

## **Skeletal Muscle Hypertrophy**

An analysis of the major regulatory pathways including training and nutrient suggestions to maximize this adaptation.

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### **Introduction**

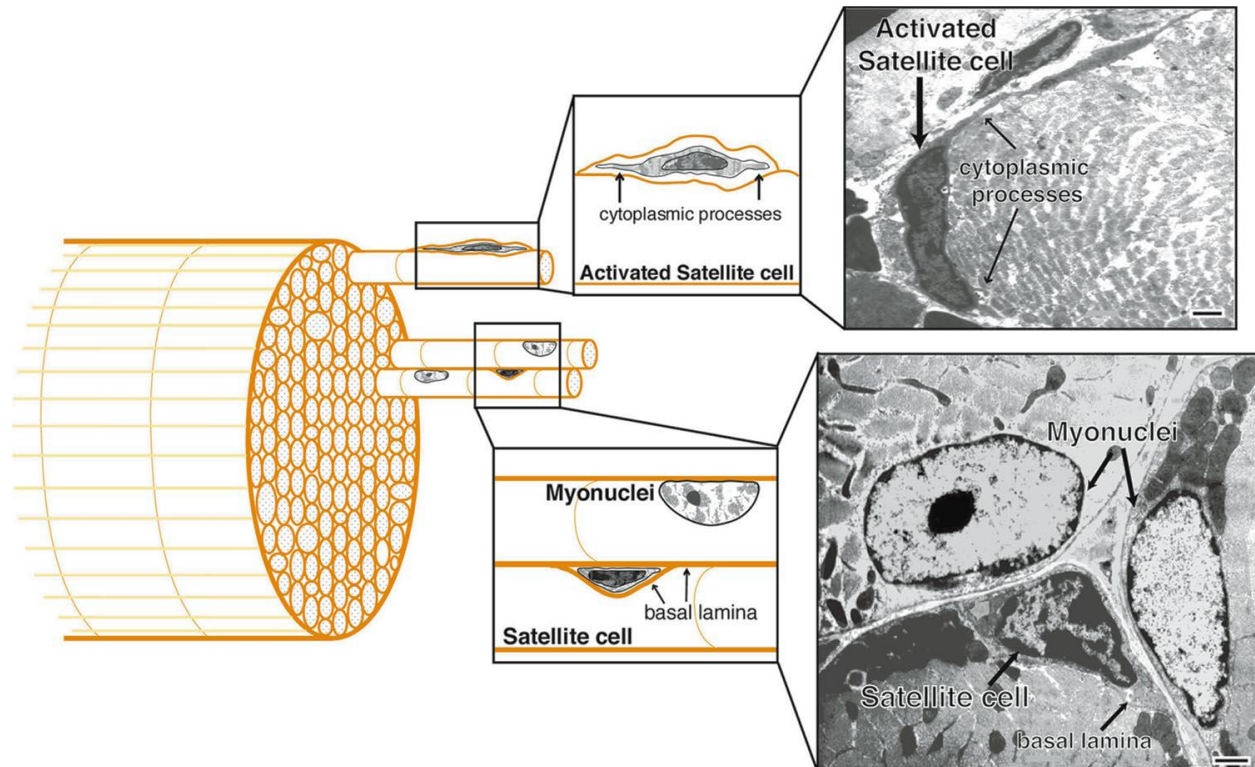
Muscle hypertrophy can simply be defined as an increase in size of the myofibril(s). Though easily defined, it is an intriguing and complex adaptive process carried out by the human body in response to external stimuli. Causing this adaptation leads to a greater cross sectional area thus a greater ability to produce force. This attribute makes it appealing to athletes and researchers alike but its application does not just lie within these two groups. With a continuously aging and overweight population in our country, we must remember some of the additional benefits of stimulating hypertrophy on issues like sarcopenia and basal metabolic rate. The aim of this review is to explore the multifaceted and interrelated components that lead to skeletal muscle growth and how in accordance with current research, we can stimulate them best through specific combinations of nutrients and training stimuli.

Skeletal muscle is an extremely adaptive tissue, with even the most intensive training modules being unable to inflict permanent damage upon the fibers [1]. Sometime after birth, myofibers are terminally differentiated, meaning they become specialized cells whose properties arise from tissue specific gene expression. Additionally, it means that skeletal muscle fibers are maintained through a system that is non-mitotic (meaning the fibers themselves are unable to

divide and replicate). They must survive the length of the organism's lifetime and possess distinct methods of cellular remodeling and repair to ensure this survival [2-4]. Carrying out an essential role in this process are intriguing molecules referred to as satellite cells which can be thought of as stem cells of the muscle. These mononucleated myoblasts (precursors to muscle cells) lie dormant outside the sarcolemma sandwiched in small pockets between adjacent muscle fibers upon normal situations, but can be triggered by muscular trauma [4]. Upon activation they fuse with the damaged tissue and donate their nuclei to initiate the repair process. Without satellite cells we would be unable to adapt and repair damaged muscle tissue. This has been displayed in rats that completely lost the hypertrophic response to mechanical overload after irradiation to destroy satellite cell populations.[4] Interestingly, it is also illustrated in the fact the cardiac muscle appears to be absent of them, explaining why after trauma such as myocardial infarction the damaged tissue is unable to restore function and becomes necrotic.[3]

Satellite cells represent an excellent starting point when addressing the development of skeletal muscle hypertrophy as they initiate the process of repair and adaptation. At this point, two important concepts should be clear to the reader: That increases in muscle size occur primarily from the repair of existing muscle fibers, not division of the muscle cells themselves (hyperplasia), and a certain degree of muscle fiber damage must take place to trigger the process [4, 5]. Though many individuals tend to relate a high level of delayed onset muscle soreness (DOMS) to a productive workout, it should be noted that muscle damage may occur without extreme levels of soreness and that DOMS may actually signify remodeling rather than

damage [6]. Additionally, recent research has suggested that the muscle fascia plays a major role in the sensation of DOMS rather than the fibers themselves [7].



**Figure 1** Adapted from Hawke T. GD: **Myogenic satellite cells: physiology to molecular biology**. *Journal of Applied Physiology* 2001, 91:534-551.

## Experimental Models

Overload is a fundamental principle in the process of adaptation. Since tissues are not accustomed to an increased workload prior to training, the first few weeks of resistance exercise commonly produce marked increases in strength and (in the longer term) hypertrophy. It also displays that if workload is not increased after this time, adaptations will stagnate. Examining the mechanisms of hypertrophy must therefore comprise at least one type of overload, of which there are three major categories: stretch, compensatory, and exercise induced.

### *Stretch induced overload*

Stretch induced overload is typically studied in birds, where a certain percentage of their total bodyweight is attached to one or both of their wings either intermittently or chronically (anywhere from 7 to 21 or more days). This method typically produces a larger amount of sarcomeres in series (elongation) and is also believed to be most strongly associated with hyperplasia. [3, 8-10] It has also been stated that this model is the least applicable to humans in the study of exercise induced muscle enlargement as almost all of the adaptations it produces differ widely from those shown in human strength training [11].

### *Compensatory overload*

Another form of chronic overload to which a large amount of research is devoted is the compensatory model. This is studied by surgically removing a given muscle's synergists or clipping the tendon of synergistic muscles, imposing more workload on the remaining muscle group(s). For example in the rat, the gastrocnemius can be removed to overload the soleus and plantaris, or the gastrocnemius and soleus can both be removed leaving just the plantaris to be overloaded. This model produces rapid and profound increases in both muscle mass and phenotype (i.e. slow/fast twitch characteristics). It is also believed to be the best animal model resembling long term adaptations to human strength training and will be the major focus later in our discussion.[3, 11]

### *Exercise Induced overload*

In this model researchers attempt to simulate the elements of human strength training through various methods. A few examples of these models include:

- Training animals to climb inclines using progressively heavier resistances.
- Using operant conditioning to get them to perform specific muscle actions in which resistance is gradually added.
- Using visual stimuli with food as positive reinforcement to get rats to perform resisted movements similar to squats.

Though exercise induced models mimic the movements carried out in human strength training more closely than the other two, many studies using this method are unable to produce measureable amounts of muscle enlargement. Those that are able to produce results only do so comparable to human studies using untrained individuals with programs <6 months duration. It is therefore used as the best model of study for short term hypertrophy in human strength training.[11]

Unfortunately at this point, our knowledge of cellular adaptation in human skeletal muscle is limited to what we can ascertain from small muscle biopsies. More in depth analysis would require the complete removal of muscle groups which would not only be nearly impossible to find willing participants for but also unethical. This is why at this point; animal models continue to be the focal point of research.

It is necessary to keep in mind that although no solitary model can encompass all the cellular mechanisms taking place in response to human resistance exercise, they should collectively

assist in displaying the fact that hypertrophy cannot be tied to just one aspect of training or muscle action. In other words, the fundamentals of strength training such as using full range of motion, progressively overloading the muscles, adequate frequency and duration of training, etc... are all critical components in the extent of muscle hypertrophy a regimen produces.

### **Types of Muscle Hypertrophy**

Simply stating that hypertrophy is the enlargement of muscle fibers is a very vague definition as it does not tell us what components are actually contributing to the increase in cross sectional area. A more in depth examination shows us that there exist two major forms of hypertrophy that occur in skeletal muscle; myofibrillar and sarcoplasmic. Myofibrillar hypertrophy is characterized by an increase in number of the actual contractile components of the sarcolemma, mainly being the myosin heavy chain proteins and actin filaments. This type of hypertrophy is responsible for the concomitant increases in muscle force production with fiber growth and should be the major focus of athletic programs aimed at increasing performance. Sarcoplasmic hypertrophy occurs when the non contractile components of the muscle fiber increase, examples of this include enlargement of the sarcoplasmic reticulum, increased intracellular fluid retention, and increased storage of metabolic fuels such as glycogen and creatine phosphate. A depiction of sarcoplasmic and myofibrillar hypertrophy can be seen in Figure 2 below. Heavy resistance training produces a combination of these types of hypertrophy but the intensity and endurance aspect of the training can play a role in which one predominates. For example, sarcoplasmic hypertrophy is typically higher in bodybuilders, while

myofibrillar tends to be the majority in Olympic and power lifters.[12] Training stimulus also effects muscle phenotype and will be discussed in the following section.

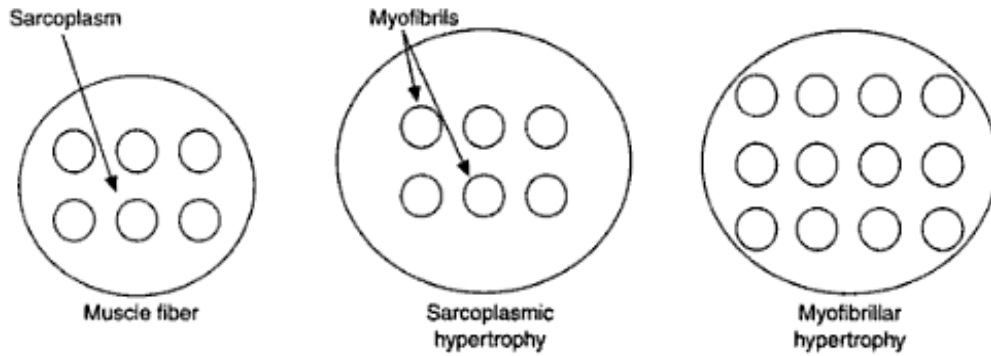


Figure 2 Adapted from William J. Kramer VZ: **Science and practice of strength training**. Champaign, IL: Human Kinetics; 2006.

*Myosin Heavy Chain Proteins (MHC)*

Any given muscle fiber possesses the genetic machinery to simultaneously produce all the MHCs e.g., slow type I, and fast type IIa, and IIx [13]. (It should be noted that some sources use the terms type IIx and IIb interchangeably; while IIb has been found in the human genome its expression is yet to be confirmed in human muscle [13, 14] therefore, we will exclusively use the term IIx to describe this fiber type). Each of these isoforms account for distinct functional differences in size, fatigueability, metabolism, and response to stimuli.[3, 13] A table has been provided below displaying some of these distinct properties in relation to the major MHC genes.

Table 1 Major Characteristics of Muscle Fiber Types

Characteristic	Type I	Type IIa	Type IIx
Motor neuron size	Small	Large	Large

Nerve conduction velocity	Slow	Fast	Fast
Contraction speed	Slow	Fast	Fast
Relaxation speed	Slow	Fast	Fast
Fatigue resistance	High	Intermediate/Low	Low
Force production	Low	Intermediate	High
Power output	Low	Intermediate/High	High
Endurance	High	Intermediate/Low	Low
Aerobic enzyme content	High	Intermediate/Low	Low
Anaerobic enzyme cont.	Low	High	High
Capillary density	High	Intermediate	Low
Myoglobin content	High	Low	Low
Mitochondria size/dens.	High	Intermediate	Low
Fiber diameter	Small	Intermediate	Large
Color	Red	White/Red	White
Major Storage Fuel	Triglycerides	Creatine phosphate, Glycogen	Creatine phosphate, Glycogen

Adapted from **Essentials of Strength Training and Conditioning**. R. W. E. Thomas R. Baechle. Champaign, IL, Human Kinetics: 10.

This table assists in illustrating the relationship between differing fiber types and their respective influences on athletic performance and muscle girth potential. Muscle groups typically coexpress multiple MHC isoforms but may dominate in one specific type [3]. For example, the soleus tends to be made up of predominantly type I fibers, while the triceps are primarily type II in moderately active individuals [13]. It is still debatable whether specific training can induce an extreme shift in fiber type expression from I to II or vice versa. Hybrid

fibers (express multiple MHCs within the fiber) have also been discovered and are believed to increase in response to muscle loading as well as possess a higher adaptive potential [3, 13].

Although all MHC isoforms possess the ability to hypertrophy, type II fibers have the greatest potential to contribute to muscle cross sectional area [15]. If this is difficult to comprehend, picture the physique of an ultra endurance marathon runner (predominantly type I) and a sprinter or powerlifter (mostly type II). The type II predominant athlete will always have greater muscle development. Furthermore, significant hypertrophy of type I fibers is rarely observed [15] explaining why, regardless of the extensive effort involved, the marathon runner will never be riddled with muscle mass.

It may somewhat come as a surprise that the fiber type possessing the highest power and force producing capabilities, IIx, is found to be in the greatest amounts in untrained individuals. With resistance training, there is a shift to the slightly more fatigue resistant IIa fibers [13, 15]. After a period of detraining or brief inactivity (about 1-2 weeks) there is a shift back to IIx and a supercompensation which leads to levels higher than previously expressed pre training [5, 13]. This explains why sprinters or powerlifters will take a brief time off before an event to “peak”. It is also why some strength trained individuals notice an increase in 1 repetition max after a deload or break from training. Further, it explains why their sets that transcend beyond the strength/power rep range into the muscle hypertrophy/endurance range tend to suffer.

A final intriguing finding in a study done by D’Antona et al on skeletal muscle hypertrophy in bodybuilders uncovered that all of the bodybuilders that participated but none of the control group expressed a fourth form of MHC called neonatal MHC [15]. This isoform is unique

because it is undifferentiated (meaning it has the ability to express any of the adult MHCs) and appears to be dependent upon environmental (weight bearing vs. non weight bearing) or hormonal (sufficient circulating levels of  $T_3$ ) stimulus to trigger its differentiation [13]. This introduces an interesting possibility for debate as transient expression of undifferentiated MHCs is typically associated with the formation of new muscle fibers [16]. If proven, this could lend serious credibility to the occurrence of hyperplasia in humans which has been postulated to occur in bodybuilders in previous studies [17]. It also raises the possibility of hyperplasia through fiber splitting as suggested by Vaughan & Goldspink [18].

### **Molecular Pathways involved in hypertrophy**

All eukaryotic cells possess the ability to adapt to a variety of external stimuli through conversion and internalization of various chemical signals. This ultimately alters the transcription and translational activity in the cell through numerous intracellular signaling pathways. Downstream, these signals lead to an influence on distinct genes which code for the production of specific proteins. Ultimately, this process leads to the synthesis or degradation of intracellular proteins. Though there are many other pathways involved in muscular adaptation we will focus on those that at this point are likely to have the most prominent roles. It must also be appreciated that the end result of muscular hypertrophy is not a function of one single confined pathway, but the intercommunication and activation (or suppression) of several complex extra- and intra- cellular systems.

*Calcineurin/Calcium-Calmodulin protein kinase (CaMK)*

Though these are two distinctively separate pathways, they have been grouped together as, at this time they have not conclusively been associated with significant effects on skeletal muscle hypertrophy. For this reason they will only be discussed briefly, highlighting each pathways respective properties and possible contributions to hypertrophy or phenotype transition.

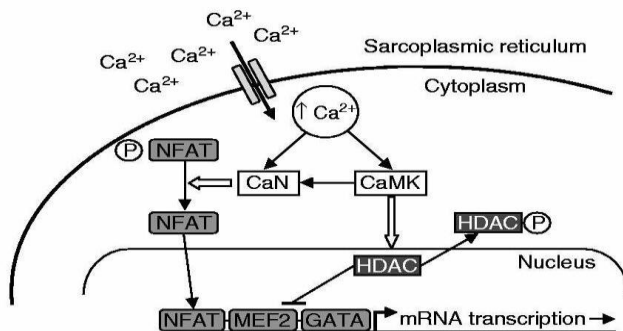
As the names imply the Calcineurin and CaMK pathways are both regulated by intracellular calcium. Calcineurin is found in the cytoplasm and functions as a serine threonine phosphatase (removes phosphate from substrate). It was first discovered as an activator of T cells through its role in dephosphorylating NFAT (Nuclear Factor of Activated T cell) proteins, allowing them to access the nucleus and activate the transcription of target genes [19, 20]. Due to the critical role of calcium in striated muscle, it led researchers to investigate its possibility in regulating muscle hypertrophy.

Initial work led to the assumption that calcineurin/NFAT did indeed play a role in hypertrophy as well as influencing phenotype transitions (specifically to type I) [19, 20]. Recent work however, has concluded that although it has a well defined role in cardiac hypertrophy it is not necessarily required for skeletal muscle growth or fiber transition. Some sources still believe it holds promise, but at this time sufficient evidence is lacking to associate a definitive role of calcineurin with hypertrophy.

Unlike calcineurin which is activated by low amplitude calcium signals, CaMK activity is regulated by short, high amplitude signals [19, 20]. Its purported method of action is on the MEF2 (myocyte enhancer factor-2) proteins which regulate transcriptional activity, cellular differentiation and tissue remodeling in skeletal muscle through the modulation of

transcriptional suppressors (histone deacetylases or HDACs) [21, 22]. This pathway is also believed to increase type I fiber gene expression but similarly to calcineurin, it is not yet conclusive [3].

A visual depiction has been given in figure 3 to improve clarity on the concept of the calcineurin/CaMK pathways.



**Fig. 2.** Proposed mechanisms for calcium-dependent increases in gene expression with skeletal muscle contractile activity. Bars denote inhibition and arrows denote activation.  $\text{Ca}^{2+}$  = calcium; **CaMK** = calmodulin kinase; **CaN** = calcineurin; **GATA** = glutamyl-tRNA amidotransferase; **HDAC** = histone deacetylase; **MEF2** = myocyte enhancer factor 2; **mRNA** = messenger RNA; **NFAT** = nuclear factor of activated T cells; **P** = phosphorylation;  $\uparrow$  indicates increase.

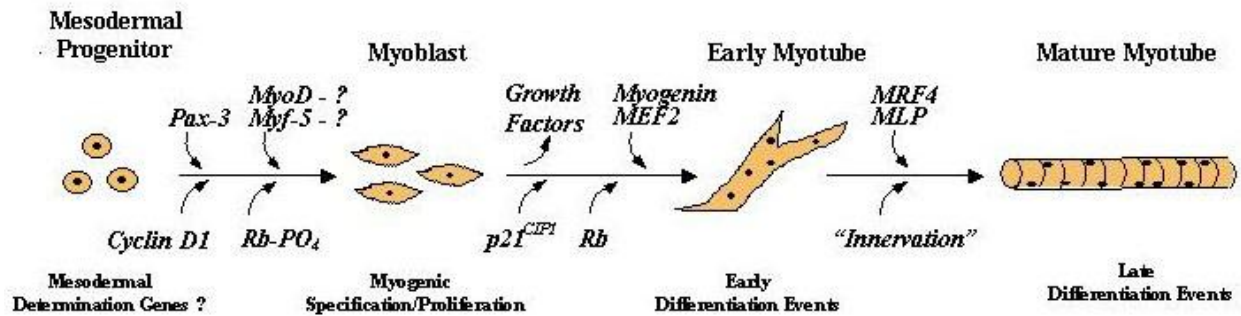
**Figure 3** Adapted from Coffey, V. G. and J. A. Hawley (2007). "The Molecular Bases of Training Adaptation." *Sports Medicine* 37(9): 737-763. .

### *The Myogenic Regulatory Factors (Myo-D, myogenin, MRF-4, myf5)*

The MRFs are muscle specific transcription factors that promote hypertrophy upon activation. They function by binding to promoter regions of various genes in the sarcomere [23]. This promoter binding facilitates the transcription of certain muscle specific genes such as myosin heavy chain, myosin light chain, tropomyosin, and troponin-C which are all vital structural components of the sarcomere [23, 24]. MRFs also cooperate with MEFs to encourage myoblast differentiation into myotubes and eventually mature myofibers [23].

Activated satellite cells express all the MRFs, with Myf5 expression itself being an indicator of satellite cell activation and designation to myogenesis. Myo-D also marks myogenic commitment and differentiation but is not believed to play as large a role as myf5 [23]. This assumption is based on the findings that Myo-D knockout mice did not show a dramatic reduction in muscular development. It is believed that this prevention occurs due to a myf5 compensation through increased expression [25]. Myo-D does however have a more prominent role in altering MHC isoform as it is found to accumulate in type II fibers and increases mRNA expression of the type IIx variety specifically [26]. Myogenin on the other hand accumulates in type I fibers and is associated with type I and IIa mRNA expression [26].

MRF-4, also referred to as herculin (or myf-6) is expressed at higher levels than any of the other three MRFs. It also shares prominent roles in differentiation as well as control of muscle phenotype. It is thought to act similarly to myogenin but distinctive roles are difficult to ascertain at this point [27]. Again, a visual depiction has been provided to increase clarity of this pathway. From this image it should be appreciated that pathways do not function in solitude, as well as the prominent role the MRFs have in the process of differentiation.



During development, mesodermal stem cells become committed to one of several different cell lineages, including the skeletal muscle cell lineage. Muscle precursor cells (myoblasts) remain in a proliferative state until they are "instructed" to differentiate. Differentiation is accompanied by cell fusion and the expression of over 50 muscle-specific genes. Understanding the role of the MyoD family of proteins in proliferating myoblasts is one of the goals of the lab.

**Figure 4** Adapted from Purdue University. "The Konieczny Lab."  
<http://www.bio.purdue.edu/people/faculty/konieczny/lab/overview.htm>.

### *IGF-1, MGF, PI(3) kinase, Akt, mTOR pathway*

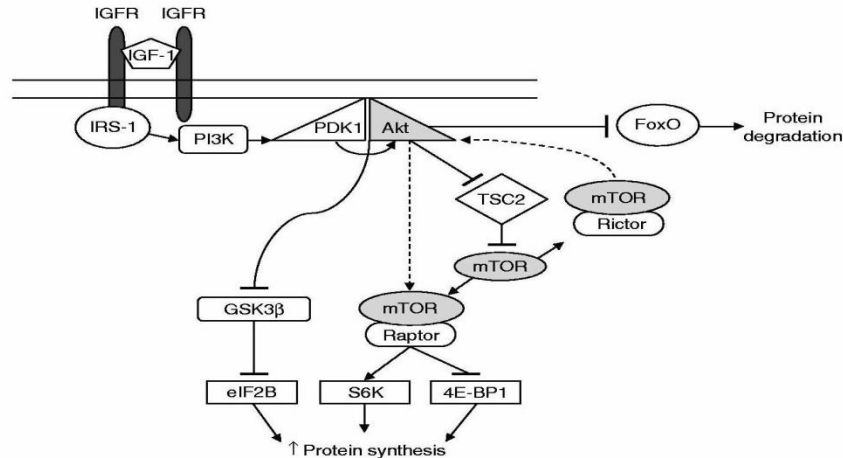
The IGF-1 signaling cascade possibly represents the most concrete and scientifically supported pathway in the development of skeletal muscle hypertrophy to this point as it has been justified by numerous cell culture models in vivo [28]. IGF-1 is crucial in muscle hypertrophy because it encompasses many of the steps in gene expression such as proliferation, differentiation, and degradation as well as stimulation of amino acid transport [14]. In fact, many of the anabolic effects attributed to growth hormone are believed to be due to the concomitant increases in IGF-1 [14]. This can be validated in mice that overexpressed IGF-1, which led to increased muscle hypertrophy [3]. Further, IGF-1 has been shown to stimulate the proliferation and differentiation of activated satellite cells [3, 23].

It is believed that it is actually a splice of IGF-1 called MGF (Mechano Growth Factor) that internalizes the signal created by mechanical stimulus to influence the morphological adaptations that take place in skeletal muscle. While IGF-1 is systemic, MGF is locally produced within the muscle and only becomes expressed upon activity [5]. This may explain why only targeted muscles experience a hypertrophic response in resistance exercise. It is also suggested that MGF is responsible for initiating activation and proliferation of satellite cells while IGF-1 influences differentiation [23]. Interestingly, sarcopenia may be largely due to the age related decrease in circulating human growth hormone which influences IGF-1 levels, further leaving less of an ability to create MGF. Aged muscle also displays a decreased ability to activate satellite cells (also likely due to impaired IGF-1), which coupled with less available MGF creates a very poor environment for muscle repair and hypertrophy [5].

Traveling further downstream requires the phosphorylation of Phosphatidylinositol-3-OH-Kinase (PI(3)K). This is an enzyme that further moves the signal downstream by phosphorylating Protein kinase B (Akt). Akt activation serves numerous intracellular functions such as modulating glucose transport, atrophy, and most importantly to our discussion protein synthesis through activation of the mammalian target of rapamycin (mTOR) [28]. Akt signaling is a vital step in the progression of muscle hypertrophy as exhibited in experiments where mice with targeted Akt gene deletion showed significant atrophy [3].

mTOR activation is associated with an increase in protein synthesis and ultimately cell growth by stimulating ribosomal s6 kinase (p70S6K) and eukaryotic translation initiation factor 4B (eIF4B) [28]. P70S6K and eIF4B phosphorylation lead to increased translational activity which

culminates in the synthesis of new proteins [28]. A visual depiction of the IGF-1 signaling pathway is provided below.



Simplified insulin-like growth factor (IGF)-1 signalling pathway from receptor binding to protein synthesis. Arrows designate that phosphorylation activates the substrate (dashed line represents putative direct activation) and bars denote inhibition. 4E-BP1 = eukaryotic initiation factor 4E-binding protein; eIF2B = eukaryotic initiation factor 2B; FoxO = forkhead box O; GSK3β = glycogen synthase kinase 3β; IGF-1 = insulin-like growth factor-1; IGFR = insulin-like growth factor receptor; IRS-1 = insulin receptor substrate-1; mTOR = mammalian target of rapamycin; PDK1 = 3'-phosphoinositide-dependent protein kinase 1; PI3K = phosphatidylinositol-3-OH kinase; S6K = ribosomal protein S6 kinase; TSC2 = tuberous sclerosis complex 2; ↑ indicates increase.

**Figure 5** Adapted from Coffey, V. G. and J. A. Hawley (2007). "The Molecular Bases of Training Adaptation." *Sports Medicine* 37(9): 737-763.

### *Nutrition Roles*

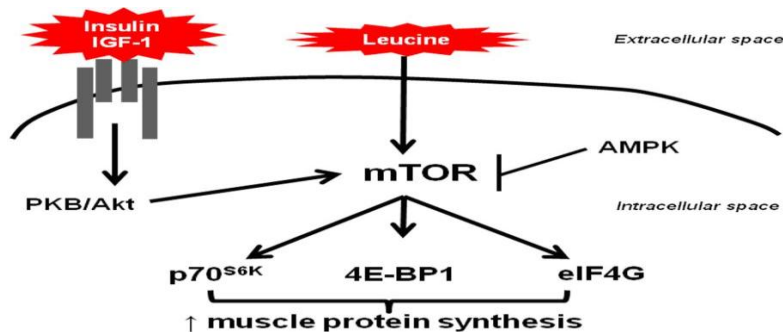
Chronic adaptations in resistance training (such as hypertrophy) are believed to be the product of acute post-exercise increases in mRNA (leading to transcriptional activity) that accumulate over time. This continued stimulus on the expression of specific genes leads to a steady signaling of new muscle specific proteins [28]. Proper caloric intake as well as specific nutrients can play a paramount role in activating many of these anabolic pathways or inhibiting those that are catabolic. Furthermore, creating measureable effects on muscle mass requires an excess of protein synthesis in relation to degradation. Following resistance exercise there is a marked rise in protein degradation and to a lesser degree synthesis, this net balance remains negative without the availability of amino acids post workout [29]. The essential amino acids

and specifically the branched chain amino acid leucine show striking effects on the stimulation of muscle protein synthesis in vivo, with leucine possessing the ability to directly activate mTOR and itself promote protein synthesis. The combination of amino acid feedings with resistance training has been supported to be a potent activator of protein synthesis causing a larger and more sustained increase than either practice alone [29]. For example, a resistance training session without nutritional provision caused a 45% increase above baseline muscle protein synthesis (MPS) rates, while resistance training plus leucine elevated levels 145% above baseline [29]. It is believed that roughly 3 grams (or 0.05 grams/kg/bw) of leucine maximizes muscle protein synthesis in individuals around 150-160 pounds of bodyweight [30, 31]. As almost all dietary recommendations are based on body size, it is recommended to use the g/kg equation if you fall outside of the 150 pound area.

It seems provision of leucine would be of greatest benefit surrounding the workout (i.e. 0.05 grams per kilogram pre workout and immediately post) but protein synthesis cannot be viewed as a onetime process, it occurs around the clock and appears to be optimally stimulated every 4-5 hours [31]. Recent work has suggested consuming a mixed meal every 4-5 hours rich in leucine (again 0.05g / kg bw) as well as a branched chain amino acid supplement in between meals (also 0.05g/kg) to optimize muscle protein synthesis as well as the hypertrophic response to training [31]. This appears to be due to an improved efficiency with spiking amino acids then proceeding to letting them fall rather than maintaining a constant elevation of amino acids by eating protein rich meals every two hours (which is what is typically seen individuals hoping to increase muscle mass).

Again, it must be appreciated that this is one single pathway in a very complex and multi-component process. In other words, one should not forego other nutrients and become heavily reliant upon amino acids. Glucose and fatty acids also make contributions to the process of muscle hypertrophy in the big picture illustrated by the fact that if total energy intake is not sufficient, protein synthesis will suffer. In the case of inadequate energy intake we are specifically referring to Adenosine Monophosphate activated protein Kinase (AMPK) phosphorylation.

AMPK can be thought of as the energy sensor of the cell. It becomes activated upon low energy states (ATP gets hydrolyzed to ADP which can be further hydrolyzed to AMP) and signals to the body that it must increase oxidative phosphorylation to restore declining ATP levels. As shown below, AMPK activation directly inhibits MTOR. To put it simply, when AMPK is active anabolic processes are halted and catabolic processes are initiated. A real world example of this is the inability of a dieting athlete to make significant gains in muscle mass while hypocaloric. Furthermore, if one desires to increase muscle hypertrophy a certain degree of “overfeeding” is essential.



**Figure 6** Leucine’s direct effect on the mTOR pathway

*Resistance Training Roles/Guidelines*

Resistance training provides the stimulus for all of the previously mentioned complex remodeling processes to occur. Moderate to high intensity resistance exercise (60-85% 1 RM) has proven activation of satellite cells through up-regulation of the MRFs, increased transcription of the MHCs, as well as activity of anabolic pathways (IGF-1 cascade) and suppression of negative regulators of hypertrophy (like myostatin) [23]. The importance of eccentric contractions have also been highlighted in numerous reviews as they appear to be responsible for CaMK, MGF, and p70S6K signaling, thus vital for hypertrophy [5, 28].

The following provides an overview of essentials and suggestions in program design to promote muscle hypertrophy:

- Must provide progressive overload through decreased rest periods, increased volume, increased intensity, increased training frequency or a combination of these methods [32].
- Should follow periodization guidelines (i.e daily undulated periodization, linear, etc..) [32].
- Research has determined muscle hypertrophy to be greatest in the 8-12 repetition range; this is likely due to the combined effects of myofibrillar and sarcoplasmic hypertrophy being greatest at this rep range [32]. This does not mean the athlete should train exclusively within this rep range! As noted earlier in the paper low rep range training increases muscle fiber density and higher repetition training (up to 20) has also recently been shown to upregulate the genes involved in hypertrophy [23].
- Should include “negatives” or eccentric only contractions at random intervals throughout the training cycle. \* A proper eccentric requires weights in excess of 1RM.

- Should be of a shorter rest period length (30 seconds-1.5 min).
- Should always include the involvement and be primarily focused upon the training of large muscle groups i.e. multijoint exercises [32].
- Should be of high frequency in experienced lifters (4-5 days/week) [32].
- Should be high volume in nature with multiple sets [32].

## **Conclusion**

The aim of this paper was to review the complex molecular processes that occur in the progression of skeletal muscle hypertrophy. It has been concluded that exercise induced hypertrophy is heavily reliant upon the activation of numerous vital pathways and processes such as activation of satellite cells, expression of MHC genes, and the signaling of proliferating, differentiating and anabolic pathways. It is the hope of the author that the reader has gained an appreciation for the complexity and interdependency of muscular adaptation while not losing sight of the grand scheme of physiology.

## ***Brief Author Biography***

Ben Esgro is a Certified Sports Nutritionist through the International Society of Sports Nutrition, he also holds a B.S. in Nutrition with a minor in Exercise Science from West Chester University. He is currently pursuing a Master's Degree in Sports Nutrition and Exercise Physiology from Marywood University. Ben is also a competitive Natural Bodybuilder and Powerlifter. He can be contacted at [besgro@gmail.com](mailto:besgro@gmail.com).

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