Chapter 6

Molecular Mechanisms Controlling Skeletal Muscle Mass

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Abstract

The interplay between multiple signaling pathways regulates the maintenance of skeletal muscle. Under physiological conditions, a network of interconnected signals serves to coordinate hypertrophic and atrophic inputs, culminating in a delicate balance between muscle protein synthesis and proteolysis. Loss of skeletal muscle mass, termed "atrophy," is a diagnostic feature of cachexia such as cancer, heart disease, and chronic obstructive pulmonary disease. Recent studies have further defined the pathways leading to gain and loss of skeletal muscle as well as the signaling events that induce post-injury regeneration. In this review, we summarize the relevant recent literature demonstrating these previously undiscovered mediators governing anabolism and catabolism of skeletal muscle.

Keywords: Skeletal muscle, hypertrophy, atrophy, mTOR, autophagy, myostatin

1. Introduction

In humans, skeletal muscle is comprises 40-50% of body mass and plays vital roles in locomotion, heat production during periods of cold stress, and overall metabolism. Skeletal muscles possess a highly plasticity in response to altered activity. Mechanical and metabolic demands elicit marked modifications of gene expression that could lead to gain (hypertrophy) or loss (atrophy) of muscle mass. Indeed, strength training induces marked hypertrophy of exercising muscles. Histochemical analyses clearly show a 10-30% increase in muscle fiber cross-sectional area after 10-12 weeks of resistance training in sedentary subjects [1].

Satellite cells are myogenic stem cells, accounting for 3-9% of the subliminal nuclei associated with adult normal muscle fiber, with the variation widely depending on animal species, age,

and muscle fiber type [2]. Satellite cells, existing between the basal lamina and the sarcolemma of the fiber, are normally found in a mitotically quiescent in adult muscles. When muscle is injured or mechanically stretched, satellite cells activate to enter the cell cycle. Activated satellite cells have been shown to migrate to the damaged site where they replicate DNA, divide, differentiate, and fuse with the adjacent muscle fiber or form new fibers [3].

It has been reported that satellite cells are activated in compensatory hypertrophy [3, 4], and addition of new nuclei to the growing fiber seems to be required for extreme hypertrophy. Since the myonuclear domain is constant in hypertrophied muscle after mechanical overloading, many satellite cells must be incorporated adjacent to muscle fibers. In fact, irradiation of satellite cells followed by a loading stimulus results in an attenuated increase in skeletal muscle mass and protein content [5]. Therefore, it is necessary for consecutive processes (the activation, proliferation, and differentiation of satellite cells) to elicit muscle hypertrophy in the case of mechanical overloading as well as normal growth. However, several researchers recently suggested satellite cell-independent muscle hypertrophy during mechanical overloading. In addition, some have debated whether the contribution of satellite cells to fiber hypertrophy in adult muscle is minor [6, 7].

In hypertrophied muscle, increasing protein synthesis and decreasing protein degradation are also important events. Phosphatidylinositol-3-kinase (PI3-K)/Akt/ mammalian target of rapamycin (mTOR) signaling has been shown to be crucial to protein synthesis [8, 9]. Mechanical stretching *in vivo* and *in vitro* activates serum response factor (SRF)-dependent signaling in skeletal muscle similar to smooth and cardiac muscles [10, 11]. In contrast, several possible mediators for muscle atrophy have been described. Many negative regulators are proposed to induce muscle atrophy by inhibiting protein synthesis and enhancing protein degradation in skeletal muscle. For example, the ubiquitin proteasome system (UPS) is thought to be a major contributor to many structural proteins [12]. The autophagy-lysosome system has been largely ignored despite the evidence that lysosomal degradation contributes to protein breakdown in atrophying muscles [13]. Recent studies demonstrated that autophagy is an important pathway for appropriate protein degradation in several neuromuscular disorders [14]. The group of Sandri et al. [15, 16] has shown that the autophagy-lysosome and UPS are coordinately regulated during muscle wasting. Furthermore, specific expression of mutant SOD (superoxide dismutase)1^{G93A} in skeletal muscle caused muscle atrophy and weakness mainly via autophagy activation [17]. In this chapter, we summarize possible candidates for proteins that regulate muscle hypertrophy and atrophy. In addition, we describe the possible modulators for switching, proliferation, and differentiation of satellite cells, a possible contributor to muscle hypertrophy.

2. Positive regulators of skeletal muscle mass

2.1. PI3-K/Akt/mTOR pathway

The serine/threonine kinase Akt regulates the translational level to be involved to a central pathway of hypertrophy. In muscle, Akt is activated by the upstream PI3-K, induced either by

receptor binding or by integrin-mediated activation of focal adhesion kinase (FAK). PI3-K activates Akt, which then has the ability to phosphorylate and change the activity of many signaling molecules. Possible downstream regulators of Akt, mTOR, and glycogen synthase 3-β (GSK-3β) play a crucial role in the regulation of translation. Akt activates mTOR via phosphorylation and inactivation of tuberous sclerosis complex (TSC)-2. Subsequently, mTOR phosphorylates and activates the 70kDa ribosomal protein S6 kinase (p70S6K), which results in increased translation either directly or indirectly by activating initiation and elongations, elongation initiation factor (eIF)-2, eIF-4E [through eukaryotic initiation factor 4E binding protein (4E-BP)], and eEF-2. In addition, Akt also phosphorylates and inactivates GSK-3β, thereby activating translation via the initiation factor eIF-2B [18]. Other functions of Akt include the negative regulation of protein degradation by inhibiting forkhead box O (FOXO)-mediated proteasome activity.

2.1.1. Akt

Disruption of the Akt1 gene causes growth retardation and apoptosis [19], whereas deletion of Akt2 causes defects in glucose metabolism but not altered growth [20]. The striking effect of Akt1 on muscle size was demonstrated by the transient transfection of a constitutively active inducible Akt1 transgene in skeletal muscle *in vivo* [15, 21]. Downstream mediators (p70S6K, S6) of protein synthesis were activated, but satellite cells were not incorporated [21]. Akt1 transgenic muscles showed increased strength, showing that a functional hypertrophy was elicited [21]. Moreover, muscle mass was completely preserved in denervated transgenic Akt mice [22]. The effects of Akt on muscle mass regulation can be mediated by several different downstream effectors, including GSK-3β, mTOR, and FOXO.

2.1.2. mTOR and mTOR signaling complex (mTORC) 1

mTOR exists in two functionally distinct multi-protein signaling complexes, mTORC1 and mTORC2. In general, only signaling by mTORC1 is inhibited by rapamycin, and thus the growth regulatory effects of rapamycin are primarily exerted through the mTORC1 complex [23]. mTORC1 regulates several anabolic processes including protein synthesis, ribosome biogenesis, and mitochondrial biogenesis, as well as catabolic processes such as autophagy [23]. Two of the most studied mTORC1 targets are the 4E-BP1 and p70S6K, which both play important roles in the initiation of mRNA translation.

mTORC1 is activated in response to hypertrophic stimuli such as increased mechanical loading, feeding, and growth factors [24, 25]. In fact, hypertrophy induced by mechanical loading, insulin-like growth factor (IGF)-I, and clenbuterol is significantly, if not completely, blocked by rapamycin [25]. In addition, overexpression of constitutively active Akt activates mTORC1 signaling and induces hypertrophy through a rapamycin-sensitive mechanism [26]. These findings support the hypothesis that mTORC1 is sufficient to induce hypertrophy, however, the hypertrophic stimuli employed in these studies also induce signaling through PI3-K and Akt. Signaling through PI3-K/Akt can regulate mTOR-independent growth regulatory molecules [GSK-3β, tuberin (TSC-2), and FOXO]. However, it was not clear if signaling by mTORC1 was sufficient, or simply permissive, for the induction of hypertrophy.

To address this issue, overexpression of Ras homolog enriched in the brain (Rheb) was recently used as a means to induce a PI3-K/Akt-independent activation of mTORC1 [27]. Marked increases in protein synthesis and hypertrophy have been recognized in several muscles of Rheb abundant mice [27]. Stretch-induced activation of mTOR signaling was not abolished in the skeletal muscle of Akt1-/- mice [28]. Therefore, mechanically induced signaling through mTOR is not dependent on Akt. Furthermore, Akt-independent stimulation of mTOR may be regulated by phosphorylation of TSC-2. For instance, TSC-2 is inhibited by FAK in 293T cells [29] indicating that up-regulated FAK with increased loading could stimulate protein synthesis via TSC-2 inhibition. All these regulatory influences may explain the rise in the level of phosphorylated p70S6K. These results suggested that the activation of mTORC1 is indeed sufficient to induce hypertrophy, at least in part by increasing protein synthesis.

Although one of the most well-characterized upstream triggers of mTOR signaling in skeletal muscle is IGF-I, mechanical loading has been shown to activate mTOR by an IGF-I independent pathway involving PLD via its metabolite phosphatidic acid. More recently, Hornberger et al. [30] extended these initial findings by showing mTOR activation following eccentric contractions via PLD synthesis but not PI3-K-Akt activity. It has been shown that PLD1, but not PLD2, was a downstream effector of Rheb's activation of mTOR. In contrast, Vps34 is a class III PI3K previously shown to mediate amino acid activation of p70S6K by mTOR. In skeletal muscle, MacKenzie et al. [31] reported that high-resistance contractions increased Vps34 activity possibly in response to increased intramuscular leucine levels. In addition to Vps34, two groups reported the exciting discovery that the Rag family of GTPases was necessary and sufficient for amino acid activation of the mTOR pathway [32]. Therefore, mTOR is currently thought to be the major hub for the integration of an array of upstream signaling pathways which, when activated, ultimately result in increased translational efficiency [8]. Figure 1 summarizes the anabolic pathway (PI3-K/Akt/mTOR and SRF-dependent) regulating skeletal muscle mass.

2.2. Serum Response Factor (SRF)

SRF is an ubiquitously expressed member of the MADS (MCM1, Agamous, Deficiens, SRF) box transcription factor family, which binds the core sequence of SRF/CArG boxes [CC (A/T)6 GG] as homodimers. Functional CArG boxes have been found in several promoter regions of muscle-specific genes such as the skeletal α-actin and myosin light chain 1/3 genes. SRF-dependent signaling plays a major role in a variety of physiological processes, including cell growth, migration, and cytoskeletal organization [33]. Previous results obtained with specific SRF knock-out models by the Cre-LoxP system emphasize a crucial role for SRF in postnatal skeletal muscle growth and regeneration by modulating interleukin (IL)-4 and IGF-I mRNA expression [34]. More recently, Mokalled et al. [35] demonstrated that members of the myocardin family of transcriptional coactivators, MASTR and myocardin-related transcription factor (MRTF)-A, are up-regulated in satellite cells during muscle regeneration. In addition, skeletal muscle regeneration exhibited the impairment in mouse possessing double-knockout satellite cells (MASTR and MRTF-A). As proposed by Mokalled et al. [35], the promoting role on muscle regeneration seems to be attributable to both MASTR/myocyte enhancer factor 2 and/or MRTF-A/SRF complexes.

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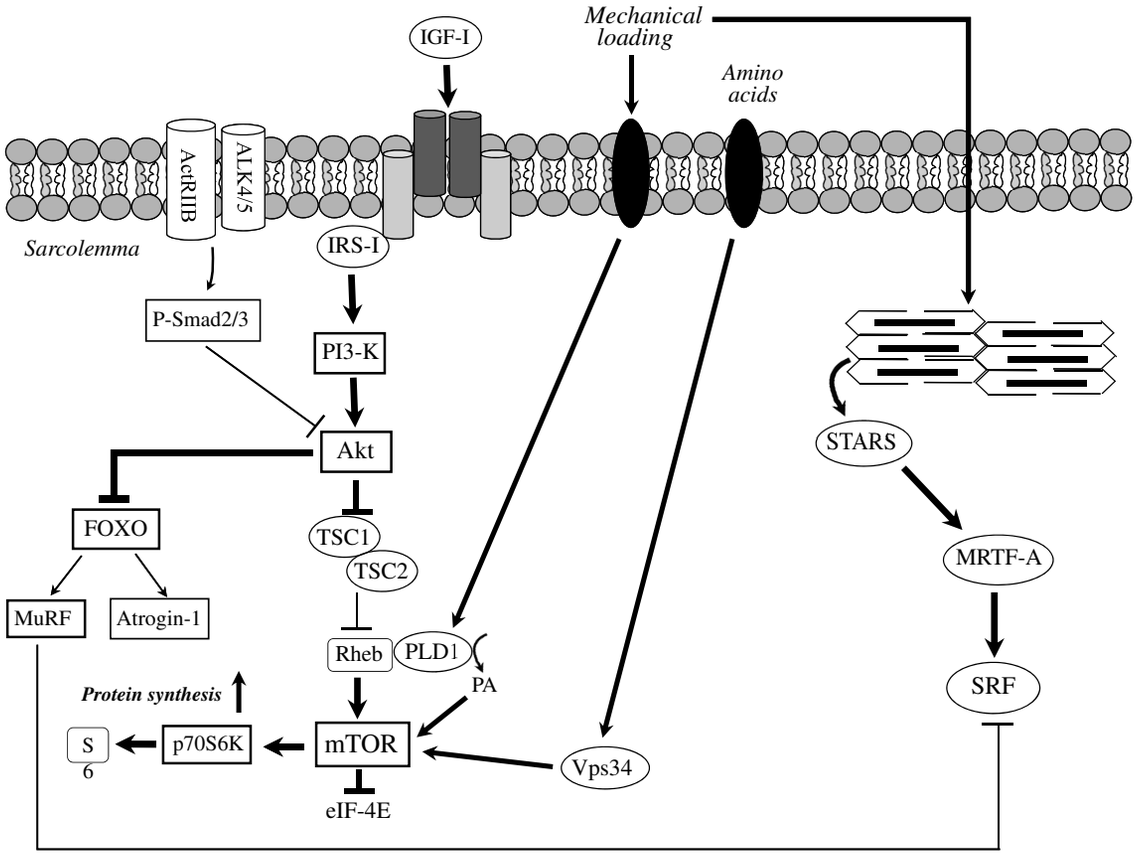

Figure 1. Anabolic pathway regulating skeletal muscle mass. The major anabolic pathway regulating protein synthesis in skeletal muscle is mTOR/TORC1 signaling. Upstream triggers (IGF-I, mechanical loading, amino acids) activate mTOR signaling through a number of different intermediary proteins such as Rheb, phospholipase D1 and its metabolite PA, and Vps34. Although myostatin signals through the ActRIIB-ALK4/5 heterodimer activate Smad2/3, reduced stimulation of myostatin in the presence of IGF-I and mechanical loading cannot block the functional role of Akt. Myosin-actin interaction by mechanical loading activates STARS /MRTF-A/SRF signaling. The accumulation of MuRF in muscle tissue during inactivity (hindlimb suspension, immobilization, etc.) is known to inhibit SRF-dependent transcription of muscle-specific genes. However, the functional role of SRF is not abrogated under such conditions, which lower MuRF expression because of marked inhibition of FOXO by abundant Akt. ActRIIB: activin receptor IIB; ALK4/5: activin-like kinase 4/5; eIF: eukaryotic initiation factor; FOXO: Forkhead box O; IGF-I: insulin-like growth factor-I; IRS-1: insulin receptor substrate-1; MRTF-A: myocardin-related transcription factor-A; mTOR: mammalian target of rapamycin; MuRF: muscle ring-finger protein; PA: phosphatidic acid; PI3-K: phosphatidylinositol 3-kinase; p70S6K: 70 kDa ribosomal protein S6 kinase; Rheb: Ras homolog enriched in brain; SRF: serum response factor; STARS: striated muscle activators of Rho signaling; TORC1: a component of TOR signaling complex 1; TSC: tuberous sclerosis complex. Data from Sakuma et al. [130]

It is proposed that the transcriptional activity of SRF is regulated by muscle ring finger (MuRF)-2 [36] and striated muscle activators of Rho signaling (STARS) [37]. At the M-band, the mechanically modulated kinase domain of titin interacts with a complex of the protein products of the atrogenes NBR1, p62/sequestosome 1 (SQSTM1), and MuRFs [36]. This complex dissociates under mechanical arrest, and MuRF-1 and MuRF-2 translocate to the cytoplasm and the nucleus [36]. One of the probable nuclear targets of MuRFs is SRF [36], suggesting that the MuRF-induced nuclear export and transcriptional repression of SRF may contribute to amplifying the transcriptional atrophy program. Thus, it is possible that MuRF-2

4. Conclusions and perspectives

Recent progress has significantly expanded our understanding of the molecular mechanisms that regulate skeletal muscle protein synthesis and degradation. Despite this, considerably more research is required to fully elucidate the many different mechanisms that potentially regulate these two processes. Successful identification of common regulatory molecules/pathways will greatly aid our understanding of how different types of stimuli promote changes in skeletal muscle mass. The Akt/mTOR/p70S6K pathway and SRF-dependent signaling have been considered to be major contributors to protein synthesis and muscle-specific transcription, respectively [11, 23]. Over the past decade, studies using rodent muscles have indicated that atrogin-1 and MuRF-1 contribute to the protein degradation in muscular wasting [60]. More recent studies using human muscle do not necessarily support such a role for these atrogenes [77]. It seems that the disorganization of the autophagy system accelerates the muscular disorder with age (sarcopenia) in rodents and human.

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