The role of mTORC1 in the regulation of skeletal muscle mass

Sue C. Bodine 1 *

1 Department of Internal Medicine, Division of Endocrinology and Metabolism, University of Iowa Carver College of Medicine, 200 Hawkins Drive, Iowa City, IA 52242, USA

Abstract

Skeletal muscle mass is a very plastic characteristic of skeletal muscle and is regulated by signaling pathways that control the balance between anabolic and catabolic processes. The serine/threonine kinase mechanistic/mammalian target of rapamycin (mTOR) has been shown to be critically important in the regulation of skeletal muscle mass through its regulation of protein synthesis and degradation pathways. In this commentary, recent advances in the understanding of the role of mTORC1 in the regulation of muscle mass under conditions that induce hypertrophy and atrophy will be highlighted.

Keywords

atrophy, hypertrophy, protein synthesis, aging

Peer Review

The peer reviewers who approve this article are:

1. Troy Hornberger, Department of Comparative Biosciences, University of Wisconsin-Madison, Madison, WI, USA
   Competing interests: No competing interests were disclosed.

2. Markus A Rüegg, Biozentrum, University of Basel, Basel, Switzerland
   Daniel J Ham, Biozentrum, University of Basel, Basel, Switzerland
   Competing interests: No competing interests were disclosed.

*Corresponding author: Sue C. Bodine (sue-bodine@uiowa.edu)

Competing interests: The author holds equity in Emmyon Inc. and receives research funding from Calico Life Sciences.

Grant information: The author is supported by VA 1I01BX005626 and NIH U01AG055133.

Copyright: © 2022 Bodine SC. This is an open access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

How to cite this article: Bodine SC. The role of mTORC1 in the regulation of skeletal muscle mass. Faculty Reviews 2022 11:(32) https://doi.org/10.12703/r/11-32

Published: 11 Nov 2022, Faculty Reviews 11:(32) https://doi.org/10.12703/r/11-32
Introduction
Skeletal muscle is a highly adaptive tissue that can modify its size throughout life in response to a variety of stimuli, including neural activity, external loading, growth factors, hormones, nutrients, inflammatory mediators, hypoxia, metabolic stress, and oxidative stress. Muscle mass is regulated primarily by signaling pathways that control the balance between protein synthesis and protein degradation. The serine/threonine kinase mechanistic/mammalian target of rapamycin (mTOR) exists in two functionally and structurally distinct protein complexes: the core components of mTORC1 are the regulatory-associated protein of TOR (raptor) and mammalian lethal with sec-13 protein 8 (mLST8), and the core components of mTORC2 are the rapamycin-insensitive companion of mTOR (RICTOR), mammalian stress-activated protein kinase-interacting protein 1 (mSIN1), and mLST8 (Figure 1)\(^1\). The mTORC1 complex has been shown to be responsive to multiple environmental signals, including nutrients (amino acids and glucose), mechanical load, growth factors (insulin-like growth factor 1, or IGF-1), hormones (insulin), and oxygen levels, suggesting that it plays a central role in the regulation of metabolism and growth\(^2\).

Manipulation of both upstream activators and downstream targets of mTORC1 in skeletal muscle has provided major advances in our understanding of the role of mTORC1 activity in the regulation of muscle mass and function (Figure 1). Investigation of the role of mTORC1 in the regulation of skeletal muscle size has been achieved through the use of pharmacological agents in humans, rats, and mice and genetic manipulation of selective genes in mouse skeletal muscles. The most common pharmacological approach has been systemic delivery of rapamycin since mTORC1 is rapamycin-sensitive and mTORC2 is rapamycin-insensitive; however, chronic delivery of high doses of rapamycin can also block mTORC2. The mTOR kinase inhibitor, AZD8055, has also been used to block both mTORC1 and mTORC2 activation. Genetically, mTORC1 can be selectively inhibited through the deletion of raptor while mTORC1 can be chronically activated through the deletion of TSC1. Pharmacological and genetic approaches have produced both complementary and variable results. The variable results may relate to the fact that mTORC1 activity is not completely blocked by systemically delivered rapamycin while genetic deletion of raptor produces a more complete block of mTORC1 activation.

In skeletal muscle, mTORC1 signaling has been shown to be an important regulator of muscle size through its regulation of mRNA translation and likely other processes such as autophagy and metabolism\(^3\). The major downstream targets of

![Figure 1. Schematic representation of the mTORC1 signaling pathway.](image-url)
mTORC1 are p70S6k (S6K1), 4E-BP1, eIF2k, and ULK-1 (Figure 1). The important role of mTORC1 activation in the regulation of skeletal muscle size has emerged over the past two decades. Early genetic manipulation studies in Drosophila of PI(3)K, PKB/Akt, and p70S6k revealed that deletion of components of this pathway resulted in smaller cells but not fewer cells, suggesting that the PI(3)K/Akt/mTOR pathway played a critical role in the regulation of cell size3. Further genetic manipulations of the PI(3)K/Akt/mTOR pathway in mice revealed the importance of this pathway in the early growth and development of skeletal muscle; however, little was known about the role of this pathway in the maintenance and growth of skeletal muscle in adult mammals. The first suggestion that activation of mTORC1 was important for muscle hypertrophy came from Baar and Esser1, who reported that an acute bout of resistance exercise-like lengthening contractions induced an increase in the phosphorylation of p70S6k (S6K1) in rat skeletal muscle and that the magnitude of the increase in p70S6k phosphorylation was correlated with the degree of hypertrophy following a 6-week training protocol. These findings were extended by Bodine et al.2, who demonstrated that the Akt/mTOR/p70S6k pathway was activated in the plantaris muscle following synergist ablation, or functional overload, leading to muscle hypertrophy. Moreover, it was demonstrated that systemic administration of rapamycin at a dose of 1.5 mg/kg per day could suppress phosphorylation of mTOR, p70S6k, and 4E-BP1 and, importantly, prevent hypertrophy of slow and fast fibers in the rat plantaris following functional overload3. Bodine et al.4 also showed that the Akt/mTOR pathway was suppressed in response to hindlimb unloading that resulted in muscle fiber atrophy and reactivated upon hindlimb reloading, which induced muscle fiber growth. Rapamycin treatment given upon reloading of the hindlimbs significantly reduced the regrowth of the soleus, plantaris, and medial gastrocnemius muscles; however, the growth inhibition was only about 50%, suggesting the involvement of additional anabolic pathways5. These initial observations have been confirmed and extended by multiple independent groups, showing that activation of mTORC1 is necessary and sufficient to induce muscle hypertrophy6,7.

Although there have been considerable investigations of the role of mTORC1 activation in the induction of muscle growth since the early 2000s, the exploration of the role of mTORC1 activity in the induction of muscle atrophy has been explored only recently. Several excellent reviews have summarized the current state of knowledge regarding the regulation of mTOR signaling and its control of metabolism in multiple tissues1,2. In this commentary, the focus will be on recent advances in the understanding of the role of mTORC1 in the regulation of skeletal muscle size in adult animals.

mTORC1 signaling and the maintenance of adult skeletal muscle mass

The prevailing evidence suggests that activation of mTORC1 is necessary for proper development and postnatal growth of skeletal muscle; however, the need for mTORC1 activation in the maintenance of muscle mass in mature, adult animals has been unclear. Previous reports have shown that selective deletion of mTOR or raptor in skeletal muscle during embryonic development leads to a reduction in postnatal growth and the development of late-onset myopathy and premature death around 6 to 8 months of age9,10,11. In contrast, inducible-skeletal muscle-specific deletion of raptor in young adult mice for 21 days did not induce skeletal muscle atrophy12. The results from genetically manipulated mice are consistent with the observation that rapamycin treatment in young adult rats (10–12 weeks old) did not affect muscle mass but that rapamycin treatment for 14 days initiated in 2-week-old rat pups resulted in a 40% decrease in the hindlimb muscle mass13. Recently, Ham et al.14 induced the deletion of raptor in the muscles of 3-month-old mice and examined the effect at different time points (10 days, 21 days, and 5 months) after deletion. Raptor deletion suppressed the phosphorylation of downstream mTORC1 targets but had no effect on hindlimb muscle weight or maximum isometric force production 5 months after deletion14. After 5 months of raptor deletion, however, an increase in fiber size variability was observed within individual muscles, with the appearance of very small and very large fibers but no change in mean fiber cross-sectional area. Furthermore, a 24% reduction in ribosomal proteins and a reduction in the percentage of heavy ribosomes were reported, suggesting a decrease in translational capacity and global translation14. These data are consistent with the 40% reduction in basal protein synthesis measured by puromycin reported by You et al.12 following 21 days of induced raptor deletion in adult mice. Additionally, acute in vivo treatment of adult rats with either rapamycin (inhibition of mTORC1 activity only) or the mTOR kinase inhibitor AZD8055 (inhibition of TORC1 and mTORC2 activity) resulted in a 40 to 50% decrease in basal protein synthesis in hindlimb muscles15. These results suggest that, in mature adult animals, a significant portion of basal protein synthesis is mTORC1-independent. Furthermore, the results suggest that maintenance of adult muscle is not solely dependent on mTORC1 activity; however, the long-term suppression of mTORC1 may not be without some negative consequences to muscle, one being an inability to positively respond to anabolic signals with an increase in muscle size and strength.

mTORC1 signaling and increases in protein synthesis following mechanical stimulation

Skeletal muscle hypertrophy occurs in adult animals as the result of repeated increases in mechanical loading, and the precise role of mTORC1 activation in stimulating an increase in protein synthesis and muscle fiber size continues to be investigated. In humans, resistance exercise training is known to produce increases in muscle size and strength, as well as protein synthesis16. In rodents, resistance exercise has been simulated using several models, the most common being functional overload (or synergist ablation) and electrical stimulation (ES). Functional overload is most often performed on the plantaris muscle through the removal of the soleus and the distal half of the medial and lateral gastrocnemius.
muscle. Functional overload induces a chronic increase in external loading as well as an increase in the neural activation of the plantaris muscle, resulting in a rapid increase in muscle mass and fiber cross-sectional area. Bodine et al. revealed that muscle growth in response to the functional overload of the rat plantaris was rapamycin-sensitive, thus suggesting that it was mTORC1-dependent. Follow-up studies have been performed in genetically modified C57BL6 mice, confirming that mTORC1 is activated in the muscle fiber in response to mechanical loading and required to induce muscle growth following functional overload. The functional overload model in C57BL6 mice, but not rats, results in an increase in the number of fibers within the plantaris and an increase in the expression of embryonic myosin heavy chain, suggestive of degeneration/regeneration or de novo myogenesis or both. In more recent studies, a modified functional overload model, referred to as myotenectomy, was developed in which the soleus muscle was left intact and only the distal tendon of the gastrocnemius muscle was removed in order to investigate the role of mTORC1 in muscle fiber growth in response to mechanical overload. With a muscle-specific, tamoxifen-inducible raptor knockout (KO) mouse, growth of the plantaris muscle was found to be completely blocked in response to mechanical overload induced by myotenectomy. Interestingly, the mechanical overload-induced increase in protein synthesis, as measured by puromycin, was not blocked in raptor KO mice or rapamycin (0.6 mg/kg)-treated wild-type mice. For comparison, 7 days of rapamycin (1.5 mg/kg) treatment in young female FVB/N mice was found to inhibit p70S6K phosphorylation, muscle growth, and the increase in protein synthesis as measured by puromycin following myotenectomy. The contradictory findings related to the suppression of protein synthesis following myotenectomy could be related to the rapamycin doses used in the two studies (0.6 vs. 1.5 mg/kg) and the potential inhibition of 4E-BP1. A rapamycin dose of 1.5 mg/kg was found to suppress both p70S6K phosphorylation and 4E-BP1 bound to eIF4E, as well as muscle growth following 14 days of functional overload in the rat plantaris.

While functional overload has been an extremely useful model for identifying the cellular and molecular mechanisms underlying skeletal muscle growth, it does induce a very rapid hypertrophy response, which is not typical of resistance exercise in humans. A rodent model that may better simulate human resistance exercise is repeated ES. In humans, it has been shown that an acute bout of resistance exercise activates mTORC1 and its downstream targets and that systemic delivery of rapamycin blocks the increase in protein synthesis and partially blocks the activation of downstream mTORC1 targets such as p70S6K. In rodents, repeated maximal ES of the sciatic nerve has been used to simulate resistance exercise. In 2019, You et al. demonstrated that mTORC1 signaling increases in response to a single bout of ES and can be blocked by rapamycin or deletion of raptor. Furthermore, raptor was found to be necessary for the targeting of mTOR to the late endosome/lysosome in response to ES. In response to a single bout of resistance exercise, protein synthesis can be elevated for up to 48 hours after exercise, and several recent studies have examined the extent to which this elevated protein synthesis is rapamycin-sensitive/mTORC1-dependent. Two independent studies used slightly different resistance exercise models in rats and found that rapamycin blocked the early increase in protein synthesis but failed to completely block the late increase in protein synthesis induced by an acute bout of exercise. In a follow-up study, Ogasawara and Suginohara showed that the ATP-competitive mTOR kinase inhibitor, AZD8055, inhibited mTORC1 activation and the phosphorylation of Akt at Ser 473 and completely inhibited the resistance exercise-induced increase in protein synthesis. In Ogasawara et al., chronic rapamycin treatment (1.5 mg/kg) was found to significantly reduce, but not fully suppress, the increase in plantaris fiber cross-sectional area in response to 4 weeks of chronic resistance exercise.

In summary, these recent studies reveal that both mTORC1-dependent and mTORC1-independent pathways are activated in response to mechanical loading and contribute to increases in protein synthesis. The data are consistent with the conclusion that activation of mTORC1 is a critical, if not necessary, step for the induction of muscle growth in response to mechanical loading. Recent evidence reveals that mTORC1 is not chronically active in response to repeated bouts of resistance exercise, and, in fact, activation of mTORC1 following repeated bouts of resistance exercise may be reduced relative to the strong activation that occurs following the initial bout of exercise. These recent studies highlight the need for further investigations into the mTORC1-independent pathways that are activated in response to resistance exercise and appear to contribute to an increase in protein synthesis. Furthermore, details of the specific proteins that are translated by mTORC1-dependent and mTORC1-independent pathways are needed.

**mTORC1 signaling and muscle atrophy**

A common misconception in the literature is that, under conditions that induce muscle atrophy, protein synthesis is suppressed and, as an extension, that mTORC1 signaling is suppressed. It is true that protein synthesis is inhibited under many atrophy-inducing conditions, such as sepsis, fasting, diabetes, and hindlimb unloading. However, under conditions of cast immobilization and denervation, mTORC1 activity has been reported to increase, not decrease, at least during the early phases of the atrophy process. These findings raise several questions: What are the upstream activators of mTORC1? What is the purpose of the increase in mTORC1 activity? Is an increase in mTORC1 protective or harmful? It is not unreasonable to think that the synthesis of selective proteins could increase in response to an atrophy-inducing event, especially given the large number of genes that are transcriptionally upregulated following atrophy-inducing conditions, such as immobilization and denervation. In this case, the mRNA species being translated could be supporting
protein degradation pathways and thus be contributing to the atrophy process.

Several studies have found that joint immobilization results in an increase in mTORC1 activity, as measured by an increase in p70S6 phosphorylation and cap-dependent translation\(^{25,26}\). This increase in mTORC1 activity, however, is associated with a decrease in protein synthesis. Recently, Lin et al.\(^{27}\) reported a significant decrease in protein synthesis in the plantar flexor muscles of male mice after 6 hours of rigid immobilization of the ankle and knee joints, which continued to decline for 72 hours. The lack of suppression of the mTORC1 pathway following immobilization differs from what is observed following hindlimb unloading, where there is a decrease in protein synthesis and mTORC1 activity, especially in the soleus\(^{28}\). The difference between joint immobilization and hindlimb unloading is unclear but could relate to the extent to which neural activation of the muscles is affected in the two models; immobilization produces a greater and more sustained decrease in neural activity than hindlimb unloading\(^{29,30}\).

To gain insight into the role of increased mTORC1 activity, rapamycin was delivered to mice during the immobilization period and found to exacerbate the immobilization-induced decrease in protein synthesis and the loss of muscle mass and fiber cross-sectional area\(^{25}\). Interestingly, further activation of mTORC1 and protein synthesis in the immobilized muscle with overexpression of Rheb resulted in attenuated atrophy\(^{28}\). It was concluded, on the basis of these data, that the increase in mTORC1 activity during immobilization was protective in that it prevented the further decline in protein synthesis. In a more recent study, Segalés et al.\(^{31}\) examined the effect of sestrin 1 and 2 overexpression on mTORC1 activity and muscle atrophy. The overexpression of sestrin 1 or sestrin 2 was able to prevent the loss of muscle mass and function following limb immobilization and denervation through proposed mechanisms of action involving inhibition of mTORC1 and activation of mTORC2, resulting in the inhibition of ubiquitin-proteasome-mediated proteolysis and the activation of autophagy\(^{31}\). Interestingly, they reported that rapamycin treatment resulted in the sparing of muscle mass following immobilization\(^{31}\). The apparent contradictory effects of mTORC1 inhibition may be related to the dose of rapamycin used (4 vs. 1.5 mg/kg), which could have differentially affected protein degradation since You et al.\(^{25}\) reported no effect of rapamycin treatment on protein degradation whereas Segalés et al.\(^{31}\) reported inhibition of FOXO-mediated upregulation of ubiquitin-proteasome proteolysis and an increase in autophagy.

As mentioned, denervation-induced muscle atrophy also results in an increase in mTORC1 activity as well as increases in Akt phosphorylation and protein synthesis\(^{24,12}\). Tang et al.\(^{24}\) suggested that activation of mTORC1 was deleterious in that it inhibited Akt phosphorylation, resulting in the activation of the FOXO transcription factors. However, increased Akt phosphorylation has been shown to be an early response to denervation as opposed to a late response\(^{33}\). Furthermore, an increase in the transcription, translation, and activity of FOXO transcription factors occurs early following denervation, even with an increase in Akt phosphorylation, and deletion of the FOXO transcription factors (FOXO1/3/4) protects against denervation-induced muscle atrophy\(^{33}\).

Previous studies in mice\(^{33}\) and rats\(^{35}\) have reported that rapamycin treatment does not protect from denervation-induced atrophy, nor does it exacerbate muscle loss. However, recent studies performed in muscle-specific raptor KO mice suggest that the activation of mTORC1 activity in response to denervation is protective since raptor KO mice have greater denervation-induced atrophy than wild-type mice\(^{36}\). Interestingly, measurement of protein synthesis in specific fiber types within the fast-twitch extensor digitorum longus (EDL) muscle revealed that protein synthesis selectively increased in the non-type IIb fibers (that is, the more oxidative fibers) following denervation and that only the non-type IIb fibers in the EDL and tibialis anterior (TA) muscles had greater atrophy in the raptor KO mice, suggesting that the mTORC1 protection is fiber type-specific\(^{36}\). The findings from the raptor KO mice suggest that activation of mTORC1 in response to denervation serves to protect the muscle from severe atrophy; however, mice with chronic activation of mTORC1 (TSC1mKO) also show more severe atrophy following denervation, especially of types IIA/X and I fibers, and denervation for an extended period (4 weeks) produces a severe myopathy similar to what is observed in 9- to 10-month-old TSC1mKO mice\(^{37}\). The more severe atrophy response was attributed to a blunted increase in Akt phosphorylation, a dysregulated autophagy response, and blunting of HDAC4 activation.

These recent findings show the complexity of mTORC1 regulation and highlight the need to better understand the role of mTORC1 activity under atrophy-inducing conditions. Both increases and decreases in mTORC1 activity have been associated with muscle atrophy induced by disuse. Moreover, increases in mTORC1 activity under disuse atrophy conditions have been associated with both increases and decreases in protein synthesis. In this regard, the extent to which changes in mTORC1 activity are responsible for the changes in global protein synthesis is unclear. Going forward, we need a better understanding of the translation and degradation of specific proteins under different atrophy conditions. One must also be cognizant of the impact of muscle type and atrophy duration on the findings, as well as the rodent species (mouse versus rat) under study and its age and sex.

**mTORC1, the neuromuscular junction, and aging**

A preponderance of evidence supports the critical role of mTORC1 activity in the formation and maintenance of the neuromuscular junction (NMJ) in mammals\(^{38}\). Interestingly, both the prolonged inhibition of mTORC1 through inducible muscle-specific deletion of raptor and the chronic activation of mTORC1 through the muscle-specific deletion of TSC1
have been shown to lead to NMJ destabilization. In the case of mTORC1 inhibition, Baraldo et al.39 found that 7 months following raptor deletion in adult mice, there was an increase in the percentage of neural cell adhesion molecule (NCAM)-positive fibers and fibrillation potentials and an increase in endplate fragmentation that suggested the presence of denervation. Interestingly, only minimal changes in body weight and muscle mass were found; however, an increase in fiber size variability with the appearance of small, angulated fibers was observed in specific muscles40. The suggested causes of the NMJ fragmentation and denervation in mice with prolonged mTORC1 inhibition were a block in autophagic flux and mitophagy leading to mitochondrial dysfunction39. The effects of long-term suppression of mTORC1 through the deletion of raptor in adult muscle could reflect the importance of mTORC1 in the regulation of metabolism and other cellular processes.

In comparison, chronic activation of mTORC1 in TSC1mKO mice also results in endplate fragmentation as well as a reduction in acetylcholine receptor density and impaired neural transmission37. In contrast to the raptor KO mice, TSC1mKO mice develop early-onset muscle atrophy followed by a severe late-stage myopathy characterized by vacuolated fibers. Prolonged activation of mTORC1 in the TSC1mKO mice also inhibits Akt phosphorylation, resulting in the activation of FOXO transcription factors and the upregulation of the E3 ligases MuRF1 and MAFbx/atrogin1 in some muscles, which may contribute to the early (3 months) atrophy, while the late-stage myopathy was linked to the suppression of autophagy and further NMJ fragmentation and denervation37.

There is growing evidence that mTORC1 activity is chronically elevated in skeletal muscle with aging and may contribute to sarcopenia36,41. The upstream factors contributing to the activation of mTORC1 with age are unknown, but it has been speculated that denervation contributes to the elevation in basal mTORC1 activity. Multiple factors have been suggested to contribute to sarcopenia, including altered proteostasis, inflammation, and NMJ instability, which could be influenced by changes in mTORC1 activity. In this regard, several studies have examined the impact of rapamycin or rapamycin analogs (rapalog) on the progression of sarcopenia36,41. Low-dose rapalog treatment, started at 22 months of age for 6 weeks in Sprague Dawley rats, was able to prevent the loss of mass in some (TA and plantaris) but not all (gastrocnemius) muscles40. Low-dose rapalog treatment also suppressed the expression of selected atrophy-associated genes and inactivity/denervation-associated genes in selected muscles. A recent study in mice examined the impact of rapamycin (4 mg/kg) treatment started at 15 or 20 months of age and followed until 30 months of age42. As seen in the rat, rapamycin treatment was differentially effective in preventing loss of muscle mass and strength. Differential gene expression analysis in multiple muscle types revealed that rapamycin treatment had significant effects on multiple cellular processes, including immune responses, NMJ, and the extracellular matrix42. The suppression of mTORC1 remains a potential target for aging; however, future studies will need to identify the optimal dose and dosing strategy if it is to remain a viable therapeutic. Future studies should also examine the effect of chronic mTORC1 inhibition on the adaptive responses to endurance and resistance exercise.

**Concluding remarks**

The accumulating evidence clearly shows that mTORC1 is an important regulator of skeletal muscle mass and function. However, the role of mTORC1 activity in skeletal muscle is complex and dependent on the life stage (that is, postnatal versus adult versus old). The published data suggest that mTORC1 activity is tightly regulated throughout the lifespan and is responsive to a variety of external stimuli. However, the mechanisms by which these external signals activate or inhibit mTORC1 are unclear. In general, the data suggest that acute, intermittent elevations in mTORC1 activity are beneficial; however, chronic elevations in mTORC1 activity in adult muscles appear to be detrimental.

Some key points are the following:

1. During postnatal development, elevated levels of mTORC1 activity are necessary for the growth of muscle fibers. However, in adult mammals, resting mTORC1 activity is reduced and does not appear to be necessary for the maintenance of muscle mass since the suppression of resting mTORC1 activity in adult muscle by rapamycin or raptor deletion does not induce muscle loss but does cause a slight reduction in basal protein synthesis.

2. Although the complete inhibition of mTORC1 activation by the deletion of raptor in adult muscles does not induce muscle atrophy in the short term, extended inhibition of mTORC1 does lead to muscle dysfunction which could be related to the fact that mTORC1 activity influences not only growth processes but other cellular processes involved in metabolism, glucose homeostasis, and proteostasis.

3. Although activation of mTORC1 may not be required for the maintenance of muscle mass in adult animals, it does appear to be a critical pathway for the induction of adaptive muscle growth, especially in response to mechanical overload. In response to a bout of resistance exercise, there is an increase in both mTORC1 activity and protein synthesis. Increases in mTORC1 activity appear to be responsible for some but not all of the increases in protein synthesis. It appears that both mTORC1-dependent and mTORC1-independent pathways are involved in the control of protein synthesis and the regulation of muscle mass.

4. The role of mTORC1 activity in regulating the loss of muscle mass is unclear. It appears that the suppression of mTORC1 alone does not induce muscle loss, at least in the short term. It remains unclear as to whether the elevated mTORC1 activity observed during disuse or denervation is beneficial or detrimental.
5. Several investigations have shown that activation of mTORC1 through Akt activation or other mechanisms can attenuate the loss of muscle mass under a variety of conditions.\textsuperscript{15,41,44} 

6. Finally, whereas intermittent activation of mTORC1 is critical for inducing muscle hypertrophy, chronic activation of mTORC1 is harmful, leading to muscle atrophy and dysfunction. Accumulating evidence suggests that resting mTORC1 activity is chronically elevated in skeletal muscle as a function of age and may lead to dysfunction, especially at the NMJ.

Although significant advancements in our understanding of the function of mTORC1 activity in muscles have been made, many questions remain to be answered. For example:

1. What are the specific upstream factors that lead to activation or suppression of mTORC1 activity under atrophy conditions?
2. What is the role of increased mTORC1 following denervation or immobilization? Is it beneficial or harmful? Is increased mTORC1 regulating the translation of specific proteins? If so, what is the mechanism for the translation of selective mRNA species?
3. Can activation of mTORC1 activity alone attenuate muscle atrophy? If not, by what mechanism does mTORC1 need to be activated in order to attenuate muscle atrophy? Is activation of Akt necessary to attenuate muscle atrophy?
4. How is mechanical load sensed and how is it transduced to activate mTORC1?
5. What mTORC1-independent pathways are responsible for the maintenance of muscle mass in adult animals?
6. What is responsible for the chronic activation of mTORC1 with aging? What is the relationship between mTORC1 activation with age and the development of sarcopenia?
7. Is long-term pharmacological suppression of mTORC1 activation harmful to skeletal muscle? Does chronic suppression of mTORC1 with rapamycin suppress muscle adaptation to endurance or resistance exercise?

References

1. Battaglioni S, Benjamin D, Wälchli M, et al.: mTOR substrate phosphorylation in growth control. Cell. 2022; 185(1): 1814–36. Published Abstract | Publisher Full Text
2. Szewczak A, Kim E, Jacinto E: Regulation and metabolic functions of mTORC1 and mTORC2. Physiol Rev. 2021; 101(3): 1371–426. Published Abstract | Publisher Full Text | Free Full Text
3. Zhang H, Stallock JP, Ng JC, et al.: Regulation of cellular growth by the Drosophila target of rapamycin mTOR. Genes Dev. 2000; 14(21): 2712–24. Published Abstract | Publisher Full Text | Free Full Text
4. Shima H, Pende M, Chen Y, et al.: Disruption of the p70\textsuperscript{s6k}*p90\textsuperscript{rictor}* gene reveals a small mouse phenotype and a new functional S6 kinase. EMBO J. 1998; 17(23): 6649–59. Published Abstract | Publisher Full Text | Free Full Text
5. Baar K, Esser K: Phosphorylation of p70\textsuperscript{s6k} correlates with increased skeletal muscle mass following resistance exercise. Am J Physiol. 1999; 276(1): C120–7. Published Abstract | Publisher Full Text | Free Full Text
6. Bodine SC, Stitt TN, Gonzalez M, et al.: Akt/mTOR pathway is a crucial regulator of skeletal muscle hypertrophy and can prevent muscle atrophy in vivo. Nat Cell Biol. 2001; 3(11): 1014–9. Published Abstract | Publisher Full Text | Free Full Text
7. Reynolds TH 4th, Bodine SC, Lawrence JC Jr: Control of Ser\textsuperscript{423} phosphorylation in the mammalian target of rapamycin by insulin and skeletal muscle load. J Biol Chem. 2002; 277(20): 17617–22. Published Abstract | Publisher Full Text | Free Full Text
8. Ogasawara R, Jensen TE, Goodman CA, et al.: Resistance Exercise-Induced Hypertrophy: A Potential Role for Rapamycin-Insensitive mTOR. Exerc Sport Sci Rev. 2019; 47(3): 188–94. Published Abstract | Publisher Full Text | Free Full Text
9. Goodman CA: Role of mTORC1 in mechanically induced increases in translation and skeletal muscle mass. J Appl Physiol. 2019; 127(2): 581–90. Published Abstract | Publisher Full Text | Free Full Text
10. Benzinger CF, Romano K, Ciotta D, et al.: Skeletal muscle-specific ablation of raptor, but not of rictor, causes metabolic changes and results in muscle dystrophy. Cell Metab. 2008; 8(5): 411–24. Published Abstract | Publisher Full Text
11. Risso V, Mazzelin L, Roceti M, et al.: Muscle inactivation of mTOR causes metabolic and dystrophic defects leading to severe myopathy. J Cell Biol. 2009; 187(6): 859–74. PubMed Abstract | Publisher Full Text | Free Full Text
12. You JS, McNally RM, Jacobs BL, et al.: The role of raptor in the mechanical load-induced regulation of mTOR signaling, protein synthesis, and skeletal muscle hypertrophy. FASEB J. 2019; 33(3): 4021–34. PubMed Abstract | Publisher Full Text | Free Full Text | Faculty Opinions Recommendation
13. Bodine SC: mTOR signaling and the molecular adaptation to resistance exercise. Med Sci Sports Exerc. 2006; 38(11): 1950–7. PubMed Abstract | Publisher Full Text | Free Full Text
14. Ham AS, Chojnowska K, Timigraj LA, et al.: mTORC1 signalling is not essential for the maintenance of muscle mass and function in adult sedentary mice. J Cachexia Sarcopenia Muscle. 2020; 11(1): 259–73. PubMed Abstract | Publisher Full Text | Free Full Text
15. Ogasawara R, Sugiohara T: Rapamycin-insensitive mechanistic target of rapamycin regulates basal and resistance exercise-induced muscle protein synthesis. FASEB J. 2018; 32(17): 14422–33. PubMed Abstract | Publisher Full Text | Faculty Opinions Recommendation
16. Adams GR, Bamman MM: Characterization and regulation of mechanical loading-induced compensatory muscle hypertrophy. Compr Physiol. 2012; 2(4): 2829–70. PubMed Abstract | Publisher Full Text | Free Full Text
17. Goodman CA, Frey JW, Malbrey DM, et al.: The role of skeletal muscle mTOR in the regulation of mechanical load-induced growth. J Physiol. 2011; 589(Pt 22): 5485–501. PubMed Abstract | Publisher Full Text | Free Full Text
18. Tabbaa M, Ruiz Gomez T, Campell DG, et al.: The regulation of polyamine pathway proteins in models of skeletal muscle hypertrophy and atrophy: A potential role for mTORC1. Am J Physiol Cell Physiol. 2021; 320(6): C976–C999. PubMed Abstract | Publisher Full Text
19. Drummond MJ, Fry CS, Glynn EL, et al.: Rapamycin administration in humans blocks the contraction-induced increase in skeletal muscle protein synthesis. J Physiol. 2009; 587(7): 1535–46. PubMed Abstract | Publisher Full Text | Free Full Text
20. West DWD, Marcotte GR, Chason CM, et al.: Normal Ribosomal Biogenesis
but Shortened Protein Synthetic Response to Acute Eccentric Resistance Exercise in Old Skeletal Muscle. Front Physiol. 2019; 9:1915. PubMed Abstract | Publisher Full Text | Free Full Text

21. Ogasawara R, Fujita S, Homburger TA, et al.: The role of mTORC1 in the regulation of skeletal muscle mass in a rodent model of resistance exercise. Sci Rep. 2016; 6: 31142. PubMed Abstract | Publisher Full Text | Free Full Text | Faculty Opinions Recommendation

22. Langer HT, West D, Senden J, et al.: Myofibrillar protein synthesis rates are increased in chronically exercised skeletal muscle despite decreased anabolic signalling. Sci Rep. 2020; 12(1): 7553. PubMed Abstract | Publisher Full Text | Free Full Text

23. Gordon BS, Kelleher AR, Kimball SR: Regulation of muscle protein synthesis and the effects of caloric states. Int J Biochem Cell Biol. 2013; 45(10): 2147–57. PubMed Abstract | Publisher Full Text | Free Full Text

24. Tang H, Inoki K, Lee M, et al.: mTORC1 promotes denervation-induced muscle atrophy through a mechanism involving the activation of FoxO and E3 ubiquitin ligases. Sci Signal. 2014; 7(314): ra18. PubMed Abstract | Publisher Full Text | Faculty Opinions Recommendation

25. You JS, Anderson GB, Dooley MS, et al.: The role of mTOR signaling in the regulation of protein synthesis and muscle mass during immobilization in mice. Dis Model Mech. 2015; 8(9): 1059–69. PubMed Abstract | Publisher Full Text | Free Full Text

26. Goodman CA, Coenen AM, Frey JW, et al.: Insights into the role and regulation of TCTP in skeletal muscle. Oncotarget. 2017; 8(12): 18754–72. PubMed Abstract | Publisher Full Text | Free Full Text

27. Lin KH, Wilson GM, Blanco R, et al.: A deep analysis of the proteomic and phosphoproteomic alterations that occur in skeletal muscle after the onset of immobilization. J Physiol. 2021; 599(11): 2887–906. PubMed Abstract | Publisher Full Text | Free Full Text

28. Baehr LM, West DWD, Marshall AO, et al.: Muscle-specific and age-related changes in protein synthesis and protein degradation in response to hindlimb unloading in rats. J Appl Physiol (1985). 2017; 122(5): 1336–50. PubMed Abstract | Publisher Full Text | Free Full Text

29. Allford EK, Roy RR, Hodgson JA, et al.: Electromyography of rat soleus, medical gastrocnemius, and tibialis anterior during hind limb suspension. Exp Neurol. 1987; 96(3): 635–49. Publisher Full Text

30. Fournier M, Roy RR, Perham H, et al.: Is limb immobilization a model of muscle disease? Exp Neurol. 1983; 80(1): 147–56. PubMed Abstract | Publisher Full Text

31. Segalés J, Perdiguero E, Serrano AL, et al.: Sestrin prevents atrophy of disused and aging muscles by integrating anabolic and catabolic signals. Nat Commun. 2020; 11(1): 189. PubMed Abstract | Publisher Full Text | Free Full Text

32. Gomes AV, Waddell DS, Siu R, et al.: Upregulation of proteasome activity in muscle RING finger 1-null mice following denervation. FASEB J. 2012; 26(7): 2986–99. PubMed Abstract | Publisher Full Text | Free Full Text

33. MacDonald EM, Andres-Mateos E, Mejias R, et al.: Denervation atrophy is independent from Akt and mTOR activation and is not rescued by myostatin inhibition. Dis Model Mech. 2014; 7(4): 471–81. PubMed Abstract | Publisher Full Text | Free Full Text

34. Milan G, Romanello V, Pescatore F, et al.: Regulation of autophagy and the ubiquitin-proteasome system by the FoxO transcriptional network during muscle atrophy. Nat Commun. 2015; 6: 6670. PubMed Abstract | Publisher Full Text | Free Full Text

35. Klwe WO, Panaro FJ, Yang H, et al.: Rapamycin inhibits the growth and muscle-sparring effects of clenbuterol. J Appl Physiol (1985). 2007; 102(2): 740–7. PubMed Abstract | Publisher Full Text

36. You JS, Ken K, Steinert ND, et al.: mTORC1 mediates fiber type-specific regulation of protein synthesis and muscle size during denervation. Cell Death Discov. 2021; 7(1): 74. PubMed Abstract | Publisher Full Text | Free Full Text

37. Castets P, Pion N, Theodore M, et al.: mTORC1 and PKB/Akt control the muscle response to denervation by regulating autophagy and HDAC4. Nat Commun. 2019; 10(1): 3187. PubMed Abstract | Publisher Full Text | Free Full Text

38. Castets P, Ham DJ, Rüegg MA: The TOR Pathway at the Neuromuscular Junction: More Than a Metabolic Player? Front Mol Neurosci. 2020; 13: 162. PubMed Abstract | Publisher Full Text | Free Full Text

39. Banardo M, Geremia A, Pirazzini M, et al.: Skeletal muscle mTORC1 regulates neuromuscular junction stability. J Cachexia Sarcopenia Muscle. 2020; 11(1): 208–25. PubMed Abstract | Publisher Full Text | Free Full Text

40. Joseph GA, Wang SX, Jacobs CE, et al.: Partial Inhibition of mTORC1 in Aged Rats Counteracts the Decline in Muscle Mass and Reverses Molecular Signaling Associated with Sarcopenia. Mol Cell Biol. 2019; 39(19): e00141–19. PubMed Abstract | Publisher Full Text | Free Full Text

41. Tang H, Inoki K, Brooks SV, et al.: mTORC1 underlies age-related muscle fiber damage and loss by inducing oxidative stress and catabolism. Aging Cell. 2019; 18(3): e12943. PubMed Abstract | Publisher Full Text | Free Full Text

42. Ham DJ, Börsch A, Lin S, et al.: The neuromuscular junction is a focal point of mTORC1 signaling in sarcopenia. Nat Commun. 2020; 11(1): 4510. PubMed Abstract | Publisher Full Text | Free Full Text | Faculty Opinions Recommendation

43. Jaiswal N, Gavin M, Loro E, et al.: AKT controls protein synthesis and oxidative metabolism via combined mTORC1 and FOXO1 signalling to govern muscle physiology. J Cachexia Sarcopenia Muscle. 2022; 13(1): 495–514. PubMed Abstract | Publisher Full Text | Free Full Text

44. Geremia A, Sartori R, Banardo M, et al.: Activation of Akt-mTORC1 signalling reverts cancer-dependent muscle wasting. J Cachexia Sarcopenia Muscle. 2022; 13(1): 648–61. PubMed Abstract | Publisher Full Text | Free Full Text