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Signaling for Muscular Hypertrophy May Exist with or without Activation of Satellite Cell

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Abstract

Skeletal muscle mass is a biomarker for health and optimizing athletic performance. Increasing skeletal muscle mass is a primary goal of many exercise regimens. Understanding hypertrophy means understanding that the extra and intracellular mechanisms of protein synthesis outweigh those of protein breakdown. Both occur from complex intracellular pathways activated or inhibited by extrinsic stimulus. Thus, this essay aims to describe the intracellular pathway and the role of satellite cells on skeletal muscle hypertrophy induced by exercise. Many aspects need stronger evidence of how these mechanisms could lead to differences between positive protein balance (synthesis higher than breakdown) and, consequently, hypertrophy.

Key words: Skeletal Muscle; Muscle Hypertrophy; Satellite Cells; Resistance Training; Exercise

INTRODUCTION

Skeletal muscle mass is a critical biomarker for maintaining health and optimizing athletic performance. Increasing skeletal muscle mass is a primary goal of many exercise regimens. Understanding hypertrophy means understanding that the extra and intracellular mechanisms of protein synthesis outweigh those of protein breakdown. Both occur from complex intracellular pathways activated

or inhibited by extrinsic stimulus (for example, exercise and nutritional status). Also, some findings showed that satellite cells play a role in substantial cell reconstruction after microdamage induced by some kinks of mechanical or metabolic fiber stress. It is estimated that the human body has about 600 muscles, which contribute 40-50% of body weight (Bagzir et al, 2017). In this context, between the basal membrane and the sarcolemma of each muscle fiber, mononuclear stem cells were discovered about 50 years ago, which by their peripheral location became known as "satellite cells" (Mauro, 1961; Cisterna et al, 2016). Subsequently, these same cells proved indispensable for the processes of muscle regeneration and repair, due to their frank capacity for self-renewal and multiple differentiation in cellular constituents (Morgan & Zammit, 2010). Thus, this essay aims to describe the intracellular pathway and the role of satellite cells on skeletal muscle hypertrophy induced by exercise.

Cell Signaling Pathways

Two well-known signaling cell pathways control skeletal muscle growth (Egerman & Glass, 2014). The first of these positively regulates muscle growth, comprising a cascade that includes growth factor IGF-1, and the activation of PI3K (phosphoinositide 3-kinase), Akt protein (kinase B protein), and mammalian rapamycin target (mTOR). In this context, the second pathway has an inhibitory effect on muscle growth and includes the interaction of myostatin protein with transcription factor SMAD3 (Schiaffino et al, 2013; Egerman & Glass, 2014).

Given the above, it has been shown that IGF-1 inactivation in animal skeletal muscle impairs growth and reduces the number and size of muscle fibers (Egan & Zierath 2013). Similarly, IGF-1 overexpression in muscle fiber promotes marked muscle hypertrophy, in a process dependent on the activation of the PI3K-Akt-mTOR cascade (Clemmons, 2009; Glass, 2010; Philippou & Barton, 2014). Akt phosphorylation is shown to increase protein synthesis by activating mTOR, which interacts with other proteins, to form mTORC1 complexes with the raptor subunit and mTORC2 with the rictor subunit (Glass, 2010; Philippou & Barton, 2014).

In addition to Akt, it has also been shown that amino acids are capable of activating mTOR, which, despite exerting control over protein synthesis, also participates in other processes such as

autophagy (Pasiakos, 2012; Egan & Zierath, 2013). Knock-out animals for mTOR have reduced postnatal muscle growth and a significant reduction in the size of fast-twitch fibers with slow preservation despite severe myopathy (Miyazaki & Esser, 2009). Despite the activation of two mTOR-associated complexes, complex 1 plays a major role in protein synthesis and is also a target for the inhibitory potential of rapamycin, whose treatment inhibits development, muscle regeneration and compensatory hypertrophy in experimental models submitted to elimination of synergists (Miyazaki & Esser, 2009; Goodman, 2014).

Given the above, although mTORC1 is able to influence the factors 4E-BP1 (Eukaryotic Translation Initiation Factor) and the S6K1 (S-6 Kinase 1), only the latter is essential for muscle hypertrophy and, in fact, its deletion results in atrophy and prevent the anabolic effect of constitutive activation of Akt (Miyazaki & Esser, 2009). It has also been shown that AMP kinase protein (AMPK), activated when intracellular energy levels are decreased, is able to block the inducing effect of mTORC1 on muscle hypertrophy, and AMPK-deficient mice demonstrate soleus muscle hypertrophy (Shaw, 2009; Huang, 2013).

Interestingly, it has recently been shown that the Yin-Yang transcription factor (YY1) is capable of physically interacting with mTORC1 and mediating the regulation of mTOR-dependent mitochondrial gene expression (Schiaffino et al, 2013). In this sense, mTORC1 appears to be able to induce YY1 phosphorylation, inducing the transcriptional repressor complex displacement of several genes that directly contributes to the expression of numerous genes involved in the insulin / IGF-1 signaling pathway, including Igf1, Irs1, Irs2, Akt1 and Akt2 (Schiaffino et al, 2013). In this context, the administration of rapamycin, by inhibiting mTORC1, and dephosphorylating YY1, again recruits the repressor complex of the promoter region of these genes and blocks its transcription (Schiaffino et al, 2013).

The second pathway for controlling muscle hypertrophy involves myostatin, a member of the growth transforming factors (TGF-ß) superfamily, which is produced by the skeletal muscle itself and negatively regulates muscle growth (Rodriguez et al, 2014). The participation of myostatin in this phenomenon has been classically represented by hypertrophy found in several mammalian species that

present mutations in the myostatin gene (Lee, 2004). In this same line of argument, exposure to purified myostatin inhibits protein synthesis of cultured myotube cells, and its systemic administration promotes muscle atrophy in mice (Rodriguez et al, 2014).

A protein known as follistatin, which is produced by the skeletal muscle and capable of inhibiting the action of myostatin, has also been identified, in addition to binding and neutralizing the activity of activin-A, another member of the TGF-β family that also acts as a negative regulator of muscle growth (Tsuchida, 2004). In this sense, follistatin exerts a deeper impact on hypertrophy than the deletion of the myostatin gene itself (Chen & Lee, 2016). Myostatin and activin-A interact with each other and activate the heterodimeric receptor in a process that antagonizes protein synthesis and muscle hypertrophy, and which may be inhibited by the administration of the soluble form of activin-A type II receptor (ACVR2B) (Tsuchida, 2004). The signal mediated by the myostatin/activin-A complex is believed to occur through phosphorylation and nuclear translocation of transcription factors SMAD2 and SMAD3 and formation of heterodimers with SMAD4. Although the targets of these factors are not yet known, it is speculated that they interfere negatively with the Akt-mTOR pathway (Esser, 2008; Sartori et al, 2009; Trendelenburg et al, 2009).

Muscle hypertrophy produced by ACVR2B transfection can be inhibited by rapamycin and that induced by follistatin is blocked by inactivation in different segments of the IGF-1/Akt/mTOR pathway (Esser, 2008; Glass, 2010). Similarly, overexpression of follistatin, induced by viral injection into skeletal muscle, increases Akt phosphorylation and signals for activation of protein synthesis, in a process dependent on mTOR activation, which is suppressed by exposure to rapamycin (Schiaffino et al, 2013). Apparently, inhibiting SMAD3 interaction with follistatin is critical for Akt-mTOR signaling, although, as demonstrated in other cellular systems, SMAD3 can interact directly with Akt and suppress protein synthesis in that environment (Remy et al, 2004; Conery et al, 2004; Esser, 2008).

Such evidence demonstrates that there is communication between the myostatin/activin-A complex and the IGF-1 signaling pathway in order to control the degree of muscle fiber hypertrophy (Guerci et al, 2012). However, more recently, it has been shown that other pathways are also involved in the process of skeletal muscle

hypertrophy. These include serum responsive factors (SRFs), which are required to induce hypertrophy in synergist ablation models, in a role mediated by interleukins 6 and 4 (IL-6 and IL-4) that act paraclinically to induce proliferation and satellite cell fusion (Charvet et al, 2006; Li et al, 2005). SRFs have also been shown to activate Akt through the miR-486 microRNA, which is capable of inhibiting PTEN phosphatase, which negatively affects PI3K-Akt signaling (Hitachi & Tsuchida, 2013).

Androgen and beta-2 adrenergic agonists are also capable of activating a PI3K-Akt-mTOR pathway and contribute to increased protein synthesis process. In this sense, administration of testosterone or mimetics that prioritizes the development of male secondary sexual characteristics may produce hypertrophy in models where testosterone is present, Igf-1 mRNA, Igf-1 mRNA, Igf-1 mRNA, Akt and reduced protein reduction rate in processes that are inverted with nandrolone (Vicencio et al, 2011). Similarly, clenbuterol or formoterol, beta-2 adrenergic agonists are capable of activating, activating a cyclic AMP, promoting Akt activation in a process blocked by rapamycin. (Berdeaux & Stewart, 2012).

Another extracellular protein known as Wnt7a is able to contribute to hypertrophy through satellite cell activation and Fzd7 receptor binding, which is also involved in activation of the PI3K-Akt-mTOR pathway (Schiaffino et al, 2013). This process seems to be potentiated by the positive impact of tension modifications of the sarcolemma and membrane containing the abundance of the enzyme nitric oxide synthetase in its neuronal isoform, which is abundant in the skeletal muscle. It is believed that the released nitric oxide would be able to interact with superoxide anions produced by contractile fiber mitochondria during exercise and promote the synthesis of peroxynitrite, an aggressive reactive oxygen species that has, however, already been involved in activation of vanilloid receptors Trpv1 present in the sarcoplasmic reticulum and subsequent release of calcium ions from its interior. Thus, the moderate increase in calcium ion concentration in cytosol would positively influence many metabolic aspects and also activate mTOR to promote changes in the protein synthesis process (Vicencio et al, 2011; Ito et al, 2013).

Mechanical membrane stimuli would also be able to activate mTOR via an Akt-independent pathway involving phosphatidic acid and activated phospholipase D (Hornberger et al, 2006; Shad et al,

2015; Bond, 2017). On the other hand, the fourth isoform of the transcription factor PGC-alpha was recently identified, whose isoform 1 is traditionally involved in mitochondrial biogenesis being the target of AMPK. Differently, PGCα-4 would be involved in the increase of muscle mass and strength being able to suppress the action of myostatin and, in fact, in clenbuterol-induced hypertrophy is abolished by deletion of the PGCα-4 gene (Ruas et al, 2012).

Finally, although we have previously addressed the role of satellite cells in the hypertrophy process, it should be noted that muscle regeneration recaptures embryonic and neonatal myogenesis in a process involving the activation, self-renewal, proliferation, and fusion of myogenic stem cells and almost always includes immune activation and inflammation (Costamagna et al., 2015). In any case, it is important to note that muscle hypertrophy may exist even in the absence of significant satellite cell activation and in fact, when this phenomenon is stimulated by clenbuterol, the muscle growth process does not involve satellite cell activation, as occurs in reintroduction of gravitational loading after intentional removal period to induce muscle atrophy (Maltin & Delday, 1992; Jackson et al, 2012).

Even in signaling for follistatin-induced hypertrophy, satellite cells do not appear to participate (Pallafacchina et al, 2013). However, in the aforementioned experimental models, where synergists are intentionally removed from animal limbs to produce compensatory hypertrophy of agonists, there is immediate proliferation and fusion of satellite cells, with well-evidenced increases in the number of myonuclei in process which is also verified after eccentric contraction performed with high load and for a long time and capable of producing micro-lesions and localized inflammation (Schiaffino et al, 1972; Costamagna et al, 2015). Such experimental models are traditionally performed in rats and involve the removal of the gastrocnemius or anterior tibial to observe, respectively, the hypertrophy of the sole or long extensor of the fingers.

Similarly, it is well demonstrated that IGF-1 mediated hypertrophy involves satellite cell activation and that IL-6 and IL-4 cytokines are directly involved in muscle growth of experimental models involving overload (Guerci et al, 2012). However, it is essential to remember that even with the elimination of 90% of satellite cells through the use of PAX7 toxins, some muscle hypertrophy can still be observed (Pallafacchina et al, 2013). Given the above, it seems evident

that in mammals, there may be hypertrophy with or without satellite cell involvement (Pallafacchina et al, 2013). In this context, acute and aggressive stimuli, such as the elimination of synergists or intense exercise with high eccentric component and presence of muscle damage, seem to involve the participation of satellite cells for regeneration and compensatory adaptive hypertrophy. On the other hand, more gradual physical exercise stimuli and experimental models that replace the load on one or both limbs after intentional removal (functional overload model), the verified hypertrophy does not appear to involve satellite cell activation, being associated exclusively with the increase in protein synthesis process (Schiaffino et al, 2013).

Satellite Cells

In fact, with recognized importance in skeletal muscle growth and regeneration, satellite cells also participate in the process of muscle hypertrophy, as they have the potential for differentiation into new nuclei, contributing to broadening the myonuclear domain of the fiber, thereby increasing its ability to synthesize new sarcomeres (Garg & Boppart, 2016). It is, therefore, a relevant reserve of myonuclei, necessary to adjust the plasticity of each fiber, the demand imposed by the amount of work performed (Cisterna et al. 2016; Garg & Boppart, 2016).

Although usually quiescent from a mitotic point of view, these cells can be activated to produce myoblasts and myonuclei necessary for regeneration, through a sequence of events that include activation, proliferation and cell differentiation (Morgan & Zammit, 2010; Snijders et al, 2015). Thus, once activated, satellite cells can be self-renewed to provide a population of new, undifferentiated, quiescent progenitor cells that replenish the parent cell and/or originate another cell which may undergo differentiation in the myogenesis pathway (Bazgir et al, 2017).

Although satellite cells can be recognized by electron microscopy, a laborious and costly process in recent years, genetic and systemic markers such as MyoD, myogenin, and PAX7 have been used to identify them (Snijders et al. 2015). In this sense, although satellite cells are usually quiescent, being activated by different physiological and pathophysiological stimuli, their characterization is not simple, since their quantity and spatial distribution vary greatly between fibers and between individuals (Garg & Boppart, 2016).

In this context, when the skeletal muscle contracts during exercise, or is injured in this and other situations, satellite cells abandon their quiescent state and become activated to subsequently proliferate, differentiate, and fuse to pre-existing myofibers, creating new myofibers or returning to their quiescent basal state (Dhawan & Rando, 2005; Snijders et al. 2015). Although there is little information about satellite cell activation, there is evidence that the group of myogenic factors (MRFs), such as Myf-5, MyoD and myogenin, control the progression of the myogenic lineage (Zanou & Gailly, 2013; Motohashi & Asakura, 2014). However, whether in response to endocrine and mechanical stimuli associated with exercise, with or without MRF control, satellite cells can be activated, proliferate and differentiate to participate in regeneration and adaptation of skeletal muscle (Zanou & Gailly, 2013; Snijders et al. 2015). In this way, they not only increase the density of myonuclear nuclei but also represent an essential factor in the regeneration of injured fibers or the constitution of new fibers in replacement for those destroyed.

There are evidences that denervation (Wozniak et al, 2005), aging (Darr & Schultz, 1987; Brooks & Myburgh, 2014), sarcopenia (Bankole et al, 2013; Brooks & Myburgh, 2014) and even caloric restriction (Cerletti et al, 2012; Sharples et al, 2015) are stimuli capable of activating satellite cells. However, physical exercise represents the most important factor capable of activating these cells, in a process that seems to be dependent on the volume and intensity load of each session, as well as the training time (Parise et al, 2008; Motohashi & Asakura, 2014). The simple mechanical stretching of muscle fibers (Tatsumi et al, 2002; Wozniak et al, 2003) affects the quiescence of satellite cells, as well as their number and state of differentiation. In this context, local and systemic growth factors such as insulin-like growth factor (IGF-1) and hepatocyte growth factor (HGF) appear to play an significant role in activating and orienting the pathway of activated satellite cells (Ten Broek et al, 2010; Shefer & Benayahu, 2012), in a process also involving nitric oxide and the aforementioned mechanical stretching of the fibers (Wozniak et al, 2003; Motohashi & Asakura 2014).

As previously suggested, the addition of satellite cells to the muscle fiber cytosol positively influences muscle hypertrophy, represented by the increase in muscle fiber size, which is frequently observed in strength training and sports activities (Phillips, 2014). In

this sense, according to the theory of the myonuclear domain, the increase of myonuclei is obligatory for the substantial increase of the muscle fiber cross-sectional area (Mozdziak et al, 1997; Qaisar & Larsson, 2014). This theory assumes that the increase of sarcomeres occurs with the addition of new nuclei, capable of synthesizing proteins to a greater extent, and that atrophy would occur with apoptosis subtraction of these same nuclei (Brooks & Myburgh, 2014; Gundersen & Bruusgaard, 2008).

The addition of new nuclei from satellite cell activation promotes muscle growth since each nucleus can only sustain a maximum domain of approximately 2000 μm2 per nucleus (Petrella et al, 2006; Petrella et al, 2008). Nevertheless, trained individuals who have discontinued training for decades may have higher nucleus density from satellite cells that were once activated during the training period ("muscle memory"), and once again exposed to muscle training stimuli, recover more quickly, muscle strength and mass, compared to those who had lifelong sedentary behavior (Petrella et al, 2006; Hoppeler et al, 2011).

In this sense, although young and old individuals have similar responses to strength training, satellite cell content, as well as muscle mass, tends to decline with aging, an effect that is more exacerbated in women than men. Men have the collaboration of testosterone, which is another critical activating agent of these cells (Kadi & Thornell, 2000; Kosek et al, 2006). Also, in this context, satellite cells and myoblasts express myostatin, one of the most potent inhibitors of muscle hypertrophy (Ten Broek et al, 2010), which is capable of suppressing MyoD factor and, despite increasing the capacity of satellite cells to maintain their quiescent condition (Shi & Garry, 2006).

Because of the above, it is believed that the muscle regeneration process includes the initial, repair and remodeling phases that seem to be controlled by endocrine and autocrine factors. In this context, satellite cells are directly involved in the regeneration process, especially in the repair and remodeling phases (Brack et al, 2007). Positive satellite cell activators include macrophages (Chazaud et al, 2003), microvascular angiogenesis (Rhoads et al, 2009), mechanical or nitric oxide synthesis growth factor induction (Tatsumi et al, 2009), fibroblasts and smooth muscle cells (Abou-Khalil et al, 2009), and muscle fiber characteristics (Brack & Rando, 2007). Many

pieces of evidence also indicate that the presence of inflammation and growth factors produced by muscle such as MGF, LIF, HGF and FGF increase muscle regeneration in humans and animals (Kurek et al, 1997; Miller et al, 2000; Brimah et al, 2004; Mourkioti & Rosenthal, 2005; Broholm & Pedersen, 2010; Shefer & Benayahu, 2012; Zanou & Gailly, 2013).

It is well evidenced that muscle activity increases satellite cell proliferation (Darr & Schultz, 1987), while inactivity reduces this proliferation (Schultz, 1984). Thus, different exercise interventions may modulate satellite cell activation differently (Macaluso & Myburgh, 2012). Micro lesions seen after prolonged aerobic exercise appear to be able to activate satellite cells directly proportional to increases in intensity that, together with the eccentric contraction component alone (Crameri et al. 2004; O'Reilly et al, 2008; Burd et al, 2010; Dreyer et al, 2006) or combined with nutritional supplements (Shelmadine et al, 2009), represent the most important factors in its activation (Kurosaka et al, 2012). Even so, it is still difficult to define a specific exercise type or minimum intensity responsible for satellite cell activation (Burd et al, 2010).

Besides, the volume of eccentric contractions associated with prolonged aerobic exercise also appears to play an essential role in satellite cell activation (Burd et al, 2010). Indeed, it has been suggested that low intensity, high volume strength training has a greater impact on satellite cell activation than low volume and high intensity methodologies, suggesting that fatigue represents an important stimulus for activation, proliferation and satellite cell differentiation, and indicating that there is also a volume threshold for this purpose. In this sense, aerobic training, similar to strength training, also induces satellite cell activation and selective muscle hypertrophy (Petrella et al, 2008; Bruusgaard et al, 2010).

However, aerobic training does not appear to alter the satellite cell content (Hoppeler et al, 1985; Ingjer, 1979) or increase the density of myonuclei, activating satellite cells predominantly for regenerative processes (Petrella et al, 2006; Smith & Merry, 2012). It has already been suggested that the antagonism of aerobic training on the adaptive process associated with strength training (concurrent training) is associated with the impediment of the formation of new myonuclei associated with the first methodology (Babcock et al, 2012).

In this sense, type I fibers have more satellite cells than type II fibers and therefore have lower adaptive potential. The contribution to type II fiber hypertrophy seems to be higher than type I fibers, precisely because of the potential for a positive response to satellite cell activation. Although the previously proposed mechanism needs further scientific clarification, it is consistent with the need for greater exercise intensity to promote activation of significant numbers of satellite cells in the process, which probably include tissue damage and local inflammation, although it has also been evidenced activation of satellite cells in the absence of inflammation (Burd et al, 2010; Paulsen et al, 2012; Schoenfeld, 2012b; Belizario et al, 2016).

Interestingly, it has recently been proposed that stem cells known as Sca-1 would be able, despite the low rate of renewal, to regenerate aged mammalian heart fibers (Uchida et al, 2013). Further studies need to be performed to understand the satellite cell activation process and to elaborate activation strategies in patients with sarcopenia, cachexia, or muscle diseases characterized by atrophy and, therefore, severe metabolic impact on the human body (Always et al, 2014).

Similarly, it is important to disclose the participation of the Hippo signaling pathway and the microRNAs, which have recently been shown to influence satellite cell activation in response to exercise (Burd et al, 2010, Yu & Zuo, 2013), as well as the attenuation procedures of the inflammatory process through drugs used by some individuals that may compromise muscle regeneration (Mackey, 2013; Schoenfeld, 2012a). Briefly, satellite cell activation can be said to depend on the influence of injury-associated inflammatory cytokines such as IL-1 and TNF-α, or even interleukin-6 (IL-6), produced by the contractile muscle even in the absence of muscle injury, as well as nitric oxide, which may have reduced availability in the presence of high oxidative stress, and growth factors and anabolic hormones that may also be negatively influenced by overtraining (Munoz-Canoves et al, 2013; Belizario et al, 2016; Saini et al,. 2016; Hoppeler, 2016).

CONCLUSION

The way of understanding skeletal muscle hypertrophy is open. Many aspects need stronger evidence of how these mechanisms could lead to differences between positive protein balance (synthesis higher than

breakdown) and, consequently, hypertrophy. There is a consensus that different kinds of stimuli are necessary to optimize muscle hypertrophy, but some pieces of information are sustained on anecdotal claims.

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