$ activation (Karlsson et al., 2004). The observation that $p70^{S6K}$ activation is stimulated by resistance exercise alone (Eliasson et al., 2006) but also potentiated by the provision of amino acids (Karlsson et al., 2004) may explain why its level of activation after an acute bout is in good agreement with increases in muscle mass. It is also important to note that the dynamic measurement of acute post-exercise protein synthesis (West et al., 2009b; Wilkinson et al., 2007), which is acutely related to activation of $p70^{S6K}$, is reflective of a long-term hypertrophy response (Hartman et al., 2007; West et al., 2009a) a point we have discussed elsewhere (Burd et al., 2009).

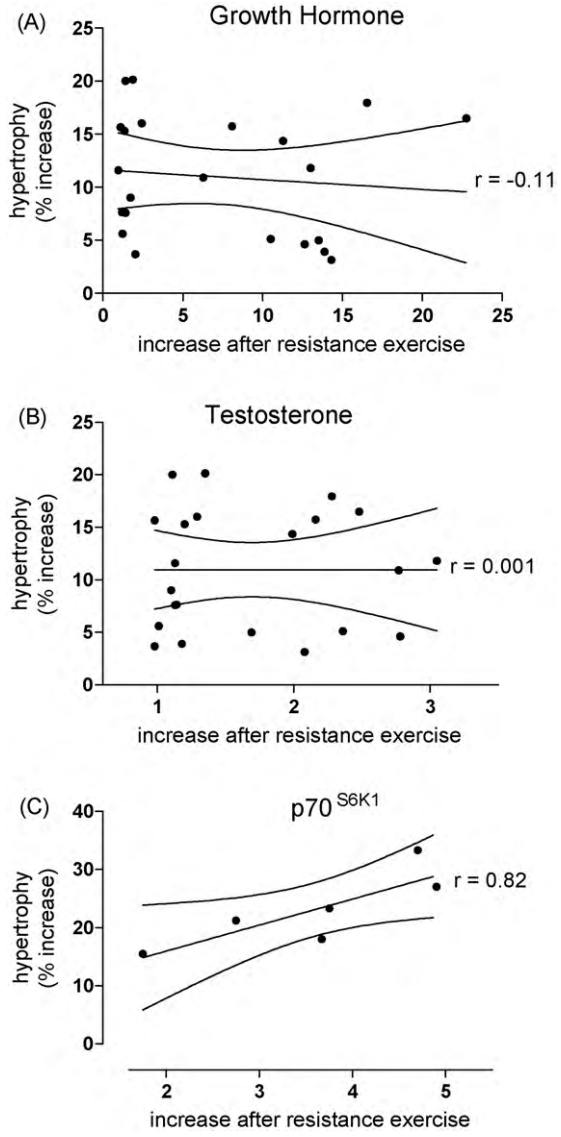


**Fig. 3.** (A and B) Correlations between the fold increase of growth hormone and testosterone (respectively) after resistance exercise and the increase in elbow flexor cross-sectional area after training (West et al., 2009a). (C) Correlation between the increase in p70 activation after an acute bout of exercise and the increase in type II fibre area after training redrawn with permission using data from Terzis et al. (2008).

### 2.6. Function

Skeletal muscle cells are bundled into fasicles and are connected to bone via myotendinous junctions. Muscle contractions can move the skeletal system in a coordinated fashion, generating locomotion. Among other functions, skeletal muscle: produces heat, protects organs, facilitates respiration, acts as a reservoir of amino acids and interacts with other organs (e.g., liver) through the circulatory system to regulate metabolism.

### 2.7. Associated pathologies

Skeletal muscle cells are associated with both pathologies of muscle tissue itself but also with systemic chronic diseases (e.g., diabetes, sarcopenia). Within the cell itself, muscular dystrophy is a disease that is characterized by a disruption of the complex that connects the cytoskeleton of the muscle cell to the extracellular matrix. This results in repeated cycles of degeneration and regeneration, connective tissue and fat infiltration, calcium dysregulation and muscle weakness among other effects.

## 3. Conclusions

Membrane-derived and tension-sensing mechanisms are excellent candidates to initiate anabolic intracellular signals to increase MPS prior to the more latent events of de novo myofibrillar synthesis, myofibril remodelling and ultimately hypertrophy. Proxy markers such as acute $p70^{S6K}$ phosphorylation or the acute increase MPS can predict a hypertrophy response whereas exercise-induced rises in hormones clearly do not. It is worth noting that recent refinement in the methodology used to determine fractional synthetic rates allows for the synthetic rates of specific protein sub-fractions (e.g., myofibrillar) to be determined which may prove to be a better predictor of hypertrophy. In summary, loaded contractions stimulate multiple local mechanisms that work in concert to mount the overall anabolic response. These intrinsic mechanisms, which govern the pathways that elevate MPS and which lead to hypertrophy, appear to reach some convergence at $p70^{S6K}$; however, the basis for the sustained elevation of MPS after resistance exercise (e.g., 16–48 h) requires further attention.

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