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Review

Recent progress toward understanding the molecular mechanisms that regulate skeletal muscle mass

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ABSTRACT

The maintenance of muscle mass is critical for health and issues associated with the quality of life. Over the last decade, extensive progress has been made with regard to our understanding of the molecules that regulate skeletal muscle mass. Not surprisingly, many of these molecules are intimately involved in the regulation of protein synthesis and protein degradation [*e.g.* the mammalian target of rapamycin (mTOR), eukaryotic initiation factor 2B (eIF2B), eukaryotic initiation factor 3f (eIF3f) and the forkhead box O (FoxO) transcription factors]. It is also becoming apparent that molecules which sense, or control, the energetic status of the cell play a key role in the regulation of muscle mass [*e.g.* AMP-activated protein kinase (AMPK) and peroxisome proliferator-activated receptor gamma coactivator-1 α (PGC1α)]. In this review we will attempt to summarize the current knowledge of how these molecules regulate skeletal muscle mass.

Contents

Abbreviations: 4E-BP1, 4E binding protein 1; 5′UTR, 5′ untranslated region; AICAR, 5-aminoimidazole-4-carboxamide riboside; AMP, adenosine monophosphate; AMPK, 5′-AMP-activated protein kinase; AMPK $\alpha_1^{-/-}$, AMPK α_1 subunit knockout; AMPK$\alpha_1^{-/-}\alpha_2^{-/-}$, AMPK α_1 and α_2 subunit knockout; AFX, acute leukemia fusion gene located in chromosome X; ATF4, activating transcription factor 4; Atg13, autophagy gene 13; ATP, adenosine triphosphate; Bnip3, Bcl-2/adenovirus E1B 19-kDa interacting protein 3; c.a., constitutively active; DNA, deoxyribonucleic acid; DRP1, dynamin-related protein 1; eIF2B, eukaryotic initiation factor 2B; ERRα, estrogen-related receptor alpha; eIF2Bε, eukaryotic initiation factor 2B epsilon subunit; eIF3, eukaryotic initiation factor 3; eIF3f, eukaryotic initiation factor 3 subunit f; eIF4B, eukaryotic initiation factor 4B; eIF4G, eukaryotic initiation factor 4G; FIP200, focal adhesion kinase family interacting protein of 200 kD; Fis1, fission 1 gene; FKBP12, FK506 binding protein 12; FKHR, forkhead in Rhabdomyosarcomas; FKHRL1, FKHR-like protein 1; FoxO, Forkhead box containing protein, O-subclass; GAP, GTP-activating protein; GSK3β, glycogen synthase kinase 3β; GDP, guanosine diphosphate; GTP, guanosine triphosphate; IGF, insulin-like growth factor; JNK, c-Jun NH2-terminal kinase; LC3, microtubule-associated protein1 light chain 3; MEF2, myocyte enhancer factor-2; Met-tRNA$_i$, eukaryotic initiation factor methionyl transfer ribonucleic acid; mRNA, messenger ribonucleic acid; mTOR, mammalian target of rapamycin; mTORC1, mTOR complex 1; mTORC2, mTOR complex 2; MuRF1, muscle ring finger 1; NFκB, nuclear factor kappa B; NRF-1, nuclear respiratory factor 1; p70^{S6k1}, ribosomal S6 kinase 1; PI3K, phosphoinositide-3 kinase; PGC1α, peroxisome proliferator-activated receptor-γ coactivator-1α; PIC, pre-initiation complex; PKB, protein kinase B; PPARα, peroxisome proliferator-activated receptor-alpha; PPAR-γ, peroxisome proliferator-activated receptor-gamma; Rheb, ras homologue enriched in brain; rpS6, ribosomal protein S6; RR-mTOR, rapamycin-resistant mutant of mTOR; RRKD-mTOR, rapamycin-resistant kinase dead mutant of mTOR; TGF-β, transforming growth factor-beta; Thr, threonine; TOR, target of rapamycin; tRNA, transfer ribonucleic acid; TSC1/2, tuberous sclerosis complex; TSC1, hamartin; TSC2, tuberin; ULK1, UNC-51 like kinase; UPS, ubiquitin proteasome system.

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1. Introduction

Skeletal muscles, which comprise up to 40–50% of the body's mass, are not only the motors that drive locomotion, but they also play a crucial role in whole body metabolism [1,2]. It has also been well recognized that the maintenance of skeletal muscle mass plays an important role in disease prevention and issues associated with the quality of life [3]. Skeletal muscle mass can change quite rapidly and these changes can be evoked by a variety of stimuli including mechanical loads, nutrients, neural activity, cytokines, growth factors and hormones [4–6]. All of these stimuli induce changes in muscle mass by altering the net balance between protein synthesis and protein degradation. Hence, it should not be surprising that molecules involved in the regulation of protein synthesis (*e.g.* mTOR, eIF3f, eIF2B) have recently been shown to induce an increase in muscle mass, while molecules that activate protein degradation (*e.g.* FoxO, atrogin-1) induce a decrease in muscle mass. What might be less apparent is that many of the regulatory events that control protein metabolism are influenced by molecules that sense and/or are involved in the regulation of cellular energetic status (*e.g.* AMPK and PGC1α), and recent studies have indicated that these molecules also play an important role in the regulation of skeletal muscle mass. In this review, we will provide a brief background with regard to why these molecules have been implicated in the regulation of skeletal muscle mass and summarize recent data which shed light on how these molecules may exert their regulatory effects. We would also like to acknowledge that many other signaling molecules and transcription factors have also been shown to play a role in the regulation of skeletal muscle mass. However, due to limited space, we are not able to discuss all of these factors in the current review. Hence, the reader is referred to the following recent original papers and reviews [7–20].

2. The role of mTOR in the regulation of skeletal muscle mass

2.1. mTOR, mTORC1 and protein synthesis

In 1965 it was discovered that a microorganism (*Streptomyces hygroscopicus*) in the soil from the island of Rapa Nui (Easter Island) produced a compound that possessed antibiotic properties [21]. This compound was subsequently given the name rapamycin [22]. After its identification, rapamycin was found to be capable of inhibiting the growth of a variety of eukaryotic organisms [23]. It was later determined that the growth regulatory effects of rapamycin were a result of its ability to inhibit signaling by two closely related serine/threonine kinases in yeast, which were designated the target of rapamycin (TOR) 1 and 2 [24]. A single mammalian ortholog of the yeast TOR genes was discovered [25,26] and later termed the mammalian target of rapamycin (mTOR) [27]. More recently, it has been shown that mTOR exists in two functionally distinct multi-protein signaling complexes, mTORC1 and mTORC2 [28,29]. In general, only signaling by mTORC1 is inhibited by rapamycin, and thus the growth regulatory effects of rapamycin are believed to be primarily exerted through the mTORC1 complex [30,31]. Over the last decade, our knowledge of mTOR has rapidly expanded and it is now widely appreciated that signaling by mTORC1 is involved in the regulation of several anabolic processes including protein synthesis, ribosome biogenesis, and mitochondrial biogenesis, as well as catabolic processes such as autophagy [31–33].

Two of the most studied mTORC1 targets are the eukaryotic initiation factor 4E binding protein (4E-BP1) and the ribosomal S6 kinase ($p70^{S6k1}$), which both play important roles in the initiation of mRNA translation. For example, eIF4E, which binds to the 7-methyl-guanosine 'cap' (found on the 5′-end of all cellular mRNAs), is inhibited from binding to eIF4G by 4E-BP1, thus suppressing cap-dependent translation initiation [34]. The phosphorylation of 4E-BP1 by mTORC1 results in the dissociation of 4E-BP1 from eIF4E which allows eIF4G to bind to eIF4E and this, in-turn, promotes an increase in cap-dependent translation (Fig. 1) [34]. Another widely recognized function of mTORC1 involves its ability to control the selective translation of mRNAs that contain a long and highly structured 5′ untranslated region (5′UTR). These types of mRNAs often encode proteins with growth regulatory functions such as myc, HIF1α, cyclin D1, and insulin-like growth factor II (IGF-II) [34–36]. For a comprehensive review of these topics see Ma and Blenis, 2009 [34].

In skeletal muscle, signaling by mTORC1 has been shown to be regulated by a variety of different stimuli that control skeletal muscle mass. For example, signaling by mTORC1 is activated in response to hypertrophic stimuli such as increased mechanical loading, feeding and growth factors [37–39]. On the other hand, signaling by mTORC1 is inhibited by atrophic stimuli such as decreased mechanical loading, food deprivation and glucocorticoids[40–42]. Studies with rapamycin also suggest that signaling through mTORC1 is necessary for the hypertrophic effects of several stimuli. For instance, hypertrophy induced by mechanical loading, IGF-I and clenbuterol has been shown to be significantly, if not completely, blocked by rapamycin [38,43,44]. There is also evidence which suggests that the activation of mTORC1 signaling is sufficient to induce hypertrophy. For example, over-expression of constitutively active PKB (c.a.-PKB) activates mTORC1 signaling and induces hypertrophy through a rapamycin-sensitive mechanism [45]. Combined, these types of observations have led many to conclude that the activation of mTORC1 signaling is both necessary and sufficient for the induction of skeletal muscle hypertrophy [45,46].

The aforementioned studies support the hypothesis that signaling through mTORC1 is sufficient to induce hypertrophy, however, the hypertrophic stimuli employed in these studies also induce signaling through phosphatidyinositol 3-kinase (PI3K) and PKB. This is an important point because signaling through PI3K/PKB can regulate mTOR-independent growth regulatory molecules such as the glycogen synthase kinase 3β (GSK3β), tuberin (TSC2) and the FoxO transcription factors [4,5,47]. Thus, based on these original studies, it was not clear if signaling by mTORC1 was sufficient, or simply permissive, for the induction of hypertrophy. To address this issue, overexpression of Rheb was recently used as a means to induce a PI3K/PKB-independent activation of mTORC1 [48]. Rheb was selected for this study because *in-vitro* studies had demonstrated that purified Rheb can directly activate mTORC1 signaling [49]. Consistent with these studies, it was determined that overexpression of Rheb induced a PI3K/PKB-independent activation of mTORC1 in skeletal muscle. Furthermore, overexpression of Rheb was sufficient to induce an increase in protein synthesis and hypertrophy [48,50]. Finally, the hypertrophic effect of Rheb was shown to occur through a rapamycin-sensitive mechanism [48]. Taken together, these results suggested that the activation of mTORC1 is indeed sufficient to induce hypertrophy, at least in part by increasing protein synthesis.

Rapamycin is considered to be a highly specific inhibitor of mTORC1, and thus, it has been widely accepted that a rapamycin-sensitive hypertrophic response implies an mTORC1-dependent