mTOR Signaling and the Molecular Adaptation to Resistance Exercise

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ABSTRACT

BODINE, S. C. mTOR Signaling and the Molecular Adaptation to Resistance Exercise. Med. Sci. Sports Exerc., Vol. 38, No. 11, pp. 1950–1957, 2006. Skeletal muscle size is dynamic and responsive to extracellular signals such as mechanical load, neural activity, hormones, growth factors, and cytokines. The signaling pathways responsible for regulating cell size in adult skeletal muscle under growth and atrophy conditions are poorly understood. Recent evidence suggests a role for the PI3K/Akt/mTOR pathway. Protein translation is regulated through the phosphorylation of initiation factors that are controlled by signaling pathways downstream of PI3K/Akt. Recent work in mammals has suggested that activation of Akt/PKB, a Ser- Thr phosphatidylinositol-regulated kinase, and its downstream targets, glycogen synthase kinase-3 (GSK3) and the mammalian target of rapamycin (mTOR), may be critical regulators of postnatal cell size in multiple organ systems, including skeletal muscle. This paper will review some of the recent data that demonstrate the critical role of Akt/mTOR signaling in the regulation of postnatal muscle size, especially under conditions of increased external loading. Key Words: SKELETAL MUSCLE, HYPERTROPHY, PROTEIN TRANSLATION, PROTEIN KINASE B/AKT

It is well established that chronic loading and resistance exercise lead to increases in muscle fiber size and tension output (2,22,41,45). The cellular and molecular mechanisms responsible for signaling muscle growth in response to increases in external load are poorly understood. However, recent studies suggest that activation of the Akt/mTOR signaling pathways plays a critical role in the regulation of skeletal muscle size, especially under conditions of altered external loading (5–7,18,33,37). The target of rapamycin (TOR) is a highly conserved protein kinase that integrates signals from nutrients and growth factors to regulate cell growth (an increase in cell mass and size) and cell cycle progression (14,19). Although mTOR is best known as a regulator of cell cycle progression and cell proliferation, recent data have highlighted its important role in the regulation of cell growth (15,34). The purpose of this paper is to summarize some of the evidence supporting the hypothesis that adaptive muscle growth is dependent on the activation of mTOR, a Ser/Thr protein kinase, and its downstream targets, the ribosomal protein S6 kinase (S6K1/p70S6K) and the translational repressor eukaryotic initiation factor 4E-binding protein 1 (4E-BP1/PHAS-1).

REGULATION OF PROTEIN TRANSLATION

Skeletal muscle growth occurs when the balance between protein synthesis and degradation shifts toward protein synthesis. Protein synthesis is known to increase under conditions of increased loading and during the recovery phase after resistance exercise (24,41,52). Increases in protein synthesis occur before an increase in RNA and DNA levels (52) and can be explained in part by an increase in the initiation of mRNA translation, a key regulatory step in protein synthesis. The initiation of protein translation requires the assembly of a translationally competent ribosome at the AUG start site near the 5′-end of the mRNA (24). Protein translation can be controlled at two key steps: 1) modulation of the binding of the initiator methionyl-tRNA (met-tRNAi) to the 40S ribosomal subunit to form the 43S preinitiation complex, and 2) the binding of the mRNA to the 43S preinitiation complex to form the 48S preinitiation complex. Regulation of these translation initiation steps is controlled through the phosphorylation of initiation factors and protein kinases that are controlled by signaling pathways downstream of phosphatidylinositol 3-kinase (PI3K) (24,40).

Recent work in mammals has suggested that activation of PKB/Akt, a Ser- Thr phosphatidylinositol-regulated kinase, and its downstream targets, glycogen synthase kinase (GSK3) and the mammalian target of rapamycin (mTOR), may be critical regulators of postnatal cell size in multiple organ systems, including skeletal and cardiac muscle (Fig. 1) (14,24,39). Akt signaling promotes protein synthesis in a number of ways. For example, Akt phosphorylation of GSK3 leads to its inhibition and an increase in global protein synthesis through an increase in the activity of eukaryotic initiation factor 2B (eIF2B) (24). eIF2B is a guanine nucleotide exchange factor...
that mediates the exchange of GDP for GTP on eukaryotic initiation factor 2 (eIF2). The active eIF2-GTP binds to met-tRNAi, which then binds to the 40S ribosomal subunit. In addition, Akt can phosphorylate mTOR, which, in turn, leads to phosphorylation of p70S6k and 4E-BP1/PHAS-I (14,19). Phosphorylation and activation of p70S6k lead to hyper-phosphorylation of the ribosomal protein S6, which is associated with enhanced translation of a specific class of mRNAs that contain a 5-terminal oligopyrimidine structure. Proteins encoded by such mRNAs include the ribosomal proteins and elongation factors. Phosphorylation of the translational repressor 4E-BP1 leads to its release from within an inhibitory complex with the translation initiation factor 4E (eIF4E). eIF4E is the rate-limiting translation initiation factor that binds to the cap structure at the 5-end of mRNA transcripts to initiate cap-dependent translation. Release of eIF4E from 4E-BP1 permits eIF4E to bind to the scaffolding protein eIF4G, which then binds to the cap structure of the mRNA and assembles the eIF4F initiation complex by recruiting other initiation factors.

mTOR AND THE REGULATION OF ORGAN GROWTH

The growth of an organ is mediated by increases in both cell size and cell number. Genetic studies in drosophilas and mice have clearly demonstrated that the PI3K and TOR pathways are important regulators of cell and organ growth. In drosophilas, inactivation of PI3K, chico (insulin-receptor substrate (IRS) ortholog), PDK1, Akt, TOR, and S6K decreases organ and cell size, whereas overexpression of many of these molecules increases organ and cell size (35,51). Inactivation of PI3K results in a reduction in organ size through a decrease in both cell size and number, and inactivation of S6K reduces organ size through a decrease in cell size only (51). In mice, homozygous deletion of IRS-1, Akt1, or S6K1 results in a small animal phenotype (11,29,49). In the S6K1 knockout mice, skeletal muscle mass is reduced by a decrease in fiber cross-sectional area, with no decrease in the number of myonuclei per fiber (34). Furthermore, modulation of PI3K, PDK1, or Akt expression in the heart affects heart size as a result of changes in cardiomyocyte size but not cell number (28,39).

The activation of mTOR-mediated pathways seems to be critical for normal postnatal growth of mammalian skeletal muscle, but it is not required for the maintenance of muscle mass. The phosphorylation state of p70S6k is elevated in skeletal muscle of early postnatal versus young adult rats (Fig. 2A). The relative importance of mTOR in the control of early postnatal muscle growth was demonstrated by treating growing rat pups with rapamycin, a selective inhibitor of mTOR. Rapamycin binds to its intracellular receptor, FKBP12, forming a complex that binds mTOR with high affinity and blocks its ability to phosphorylate its downstream targets (19). Delivery of rapamycin (1.5 mg·kg⁻¹·d⁻¹ intraperitoneally) to 2-wk-old rat pups for 11 d resulted in a 30% reduction in body weight in both male and female pups (Fig. 2B). Interestingly, the effects of rapamycin on muscle growth were reduced as the rats developed into young adults. Fourteen days of rapamycin treatment beginning at 2 wk of age resulted in a 40% decrease in hindlimb muscle mass, and treatment beginning at 4 wk of age produced only a 20–25% decrease in muscle mass relative to untreated controls (Fig. 2C). Most surprising was the observation that rapamycin treatment in young adult rats (10–12 wk old) produced no change in muscle mass, suggesting that the maintenance of muscle mass under steady-state conditions is not dependent on the activation of mTOR pathways.

It should be noted that much of what is known about mTOR function has been inferred from experiments employing rapamycin. Rapamycin-dependent inhibition of mTOR decreases cell growth through inhibition of protein translation and ribosome biosynthesis (19). However, inhibition of mTOR with rapamycin can also decrease the rate of cell cycle progression and proliferation of mammalian cells in vitro for reasons not currently understood (15,34). The mechanism by which mTOR coordinates cell growth and cell cycle progression are currently unknown. The deletion of S6K1/2 genes in combination with the expression of a hypophosphorylated form of 4E-BP1 (which would bind eIF4E) is not sufficient to mimic the effect of rapamycin on cell proliferation (34). Consequently, mTOR must regulate cell proliferation through effectors other than S6K1/2 and 4E-BP1. It is not known whether there is a direct effect of rapamycin on the activation, proliferation, and/or fusion of satellite cells in vivo in skeletal muscle under growth conditions. Several studies have demonstrated that during hypertrophic growth of myotubes in vitro, there is an upregulation of the cell cycle gene, cyclin D1, and an increase in cyclin D1–dependent CDK4 activity (20,33). The upregulation of cell cycle genes, however, was not associated with an increase in the number of myonuclei per fiber. The
activation of cell cycle regulators during hypertrophy may be controlling processes other than cell cycle progression, such as ribosome biosynthesis (33) or the transcription of specific genes (20).

mTOR AND THE REGULATION OF ADAPTIVE MUSCLE GROWTH

Protein kinase B/Akt activity increases in response to numerous stimuli, including a wide variety of growth factors and hormones (e.g., insulin-like growth factor-1 (IGF1) and insulin) (24,43). IGF1 binding to its receptor leads to the production of phosphatidylinositol 3,4,5-triphosphate, which leads to the recruitment of Akt from the cytosol to the membrane, where it becomes activated through the phosphorylation of Thr 308 and Ser 473 (36). Transgenic overexpression of IGF-1 from a muscle-specific promoter results in an enlargement in skeletal muscle size (12,48). Furthermore, IGF-1 given to C2C12 myotubes in vitro leads to an increase in cell size because of activation of the PI3k/Akt/mTOR signaling pathway (43). The IGF-1–induced growth of myotubes in culture is not the result of an increase in the number of myonuclei and can be inhibited by the coadministration of rapamycin (34,43).

To obtain evidence for a role of the Akt/mTOR pathway in regulating adaptive muscle hypertrophy in adult animals, the phosphorylation status of key protein kinases and initiation factors in the Akt/mTOR pathway were examined in the plantaris muscle of young adult female Sprague–Dawley rats after functional overload (compensatory hypertrophy). The plantaris was exposed to a chronic increase in activity and external loading after bilateral removal of its functional synergists, the soleus, and medial/lateral gastrocnemius muscles (6). The amount of Akt and, more importantly, the phosphorylation state representing activated Akt, increased throughout the hypertrophy process (from day 3 to 14) (Fig. 3A). After 14 d, the total amount of Akt had increased fourfold more than controls, and the level of phosphorylated/activated form increased ninefold in the hypertrophied plantaris. In addition, phosphorylation of mTOR on Ser 2448 increased twofold (42). Examination of the downstream targets of mTOR revealed an increase in the phosphorylation status and activity of p70S6K, as well as hyperphosphorylation of PHAS-1/4E-BP1 (Fig. 3B). Hyperphosphorylation of 4E-BP1 resulted in its release from eIF4E, allowing it to bind eIF4G, as demonstrated by a decrease in the amount of 4E-BP1:eIF4E complex and an increase in 4E-BP1:eIF4G complex (6,42).

These findings indicated that Akt and its downstream targets were activated in vivo during load-induced muscle hypertrophy. To determine whether activation of mTOR was necessary to produce muscle hypertrophy, rats subjected to functional overload were treated with rapamycin. Daily treatment with rapamycin (1.5 mg kg⁻¹ intraperitoneally) did not alter phosphorylation or activity of Akt itself or its mTOR-independent target GSK-3β, but it did specifically block the activation of targets known to be downstream of mTOR (6). Most importantly, rapamycin treatment led to a 95% reduction in plantaris growth relative to control at 7 and 14 d of functional overload, as assessed by both muscle mass (Fig. 4A) and fiber cross-sectional area (6). These data demonstrate that Akt and its
downstream target, mTOR, were phosphorylated/activated during load-induced adaptive muscle hypertrophy. Further, the finding that specific inhibition of mTOR with rapamycin resulted in a nearly complete blockage of growth suggests that the activation of mTOR and its targets, p70S6K and PHAS-1/4E-BP1, were necessary for adaptive hypertrophy.

The relative importance of p70S6K versus PHAS-1/4E-BP1 in the regulation of muscle fiber growth is unclear. Manipulation of S6K1, S6K2, 4E-BP1, and eIF4E levels in myotubes suggests that S6K1 is the primary regulator of muscle fiber size (34). However, another study (15) suggests that both S6K1 and 4EBP1/eIF4E can influence mammalian cell size. Increases in protein synthesis can be achieved by increasing protein translation through pathways that increase translation initiation and/or elongation, or through the addition of myonuclei. The extent to which each mechanism is required to produce growth in response to load is debated, and it may differ depending on the extent of the increase in cell size. It is well established that activation, proliferation, and fusion of satellite cells is critical for growth and repair after injuries that induce muscle degeneration (10). However, the role of satellite

FIGURE 3—Muscle hypertrophy is associated with activation of the Akt/mTOR pathway. A, Western blots of native and phosphorylated Akt in the rat plantaris during compensatory hypertrophy (CH). Each lane represents 200 µg of total protein extracted from a pool of three plantaris muscles after control (Con, lane 1), 3d of CH (lane 2), 7 d of CH (lane 3), or 14 d of CH (lane 4). For each group, duplicate lanes represent different pools of plantaris muscles. B, Western blot of p70S6K in the rat plantaris after 7 and 14 d of CH. The p70S6K gel shift observed during hypertrophy (CH+, lanes 2 and 5) was inhibited by daily injections of rapamycin (CH/rap, lanes 3 and 6). Each lane represents 25 µg of total protein extracted from a pool of three plantaris muscles. C, Western blots of native and phosphorylated Akt and p70S6K in the medial gastrocnemius (MG) after hindlimb suspension (HLS) and reloading (Rec). Each lane represents 200 µg (Akt) or 25 µg (p70S6K) of total protein extracted from a pool of three MG muscles after control (Con, lanes 1), 14 d of HLS (lanes 2), or 14 HLS followed by 7 d of recovery (lanes 3). For each group, duplicate lanes represent different pools of MG muscles.

FIGURE 4—Muscle hypertrophy in response to altered mechanical loading is blocked by rapamycin. A, Mass of the plantaris muscle, expressed as a percent increase relative to control, after 7 and 14 d of compensatory hypertrophy with vehicle (CH, empty bars) or rapamycin treatment (CH + rap, solid bars). Data are expressed as mean ± SD (10 rats per group). * Significant difference from CH group (P < 0.05). B, Muscle mass, expressed as a percent loss relative to control, for the medial gastrocnemius (MG), lateral gastrocnemius (LG), plantaris (PL), soleus (SOL), and tibialis anterior (TA). Muscle wet weights were taken after 14 d of hindlimb suspension (HLS), 14 d of HLS followed by 7 d of reloading (Rec), and 14 d HLS followed by 7 d of reloading plus treatment with rapamycin (REC/RAP). Data are expressed as mean ± SD (10 rats per group). * Significant difference between REC and REC/RAP (P < 0.05).
cells in adaptive hypertrophy and regrowth after atrophy is less clear. During compensatory hypertrophy it has been postulated that increases in protein synthesis are initially derived through increases in translational efficiency, followed later by changes in translational capacity through the addition of myonuclei. Indeed, increases have been found in the number of myonuclei/fiber after months of functional overload (3), and irradiation studies suggest that satellite cell incorporation is critical for compensatory hypertrophy of the rat EDL and plantaris muscles (1,44). However, irradiation results in the loss of all proliferating cells, including satellite cells, and may interfere with the activation of protein synthesis pathways (1). For example, Adams et al. (1) demonstrated that the rat plantaris is capable of early muscle growth (15 d) after irradiation and functional overload, whereas the later growth is blocked, suggesting the need for myonuclei addition (1). However, in those overloaded plantaris muscles exposed to irradiation, there was a decrease in p70^65k and 4EBP1 phosphorylation, relative to overloaded nonirradiated, which could impact protein synthesis (1).

Functional overload represents a very specific model of altered use and external loading. To determine whether activation of Akt/mTOR signaling pathways represented a general response to increased loading, the response of muscle to reloading after disuse muscle atrophy was examined. Fourteen days of hindlimb suspension (HLS) in young adult female Sprague–Dawley rats resulted in a 15–55% loss of mass in various lower-limb muscles (Fig. 4B). On release from suspension, the atrophied hindlimb muscles experience a chronic increase in external loading and hypertrophy, achieving a 15–20% recovery in muscle mass after 7 d of reloading (Fig. 4B). The exception was the tibialis anterior muscle, which showed a 4% decrease in muscle mass during the first 7 d of recovery. Hindlimb unloading of the medial gastrocnemius resulted in a decrease in the phosphorylation state of Akt, as measured by phospho-specific antibodies (Fig. 3C). Further, there was a 60% decrease in phosphorylation of mTOR on Ser 2448, with no change in total protein (42). Consistent with the changes in Akt and mTOR activation, there was a decrease in the activation state of p70^65k and an increase in the amount of 4E-BP1 bound to eIF4E (6). These changes reverted on reloading of the muscle (Fig. 3C).

As in the functional overload model, treatment with rapamycin during the reloading period resulted in a significant block of muscle growth (Fig. 4B). The inhibition of growth by rapamycin varied across the muscle types and was less complete in the HLS/reloading model compared with the functional overload model. This suggests that muscle growth after atrophy differs from functional overload in that it requires the activation of mTOR and additional signaling pathways. One possible candidate is the GSK3/eIF2 pathway, which was inhibited during HLS and activated during reloading (data not shown). Another protein that was modified during HLS was elongation factor 2 (eEF2). eEF2 is regulated through the mTOR pathway and by cellular energy stress status (9) and mediates the translation step of elongation. Phosphorylation of eEF2 at Thr 56 inhibits its activity by preventing binding to the ribosome. After HLS, eEF2 phosphorylation increased immediately (day 1) and remained elevated relative to control for at least 7 d (data not shown). Phosphorylation of eEF2 is catalyzed by eEF2 kinase, the activity of which is also inhibited by phosphorylation. Recent studies have reported that eEF2 kinase is phosphorylated by p70^65k and p90^RSK1, suggesting control not only by mTOR pathways but also by MAP kinase pathways (8,9).

**mTOR AND CLENBUTEROL-INDUCED MUSCLE GROWTH**

Muscle growth occurs in response to increases in mechanical loading and also in response to selective chemical agents, such as the β2-adrenergic agonist, clenbuterol (21,30). The mechanism by which clenbuterol induces muscle growth is unclear, although increases in protein synthesis have been measured after clenbuterol treatment (21). The phosphorylation status of p70^65k and PHAS-1/4EBP1 is elevated in the rat plantaris (50) and the medial gastrocnemius (unpublished data) after daily clenbuterol treatment. Further, a role for mTOR in mediating the effects of clenbuterol was demonstrated by the ability of rapamycin to inhibit muscle growth during clenbuterol treatment. Clenbuterol (3 mg·kg^-1 intraperitoneally) treatment produced a 30–35% increase in the mass of the medial gastrocnemius and tibialis anterior muscles, whereas coadministration of clenbuterol and rapamycin (1.5 mg·kg^-1 intraperitoneally) treatment produced no significant muscle growth (Fig. 5). These data suggest that clenbuterol-induced muscle growth is mediated through the activation of mTOR and its downstream targets. The inhibition of clenbuterol-induced growth by rapamycin is most likely the result of blocking protein synthesis and

![FIGURE 5—Muscle hypertrophy in response to clenbuterol is blocked by rapamycin. Mass of the medial gastrocnemius muscle, expressed as a percent increase relative to control, after 14 d of clenbuterol treatment (Clen, empty bars) or clenbuterol plus rapamycin treatment (Clen + rapa, solid bars). Data are expressed as mean ± SEM (10 rats per group). * Significant difference from the Clen group (P < 0.05).](http://www.acsm-msse.org)
not satellite cell proliferation/fusion, because satellite cell fusion into myofibers has not been observed during clenbuterol-induced hypertrophy (31).

The above data demonstrate that the Akt/mTOR pathway is activated in, and requisite for, muscle hypertrophy. To demonstrate that activation of Akt/mTOR is sufficient to induce muscle hypertrophy, constitutively activate Akt (c.a.Akt) has been overexpressed in skeletal muscle using two methods: plasmid injection and electroporation of individual muscles in adult animals (6,37), and transgenic overexpression (27). Overexpression of c.a.Akt in skeletal muscles results in an increase in muscle fiber size (6,27,37). Further, the effects of c.a.Akt can be blocked by the concurrent administration of rapamycin (6,37), demonstrating that the growth of muscle fibers in response to c.a.Akt is mediated through the activation of mTOR and its downstream targets.

mTOR AND RESISTANCE EXERCISE

Finally, are the effects of resistance exercise mediated through the Akt/mTOR pathway? The first evidence that mTOR and its downstream targets could have a role in mediating the effects of resistance exercise came from a study by Barr and Esser (5). In this study, p70^65k phosphorylation was shown to increase in the tibialis anterior and extensor digitorum longus muscles at 3 and 6 h after an acute bout of lengthening contractions produced by high-frequency neural stimulation. More interesting was the observation that there was a direct correlation \( r = 0.998 \) between the increase in p70^65k measured at 6 h after an acute exercise bout and the percent change in muscle mass measured after 6 wk of training (5). These data suggested that p70^65k activation was involved in the adaptive growth response to chronic exercise. However, no studies to date have examined the activation of Akt and its downstream targets during chronic resistance exercise training in vivo.

An increase in the phosphorylation of Akt, mTOR, and GSK3 is detected in isolated rat muscles immediately after high-frequency stimulation (4). Further, activation of the translational regulators p70^65k, 4E-BP1, eIF2B, and eEF2 is observed at 3 h poststimulation (4). The best in vivo support for a role of mTOR signaling in resistance exercise, however, comes from the work of Kubica et al. (25,26). In these studies, male Sprague–Dawley rats were trained to perform repetitive ankle extensions with a 0.6-g weighted vest. In this model, protein synthesis and polysomal aggregation were shown to significantly increase in the medial gastrocnemius at 16 h postexercise. The status of ribosomal assembly can be assessed from the separation of muscle extracts on a sucrose gradient where polysomes migrate to the denser fractions and monosomes remain in the less dense fractions. A shift in the distribution of ribosomes from monosomes to polysomes is interpreted as an increase in protein translation. The increase in protein synthesis and polysomal aggregation observed after the acute resistance exercise was completely prevented with the administration of rapamycin 2 h before the exercise. At 16 h postexercise, a small but significant increase in p70^65k and 4E-BP1 phosphorylation relative to sedentary controls was measured. Interestingly, although there was an increase in S6 phosphorylation, there was no detectable change in the amount of 4E-BP1 bound to eIF4E or eIF4G. Of particular interest was the finding that the increase in eIF2B protein expression after resistance exercise was rapamycin dependent, suggesting that mTOR activation was responsible for the early increase in eIF2B translation.

These data and others (5,18,32,38) provide strong support for the hypothesis that mTOR signaling is a critical mediator of muscle growth after resistance training. Although the majority of studies have examined acute exercise from muscles that have experienced lengthening contractions, muscle hypertrophy can occur in response to isometric and shortening contractions as demonstrated by Adams et al. (2). The extent to which mTOR and its downstream targets are activated under all types of muscle contractions remains to be determined. Additional pathways may also be important in signaling protein synthesis after both acute and chronic resistance exercise. For example, activation of MAPK (17,39) and GSK3 (46) pathways have been measured after mechanical loading, which could enhance protein synthesis.

CONCLUSIONS

The present literature supports a role for the activation of Akt/mTOR signaling pathways in regulating muscle growth through an increase in protein synthesis. However, the mechanisms regulating muscle fiber size are complex, and the relative contribution of changes in translation efficiency and/or addition of myonuclei to adaptive hypertrophy require further study. The use of rapamycin has greatly increased our understanding of the role of mTOR in regulating muscle growth. However, the generation of mice with muscle-specific conditional deletions and overexpression of mTOR, S6K1, 4E-BP1, and eIF4E would assist in defining the specific function of mTOR and its downstream targets in muscle growth under varying conditions. The relative contribution of mTOR pathways in regulating load-induced fiber growth in normal versus atrophied muscles is unclear and needs further investigation. For example, whereas activation of mTOR and its downstream pathways seem to be critical for muscle growth after functional overload (6), “regrowth” of muscle after atrophy may rely on mTOR as well as additional pathways (6,16). Cell growth (an increase in cell size or mass) is tightly coupled to nutrient availability, growth factors, and the energy status of the cell (13,23). mTOR is capable of integrating signals from all of these inputs in the regulation of protein translation and cell growth. The extent to which any or all of these signals are involved in regulating the activity of mTOR during mechanical loading requires further investigation. It is interesting to note that Akt activation occurs after low-intensity, long-duration contractions, which are typically associated with endurance-type training, with no activation of mTOR and its downstream
targets (47). The upstream effectors responsible for the selective activation of Akt and mTOR signaling after increases in activity and load are unknown. Potential upstream effectors include growth factors, insulin, integrins, G protein–coupled receptors, and amino acids. Our knowledge of the mechanisms that regulate muscle fiber size has grown considerably in recent years. However, additional research is needed to identify the critical signal-

ing pathways that translate external signals into changes in muscle size. A better understanding of the cellular pathways regulating skeletal muscle size should assist in the development of treatments for muscle disorders.

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