ABSTRACT

Satellite cells are undifferentiated skeletal muscle stem cells lying at the periphery of muscle fiber. The role of satellite cells is now being much appreciated, not only as crucial players during growth and regeneration, but also as mediators in exercise-induced skeletal muscle hypertrophy. This enlargement of muscle mass mainly results from resistance training which initiates five steps of cellular mechanism: signals to synthesis protein, alteration of skeletal muscle growth factor expression and/or release, regulation of gene transcription, activation of mTOR signaling pathways and finally increased satellite cell proliferation and differentiation. Thus, activated satellite cells are crucial contributors of hypertrophied muscle by providing additional nuclei.

Keywords: satellite cell, exercise, muscle hypertrophy

INTRODUCTION

Facing the challenge of physiological demands during growth, training and injury, human skeletal muscles demonstrate an incredible adaptation capability. The crucial players of this adaptation process are now attributed to the stem cells of skeletal muscle, known as the myogenic satellite cells. Previously, satellite cells are considered as quiescent resident cells in adult skeletal muscle that are activated in response to muscle injury (trauma). Nowadays, researchers become more concerned on the significant contributions of these cells, particularly to the development of muscle hypertrophy, atrophy and muscular disease.
By definition, muscle hypertrophy is an enlargement of muscle mass due to an increase in the diameter (not length) of individual muscle fibers and thus, an increase in cross-sectional area. Muscle hypertrophy may be induced by specific training and working. Several mechanisms have been proposed including the involvement of immune reaction, specific growth factor proteins and satellite cells.

This review aims to discuss the physiological mechanism of exercise-induced muscle hypertrophy, in specific, to explore the role and interaction of satellite cells during this cellular signaling pathway.

**DISCUSSION**

**Satellite Cells**

In 1961, Mauro reported a small population of mono-nucleated cells which are resident on the peripheral surface of the muscle fiber, in between the sarcolemma and basal lamina. In a normal environment, these cells remain silent and nonproliferative. Upon stimuli such as trauma, damage or injury, satellite cells are activated, multiplied and migrated to the injured site.

Usually these cells are dormant, but they become activated when the muscle fiber receives any form of trauma, damage or injury, such as from resistance training overload. The satellite cells then proliferate or multiply, and the daughter cells are drawn to the damaged muscle site. They then fuse to the existing muscle fiber, donating their nuclei to the fiber, which helps to regenerate the muscle fiber. It is important to emphasize the point that this process is not creating more skeletal muscle fibers (in humans), but increasing the size and number of contractile proteins (actin and myosin) within the muscle fiber. This satellite cell activation and proliferation period lasts up to 48 hours after the trauma or shock from the resistance training session stimulus.

The amount of satellite cells present within in a muscle depends on the type of muscle. Type I or slow-twitch oxidative fibers, tend to have a five to six times greater satellite cell content than Type II (fast-twitch fibers), due to an increased blood and capillary supply. This may be due to the fact that Type 1 muscle fibers are used with greatest frequency, and thus, more satellite cells may be required for ongoing minor injuries to muscle.
Fig. 2. Satellite cells occupy a sublaminar position in adult skeletal muscle.
In the uninjured muscle fiber, the satellite cell is quiescent and rests in an indentation in the adult muscle fiber. The satellite cells can be distinguished from the myonuclei by a surrounding basal lamina and more abundant heterochromatin.

Muscle Hypertrophy

Hypertrophy is a common term for the increase of size, not the increase of number as in hyperplasia. In muscle hypertrophy, the number of muscle fibers does not multiply significantly but the whole muscle expands due to the increase of diameter of each muscle fiber. Hypertrophy is therefore more limited in individuals with fewer muscle fibers.

Hypertrophy occurs in muscles that have been continually stimulated to produce near maximal tension, such that generates more mitochondria, sarcoplasmic reticulum and so forth. A good example of this is the bulging biceps and chest muscles of a professional weight lifter, results mainly from high-intensity of anaerobic exercise such as resistance training.

Resistance Training

Resistance exercise, the contraction of muscles against a load that resists movement purposes to increase muscle strength and size, with little emphasis on endurance. Resistance training is designed to produce series of close-to-maximal contractions with rest periods between sets.
Resistance training consists of various components. Basic principles include program i.e. various exercise types such as aerobic training, flexibility training and strength training, different weights for different exercises within each training session, a particular exercise to strengthen a particular muscle or group of muscles, repetitions or reps the number of repetition of each exercise in a group of repetitions performed without resting (known as set), rest between sets, variety i.e. switching around the workout routine to challenge the muscles and forces them to adapt with increased size and strength, overload principle to gain benefits and recovery (muscle needs time to repair and grow after a workout).

Regular resistance training offers many benefits such as:

- develop strong bones (strength training increases bone density and reduces the risk of osteoporosis)
- control body weight (as the muscle mass increase, the body burns calories more efficiently)
- protects the joints from injury (maintain flexibility and balance to support independence)
- boost stamina (as the strength of the body grows stronger, it won’t fatigue as easily)
- improves the sense of wellbeing (strength training improve self-confidence, body image and reduce the risk of depression)
- get a better night’s sleep (people who regularly take part in a strength training program are less likely to have insomnia)
- manage chronic conditions (strength training can reduce the signs and symptoms of many chronic conditions, including arthritis, back pain, depression, diabetes and obesity)

Spurway and Wackerhage (2006) described a physiological mechanism which incorporates the roles of satellite cells, cellular signaling pathway and specific proteins, named as five step model of resistance exercise-induced muscle hypertrophy.

Model of Resistance Training induced Muscle Hypertrophy

1. Signals Initiator
The signals by which resistance exercise leads to muscle hypertrophy are currently not well-understood. Resistance training is associated with an elevated rate of protein breakdown. Therefore, the signals must be able to promote protein synthesis by activating ‘upstream’ signal such as transduction proteins (SP) and transcription factors (TF). Logically, they should be different from signaling pathways involved in endurance training.

The hypertrophic signal is intrinsic, as it is primarily the exercised muscle that undergoes hypertrophy and not all the muscles of the limb or the whole body. It appears the hypertrophying skeletal muscle produces autocrine growth factors and that the morphological basis of the mechanism involves the cytoskeleton and the extracellular matrix.

Several feasible signals have been proposed such as stretch (Figure 2), swelling, high tension and muscle damage. However, more research is required since those signals are not necessary related with protein synthesis and resistance training.

Figure 2. A possible model whereby a physical force (i.e. stretch or work overload) is converted into a chemical signal, thereby, regulating gene expression.
2. Alteration in Certain Growth Factors

Skeletal growth factors are mainly activated during growth, healing and regeneration process. In term of exercise-induced muscle hypertrophy, the ‘upstream’ signals for muscle growth above must evoke different cellular signaling cascades than those of muscle hyperplasia. Thus, the signals would then capable of changing the expression of specific proteins.

They enhance the expression of IGF-I (insulin-like growth factor-I) and MGF (Muscle Growth Factor) but on the other hand reduce the expression of myostatin. Hormones such as testosterone and cortisol also affect the expression of these proteins.

Testosterone is an androgen, or a male sex hormone. The primary physiological role of androgens is to promote the growth and development of male organs and characteristics. With skeletal muscle, testosterone, which is produced significantly greater amounts in males, has an anabolic (muscle building) effect by increasing protein synthesis, which induces hypertrophy.

Cortisol is a steroid hormone which is produced in the adrenal cortex of the kidney. It stimulates gluconeogenesis, which is the formation of glucose from sources other than glucose, such as amino acids and free fatty acids. Cortisol also inhibits the use of glucose by most body cells by initiating protein catabolism (break down). In terms of hypertrophy, an increase in cortisol is related to an increased rate of protein catabolism. Therefore, cortisol breaks down muscle proteins, inhibiting skeletal muscle hypertrophy.

IGF-I is the most important pro-growth factor while myostatin is the most important growth-inhibiting factor. IGF-I and myostatin regulate the balance of muscle hypertrophy. Nevertheless, it is not totally clear whether the change of muscle growth factor is necessary.

a. Insulin-like Growth Factor-I (IGF-I)

Skeletal muscle secretes insulin-like growth factors I and II (IGF-I and IGF-II) which are known to be important in the regulation of insulin metabolism. In addition, these growth factors are important in the regulation of skeletal muscle regeneration. IGF-I causes proliferation and differentiation of satellite cells, and IGF-II causes only proliferation of satellite cells.

In response to progressive overload resistance exercise, IGF-I levels are substantially elevated, resulting in skeletal muscle hypertrophy as evidenced by a mouse model of knock-out IGF-I gen which develops smaller muscles than normal. Other study reported that infusion of
IGF-I into muscle leads to over expression of the gen, which then promotes muscle hypertrophy. IGF-I may be elevated after resistance training, however, more human studies are required.

IGF-I and IGF-II has been associated with the increase of satellite cell proliferation and differentiation in vitro. The importance of these growth factors was demonstrated with the intramuscular administration of IGF-I into older, injured animals. In this study, IGF-I administration (using an osmotic mini pump) resulted in enhanced satellite cell proliferation and increased muscle mass. Moreover, skeletal muscle overload or eccentric exercise results in elevated IGF-I levels, increased DNA content (suggesting an increase in satellite cell proliferation), and a compensatory hypertrophy of skeletal muscle. IGF-I appears to utilize multiple signaling pathways in the regulation of the satellite cell pool. The calcineurin/NFAT, mitogen-activated protein (MAP) kinase, and phosphatidylinositol-3-OH kinase (PI-3K) pathways have all been implicated in satellite cell proliferation. IGF-I-stimulated satellite cell differentiation appears to be mediated through the PI-3K pathway.

b. Myostatin

This protein is also known as growth and development factor (GDF), which essentially inhibits muscle growth. In fact, mutation of myostatin gene causes loss-of-function leading to several abnormalities in human and animals such as double-muscled cattle, mighty mice and super toddler.

Moreover, an increase of systemic myostatin is related with atrophy observed in cancer and AIDS patients. Myostatin levels also elevate in unloaded limbs such as long-term of hospital care and in low gravity. Nonetheless, several studies argued that following resistance exercise in human results to the decrease of myostatin. In addition, myostatin expression in skeletal muscle decreases during the regeneration of skeletal muscle.

This correlation suggests that myostatin expression is inversely correlated with the rate of skeletal muscle growth. In contrast to Transforming Growth Factor-β (TGF-β), which in the presence of serum causes myoblast to become post mitotic, myostatin inhibits myoblast proliferation and protein synthesis in an autocrine/paracrine manner. However, it is still unclear at a molecular level how myostatin and TGF-β differ in this respect, as they are both members of the TGF super family.
3. Signaling Cascade: Gene Transcription

‘Upstream’ signaling and signaling initiated by IGF-I, MGF and myostatin will change the expression of hundreds to thousands of other genes in skeletal muscle, according to microarray studies. In specific, IGF-I activates and myostatin inhibits complex signaling cascade which links the signal and the growth factors evoked by the signal initiator (Figure 3, steps 1 and 2) to protein synthesis (Figure 3, steps 3 and 4).

4. Signaling Cascade: mTOR transduction pathway

Protein synthesis is initiated when IGF-I and MGF activates the mTOR signal transduction pathway, resulting in the activation of translational regulators (TR) and translation. Thus, amino acids can further activate mTOR, in this regard the timing is important. The end result will then be the greater myofibril mass in the muscle fiber. It is necessary to increase the number of nuclei per fiber as well. Therefore, the last step to accomplish this model is the activation of satellite cells.

5. Activation of satellite cells

Normally, long muscle fiber (10 cm) contains approximately 400 to 12,000 nuclei with higher nuclear density in Type 1 than Type II fibers. As fibers grow, satellite cells are needed to keep the balance ratio of nucleus : sarcoplasm. Thus, they are recruited to contribute nuclei, preventing the ratio of nucleus : sarcoplasm from decreasing. Following resistance exercise, satellite cells are activated then proliferate and fuse with the hypertrophied muscle fiber and contribute their nuclei.
Figure 3. Summary of Five Step Models in Exercise-Induced Muscle Hypertrophy

Alternative Hypothesis in Exercise-Induced Muscle Hypertrophy

1) Hyperplasia?

Up to date, major debate between muscle hypertrophy and muscle hyperplasia in terms of muscle growth following exercise still exists. Muscle fibers themselves are incapable of mitosis but there is some evidence that as they enlarge, they too many split longitudinally. Therefore, MacIntosh et al. (2006) proposed an alternative hypothesis to describe exercise-induced muscle hypertrophy. They pointed out that hypertrophied muscle fibers could divide into daughter cells that do not split. So, although the fiber size increases the number of muscle fiber actually does not increase. As evidence, type IIB fibers show greatest amount of hypertrophy while type I fibers show least amount of hypertrophy.

2) Immune Reaction
Resistance exercise causes trauma to skeletal muscle. The immune system responds with a complex sequence of immune reactions leading to inflammation. The purpose of the inflammation response is to contain the damage, repair the damage, and clean up the injured area of waste products. The immune system causes a sequence of events in response to the injury of the skeletal muscle. Macrophages, which are involved in phagocytosis (a process by which certain cells engulf and destroy microorganisms and cellular debris) of the damaged cells, move to the injury site and secrete cytokines, growth factors and other substances. Cytokines stimulate the arrival of lymphocytes, neutrophils, monocytes, and other healer cells to the injury site to repair the injured tissue.

The three important cytokines relevant to exercise are Interleukin-1 (IL-1), Interleukin-6 (IL-6), and tumor necrosis factor (TNF). These cytokines produce most of the inflammatory response, which is the reason they are called the “inflammatory or proinflammatory cytokines”. They are responsible for protein breakdown, removal of damaged muscle cells, and an increased production of prostaglandins.

CONCLUSIONS

Exercise, especially resistance training, is known to promote the increase of muscle fiber size, muscle hypertrophy. It is still unclear whether there is also an increase of muscle fiber number, muscle hyperplasia after such training.

During cascade signaling in exercise-induced muscle hypertrophy, satellite cells play an important role. By contributing their nuclei, hyperplasia of satellite cells is critical to provide additional nuclei to the hypertrophied muscle fiber, balancing the ratio of nucleus : cytoplasm.

SUGGESTIONS

More research is highly desirable particularly to identify the signals initiator following resistance training that further lead to muscle hypertrophy. Not only for the purpose of athlete development, but also therapeutic means of muscular disease, the interaction between growth factors signaling cascades and activation of satellite cells should be addressed as well.

Lack of such knowledge is a critical problem, because, until this information becomes available, it will not be possible to develop and effectively evaluate new genetic or therapeutic strategies to specifically enhance IGF-I and inhibit myostatin activity and thereby enhance skeletal muscle growth.
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