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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,

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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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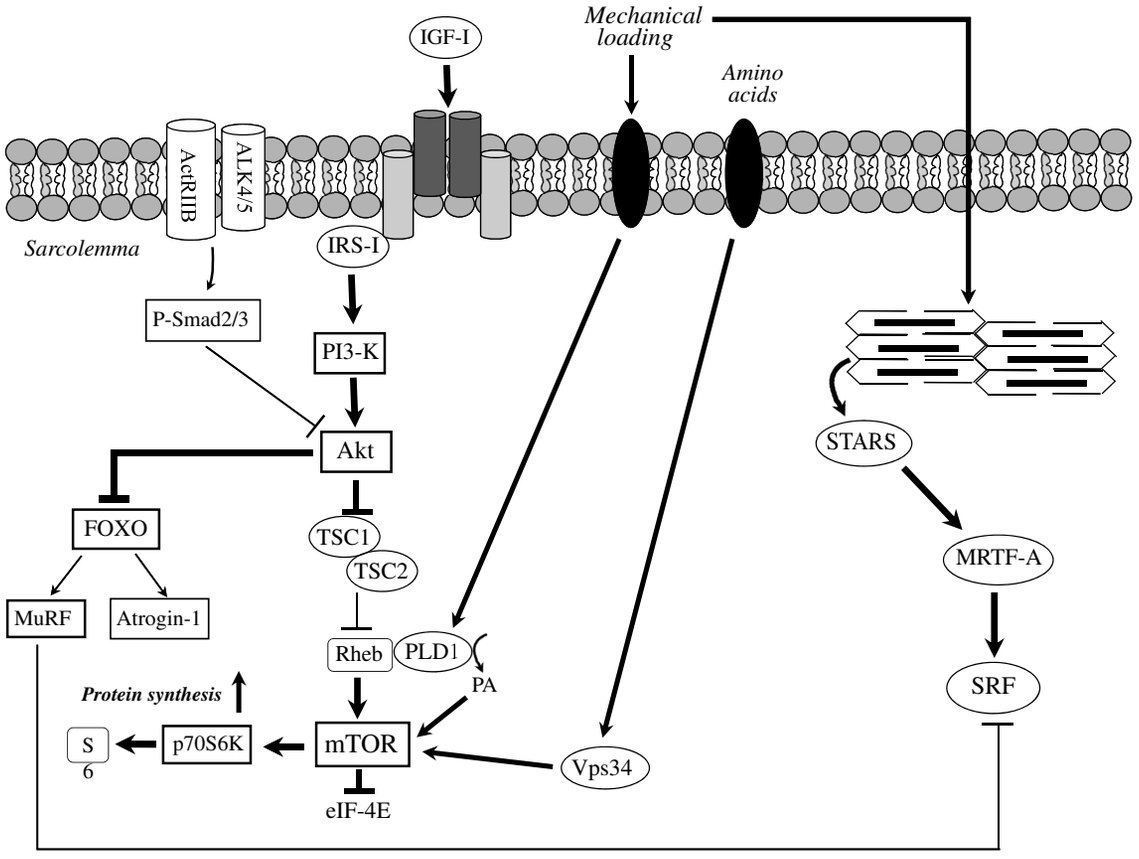

Figure 1. Anabolic pathway regulating skeletal muscle mass. The major anabolic pathway regulating protein synthesis in skeletal muscle is mTOR/TORC1 signaling. Upstream triggers (IGF-I, mechanical loading, amino acids) activate mTOR signaling through a number of different intermediary proteins such as 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

abrogates the synergistic transactivation of SRF and SRF-linked molecules *in vivo*. On the other hand, SRF activity is sensitive to the state of actin polymerization. G-actin monomers inhibit SRF activity, whereas polymerization of actin occurs in response to serum stimulation and RhoA signaling. Thus, signal inputs lower the ratio of globular actin to fibrillar actin liberating the binding of MRTF-A to globular actin resulting in the nuclear accumulation of MRTF-A and subsequent SRF-dependent gene expression [38]. It has been well established that overexpression of STARS contributes to the nuclear translocation of MRTF-A and MRTF-B [37, 39], and these factors activate SRF transcription.

2.2.1. The functional role of SRF during muscle hypertrophy

In adults, SRF activity could be important for the control of skeletal muscle mass. In fact, SRF also enhances the hypertrophic process in muscle fibers after mechanical overloading [40-42]. For example, Flück et al. [40] utilized a stretch-induced hypertrophic model, in which a weight equal to 10% of body weight was attached to the left wing of a rooster to induce enlargement of the anterior latissimus dorsi muscle. Gordon et al. [10] also indicated a significant increase in SRF protein in the soleus and plantaris muscles after 8 days of functional overload caused by surgical ablation of the gastrocnemius muscle in rats. In humans, 8 weeks of resistance training (leg presses, squats, and leg extensions) induced increases in SRF mRNA (3-fold) and nuclear protein (1.25-fold) in human muscle [41]. The same training also increases in the mRNA levels of several SRF-targeted molecules {alpha-actin, myosin heavy chain (MHC) IIa, and IGF-I [34]}. They proposed the induction of these molecules by SRF in human hypertrophied muscle, though they did not provide any direct evidence such as transcriptional activation by increased binding of SRF to the promoter region of alpha-actin, MHC IIa, and IGF-I. Although SRF would regulate proliferation and differentiation using different pathways, it would mainly activate the differentiation of satellite cells during muscle hypertrophy. Indeed, it was shown that, in mechanically overloaded muscles of rats, the SRF protein co-localized with MyoD and myogenin in myoblast-like cells during the active differentiation phase [42]. In this study, abundant SRF protein at 2 days was failed to be detected after mechanical overloading, when many proliferating satellite cells and/or myoblasts are expected to exist. In addition, the location of the SRF protein did not correspond with that of BrdU-positive satellite cells or ED-1 positive macrophages in the hypertrophied plantaris muscle [42].

As indicated earlier, by reducing the cytoplasmic concentration of monomeric G-actin, STARS promotes the nuclear translocation of SRF transcriptional co-activator-A and -B (MRTF-A and MRTF-B), resulting in an increase in SRF-mediated gene transcription [37]. A real-time PCR analysis conducted by Lamon et al. [41] demonstrated that increased mechanical loading from resistance training in humans caused significant increases in the upstream modulators of SRF (STARS mRNA; 3.4-fold, MRTF-A mRNA; 2.5-fold, MRTF-B mRNA; 3.6-fold, and RhoA protein; 2-fold). SRF seems to regulate the transcriptional facilitation of the alpha-actin promoter by the androgen receptor (AR) during muscle hypertrophy. Using male adult Sprague-Dawley rats, Lee et al. [43] showed an increase in AR protein of 106% and 279% after 7 and 21 days in mechanically overloaded plantaris muscles by surgical ablation of two synergistic muscles. Co-overexpression of either SRF or active RhoA with AR indicated a

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synergistic 36- and 28-fold increase in the skeletal alpha-actin promoter activity. In contrast, cotransfection of AR, SRF, and active RhoA induced a 180-fold increase in skeletal a-actin promoter activity. Therefore, it is possible that intimate linkages among these three modulators induce alpha-actin expression in hypertrophied muscle *in vivo*. Intriguingly, experiments using C2C12 cells indicated that this AR coactivation for the alpha-actin promoter requires a co-expressed full-length SRF and SRF-binding site but not AR's direct binding to GRE sites [44].

More recently, Guerci et al. [45] investigated the functional role of SRF in adult mammalian muscle using $SRF^{flox/flox}$: HAS-Cre-ER^{T2} mice injected with tamoxifen. During the compensatory hypertrophy phase, growth was completely slow in the SRF-deleted plantaris muscle, demonstrating that SRF is necessary for overloaded-induced myofiber hypertrophy. Intriguingly, Guerci et al. [45] showed that the lack of SRF in myofibers affected satellite cell proliferation and fusion to the growing fibers. In their genetic mouse model, Cre recombinase is expressed only in myofibers but not in satellite cells. Furthermore, Guerci et al. [45] identified the secreted molecules mediating these paracrine effects and whose expression is under the control of SRF by using a global transcriptomic approach allowing the identification of genes activated by SRF. In SRF-deleted muscles, the overexpression of IL-6 is sufficient to restore satellite cell proliferation, but not satellite cell fusion and overall growth. Cox2/IL-4 overexpression rescues satellite cell recruitment and muscle growth without affecting satellite cell proliferation, identifying altered fusion as the limiting cellular events precluding the hypertrophic growth of SRF-deleted muscles. Guerci's excellent finding was further supported by Bruusgaard et al. [46], showing that the addition of nuclei precedes increased fiber size during compensatory hypertrophy and that this constituted the major cause of hypertrophy. However, the contribution of satellite cells to muscle hypertrophy has been a controversial issue [6, 47]. In fact, McCarthy et al. [48] suggested that satellite cell-depleted skeletal muscle undergoes extensive fiber hypertrophy after mechanical overloading. Therefore, further examination of SRF's role in muscle hypertrophy is needed.

2.2.2. Defects of SRF signaling with muscle wasting

Sarcopenia

Aging is associated with progressive declines in muscle mass, quality, and strength, a condition known as sarcopenia. Lean muscle mass generally contributes to ~50% of total body weight in young adults, but this value declines with aging, to just 25% at 75-80 years of age [49]. At the muscle fiber level, sarcopenia is characterized with specific type II fiber atrophy and fiber loss. Although the specific contribution of each is unknown, several possible signaling factors (Akt-mTOR, RhoA-SRF, and autophagy) have been proposed to contribute to age-related muscle atrophy [50, 51]. In fact, using crude and fractionated homogenates, our recent study has clearly demonstrated a blunted expression of SRF protein in the quadriceps and triceps brachii in aged mice [52]. Immunofluorescence microscopy also indicated the selective loss of SRF protein in the cell cytosol but not in satellite cells in sarcopenic mice. In addition, our data showed a decrease in MRTF-A mRNA (50-70%) and protein (76%) levels in only the nuclear fraction with age. Furthermore, we observed 40-60% decreases in the amount of STARS mRNA in the quadriceps and triceps brachii of 24-month-old mice [52].

A decrease of SRF expression achieved using a transgenic approach was found to accelerate the atrophic process in muscle fibers with age [53]. These SRF-deleted mice showed marked deposition of intermuscle lipid with aging. One morphologic aspect of sarcopenia is the infiltration of muscle tissue components by lipids, because of the increased frequency of adipocyte or lipid deposition [54] within muscle fibers. As with precursor cells in bone marrow, liver, and kidney, muscle satellite cells expressing the adipocytic phenotype increased with age [55], although this process is still relatively poorly understood in terms of its extent and spatial distribution. Lipid deposition may result from a net buildup of lipids due to the reduced oxidative capacity of muscle fibers with aging [54]. These lines of evidence clearly showed a defect of SRF-signaling in aged mammalian muscle.

2.3. Muscular disorder

SRF appears to be linked to the degenerative process during muscular dystrophy. Significant reduction in the amount of SRF has been observed [56], 40-50% and 50-65% at 2 and 12 weeks of age, respectively, in merosin-deficient congenital muscular dystrophy. Our immunohistochemical analysis demonstrated that mature normal mice exhibited an abundant SRF protein in the cytoplasm of several muscle fibers, while the *dy* mice did not. There is no direct evidence of a link between SRF disorders and the pathogenesis of disease in the skeletal muscle.

However, Lange et al. [36] observed that a mutation in the TK domain of titin, a possible modulator of SRF, disrupted Nbr1 binding and led to hereditary myopathy with early respiratory failure (HMERF). HMERF patient muscle biopsies revealed a Nbr1 diffusible localization, cytoplasmic p62/SQSTM1 aggregates, and the selective accumulation of MuRF-2 in centralized nuclei. Unfortunately, the localization of SRF has not been determined in the muscle of HMERF patients. In contrast, a natural dominant-negative form of SRF was demonstrated to be elevated in human heart failure [57]. The dominant negative SRF isoform potently inhibited SRF-dependent function, showing the biochemical phenotype seen in SRF-null mice [57]. In addition, a subsequent human heart failure study showed decreases in full-length SRF and elevated expression of a caspase-3-cleaved product of SRF [58]. A more recent review [59] proposed various disorders to be linked with the SRF mutation as shown by many reliable studies using cell-specific SRF-knockout phenotypes.

3. Negative regulators of skeletal muscle mass

3.1. Ubiquitin-Proteasome System (UPS)

The UPS is essential for protein degradation. The degradation of a protein via the UPS includes two steps: (1) tagging of the substrate by covalent attachment of multiple ubiquitin molecules and (2) degradation of the tagged protein by the 26S proteasome. The ubiquitination of proteins is regulated by at least three enzymes: ubiquitin-activating enzyme (E1), ubiquitin-conjugating enzyme (E2), and ubiquitin ligase (E3). Consistent increases in two important E3 ubiquitin ligases (atrogin-1 and MuRF-1) gene expression have been observed in a wide range of in vivo

models of skeletal muscle atrophy including diabetes, cancer, denervation, unweighting, or glucocorticoid treatment [60].

eIF 3 subunit 5 (eIF3-f) appears to be a key effector of atrogin-1 as targeted increases and decreases in eIF3-f levels cause skeletal muscle hypertrophy and atrophy, respectively [61]. Overexpression of atrogin-1 results in the polyubiquitination of MyoD and an inhibition of MyoD-induced myotube formation [62]. In contrast, the knockdown of atrogin-1 reversed endogenous MyoD proteolysis and the overexpression of a mutant MyoD, unable to be ubiquitinated, prevented muscle atrophy *in vivo* [62]. These results confirmed MyoD as a substrate of atrogin-1 during dexamethasone-induced myotube atrophy [63].

In contrast to atrogin-1, it appears that MuRF-1 mainly interacts with structural proteins. MuRF-1 binds to titin and potentially affects titin signaling. It also binds to and degrades MHC proteins following the treatment of skeletal muscle with dexamethasone. Additionally, MuRF-1 degrades myosin light chain 1 and 2 during denervation and fasting conditions [64]. These studies suggest that while numerous stimuli can activate both two atrogenes, the downstream pathways affected may be separate for each protein.

3.1.1. Adapatative changes in atrogin-1 and MuRF-1 in muscle atrophy models

UPS signaling in cachectic muscle

In many acute models of cachexia, including cancer, the UPS is thought to be fundamental in the process of muscle atrophy [60, 65]. Weight-losing mice bearing MAC16 adenocarcinoma exhibited the increased expression of mRNA for both α- and β-proteasome subunits in gastrocnemius muscle [66]. Several experimental models of cancer cachexia [e.g., AH-130, C26, Lewis lung carcinoma (LLC)] had increased UPS activity, as well as overexpression of atrogin-1 and MuRF-1 [67]. However, investigations in humans have failed to be conclusive. An earlier study suggested that the UPS plays a prominent role in the degradation of myofibrillar proteins, particularly in cancer patients with weight loss of > 10% [68]. In gastric cancer patients with average weight loss of 5.2%, increased UPS activity (determined by measurements of RNA and cleavage of specific fluorogenic substrates) was seen compared with that in controls, which was exacerbated by increasing tumor stage and weight loss [69]. In contrast, investigations of UPS activity in quadriceps muscle biopsies have shown levels similar to those in healthy controls in patients with lung cancer and weight loss < 10% (termed pre-cachexia) [70]. In a transcriptomic study of UGI patients, candidate genes, including FOXO and ubiquitin E3 ligases, were not related to weight loss. Another study in lung cancer patients with low weight loss demonstrated no change in the components of the UPS using Northern blotting, but there was a suggestion that the activity of the lysosomal pathway was increased [71]. Similarly, a more recent study also failed to show an increase of proteasome activity in muscle of esophageal cancer patients [72]. Although more descriptive studies are needed to determine whether UPS is activated in muscle in cancer cachexia, the adaptive manner of UPS components may differ between rodents and humans in cancer-cachectic muscles.

In chronic obstructive pulmonary disease (COPD) patients, the reported findings on the adaptive changes in the UPS in skeletal muscle are highly contradictory. Doucet et al. [73]

found significant increases in atrogin-1, MuRF-1, and FOXO1 mRNA in the muscle of COPD patients showing irreversible airflow obstruction [post-bronchodilator forced expiratory volume in one second (FEV_1) < 80% predicted and FEV_1/forced vital capacity (FVC) < 70%] by pulmonary function testing. They also observed an increase, albeit not significant, in the atrogin-1 protein content in the muscle of COPD patients. Such inconsistency in the protein levels of ubiquitin ligases was recognized in COPD patients by Natanek et al. [74]. In contrast, Natanek et al. [74] reported a significant decrease in atrogin-1 protein content in quadriceps in COPD compared with those in controls. Advanced cardiac heart failure (CHF) patients also did not exhibit high mRNA and protein levels of atrogin-1 in muscle [75], although CHF model mice with cardiac-specific overexpression of calsequestrin exhibited marked increases in atrogin-1 mRNA in both soleus and white vastus lateralis muscles [76]. In human studies, several investigators described a discrepancy between the mRNA expression level on atrogene and the extent of muscle atrophy [77]. Intriguingly, some recent studies have shown that atrogin-1 and MuRF-1 are not essential components for proteasome activity [78]. There have been few studies dealing with the protein levels of atrogin-1 and MuRF-1 in muscle wasting, particularly in human subjects.

UPS signaling in sarcopenic muscle

Atrogin-1 and/or MuRF-1 mRNA levels in aged muscle are reportedly increased or unchanged in humans and rats, or decreased in rats [50, 79, 80]. Even when the mRNA expression of these atrogenes increased in sarcopenic muscles, this was very limited (1.5- to 2.5-fold). Although mRNA levels of both ubiquitin ligases have been determined in several aged mammalian muscles, the analysis of protein levels did not correspond to age-related increases in the mRNA of ubiquitin ligases. For instance, the marked upregulation of phosphorylated Akt and FOXO4 have been observed in the gastrocnemius muscle of aged female rats [80]. These adaptations of protein levels probably contribute to the downregulation of atrogin-1 and MuRF-1 mRNA in aged muscle. In addition, Léger et al. [81], using human subjects aged 70 years old, demonstrated decreases in nuclear FOXO1 and FOXO3a in spite of no apparent age-related changes in the atrogin-1 and MuRF-1 mRNA. Interestingly, recent findings indicate that atrogin-1-knockout mice are short-lived and experience higher loss of muscle mass during aging than control mice [82], indicating that the activity of this E3 ubiquitin ligase is required to preserve muscle mass during aging in mice. Moreover, the muscle size of aged MuRF-1-null mice is preserved [83]. However, they exhibited a higher decay of muscle strength than controls. As indicated by Sandri et al. [82], chronic inhibition of these atrogenes should not be considered a therapeutic target to counteract sarcopenia because this does not prevent muscle loss but instead exacerbates weakness. Figure 2 summarizes a possible adaptation of atrogin-1 and MuRF-1 in sarcopenic muscle.

The adaptation of UPS in muscular dystrophy

Gene expression profiling in Limb-girdle muscular dystrophy (LGMD)2A showed overexpression of UPS-related genes [84, 85]. While the expression of atrogin-1 and MuRF-1 was not increased in mouse models of LGMD2A, FOXO1 was strongly upregulated and induced muscle atrophy in calpain-3-deficient mice [86]. More recently, LGMD2A patients have been shown to exhibit significantly higher expression of MuRF-1 protein but not atrogin-1 protein

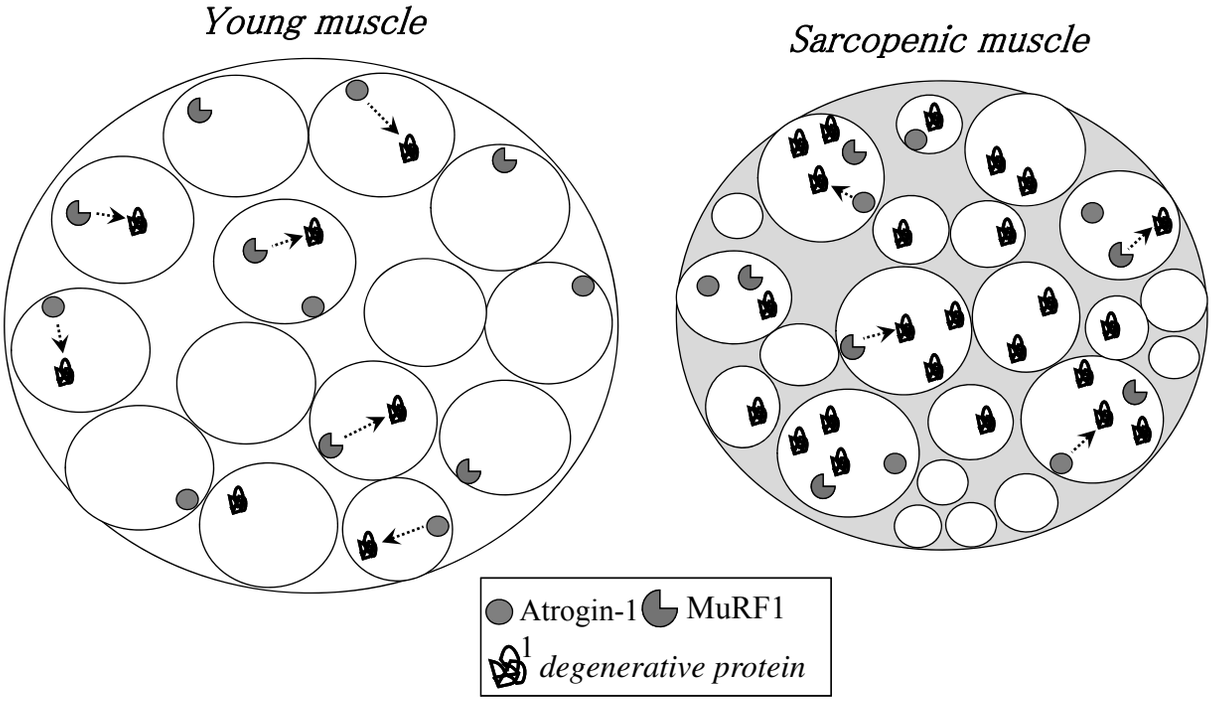

Figure 2. The comparison of ubiquitin-proteasome system between young and sarcopenic muscle. In contrast to young muscle, sarcopenic muscle exhibits no activation of atrogin-1 and MuRF-1-dependent signaling to destroy the degenerative proteins.

in skeletal muscle. LGMD2B is due to deficiency of the protein dysferlin. The loss of dysferlin causes failure in resealing of the membrane lesions generated during eccentric muscle contractions [88]. Similar to LGMD2A, dysferlinopathy patients exhibited more abundant mRNA and protein of MuRF-1 but not atrogin-1 [89]. Activation of UPS in dysferlinopathy has also been reported in cellular models (patient-derived muscle cells) [90]. UCMD is a common form of muscular dystrophy associated with defects in collagen VI, characterized by loss of muscle fibers and proliferation of connective and adipose tissues. More recently, Paco et al. [91] studied muscle biopsies of Ullrich congenital muscular dystrophy (UCMD) (n = 6), other myopathy [Duchenne muscular dystrophy (DMD)], calpain-3-deficient, Kearns-Sayre, and nemaline myopathy (n = 12), and control patients (n = 10) and found reduced expression of atrogin-1 and MuRF-1 mRNAs in UCMD cases.

Pharmacological inhibition of UPS appears to exert some beneficial effect on muscular dystrophy. Velcade, once injected locally into the gastrocnemius muscles of *mdx* mice, appears to increase the expression and membrane localization of dystrophin and members of the dystrophin-associated protein complex (DAPC) [92]. Treatment with Velcade (0.8 mg/Kg) over a 2-week period has been shown to reduce muscle degeneration and necrotic features, and to increase muscle size (gastrocnemius and diaphragm), in mdx muscle fibers [93]. In addition, Gazzerro et al. [93] observed that Velcade administration generates many myotubes and/or immature myofibers expressing embryonic myosin heavy chain in mdx muscle, probably due to upregulation of myogenic differentiating modulators.

3.2. Autophagy-dependent signaling

Macroautophagy (herein autophagy) is a catabolic process that involves the bulk degradation of cytoplasmic components by interacting a lysosome [94, 95]. This process is characterized by the engulfment of part of the cytoplasm inside double-membrane vesicles (autophagosomes). Autophagosomes subsequently fuse with lysosomes to form autophagolysosomes in which the cytoplasmic cargo is degraded. The turnover of most proteins, biological membranes, and whole organelles such as mitochondria and ribosomes is mediated by autophagy [96].

Autophagy represents an extremely refined collector of altered organelles, abnormal protein aggregates, and pathogens, similar to a selective recycling center [97]. The selectivity of the autophagy process is conferred by a growing number of specific cargo receptors such as p62/SQSTM1 and Nix (Bnip3L) [98]. These adaptor proteins are equipped with both a cargo-binding domain, with the capability to recognize and attach directly to molecular tags on organelles. At the same time, these adaptor proteins bind a microtubule-associated protein light chain LC3)-interacting region domain to recruit and bind essential autophagosome membrane proteins. Three molecular complexes mainly regulate the formation of autophagosomes: the LC3 conjugation system and the regulatory complexes governed by unc51-like kinase-1 and beclin-1. The conjugation complex is composed of different proteins encoded by autophagy-related genes (Atg). The Atg12-Atg5-Atg16L1 complex, along with Atg7, plays an essential role in the conjugation of LC3 to phosphatidylethanolamine, which is required for the elongation and closure of the isolation membrane.

The UPS and the lysosomal-autophagy system in skeletal muscle are interconnected [15, 16]. Both these studies identified FOXO3 as a regulator of these two pathways in muscle wasting [Fig. 3]. FOXO3 is a transcriptional regulator of the atrogin-1 and MuRF-1. FOXO3 modulates the expression of autophagy-related genes in mammalian skeletal muscle and C2C12 myotubes [16]. Masiero et al. [99] found an intriguing characteristic using muscle-specific autophagy knockout mice, which exhibit fiber atrophy, weakness, and mitochondrial abnormalities. Autophagy-dependent protein degradation seems to be also modulated by tumor necrosis factor (TNF) receptor associated factor 6 and peroxisome proliferator-activated receptor γ coactivator-1α (PGC1α) [100, 101]. Wenz et al. [101] recognized no significant age-related increase in the ratio of LC3-II to LC3-I in MCK-PGC1α mice. Therefore, PGC1α would attenuate the autophagic process probably through increased anti-oxidant defense and mitochondrial biogenesis.

3.2.1. Adaptation of autophagy-linked signaling during muscle atrophy

A possible contribution of autophagic signaling to cachexia

As for cancer cachexia, earlier results obtained on muscles isolated from cachectic animals led us to rule out a substantial role for lysosomes in overall protein degradation [102]. In contrast, an elevation of total lysosome protease activity has been observed in the skeletal muscle and liver of tumor-bearing rats [103]. In addition, increased levels of cathepsin L mRNA have been reported in the skeletal muscle of septic or tumor-bearing rats, whereas cathepsin B gene expression has been shown to be enhanced in muscle biopsy samples obtained from patients

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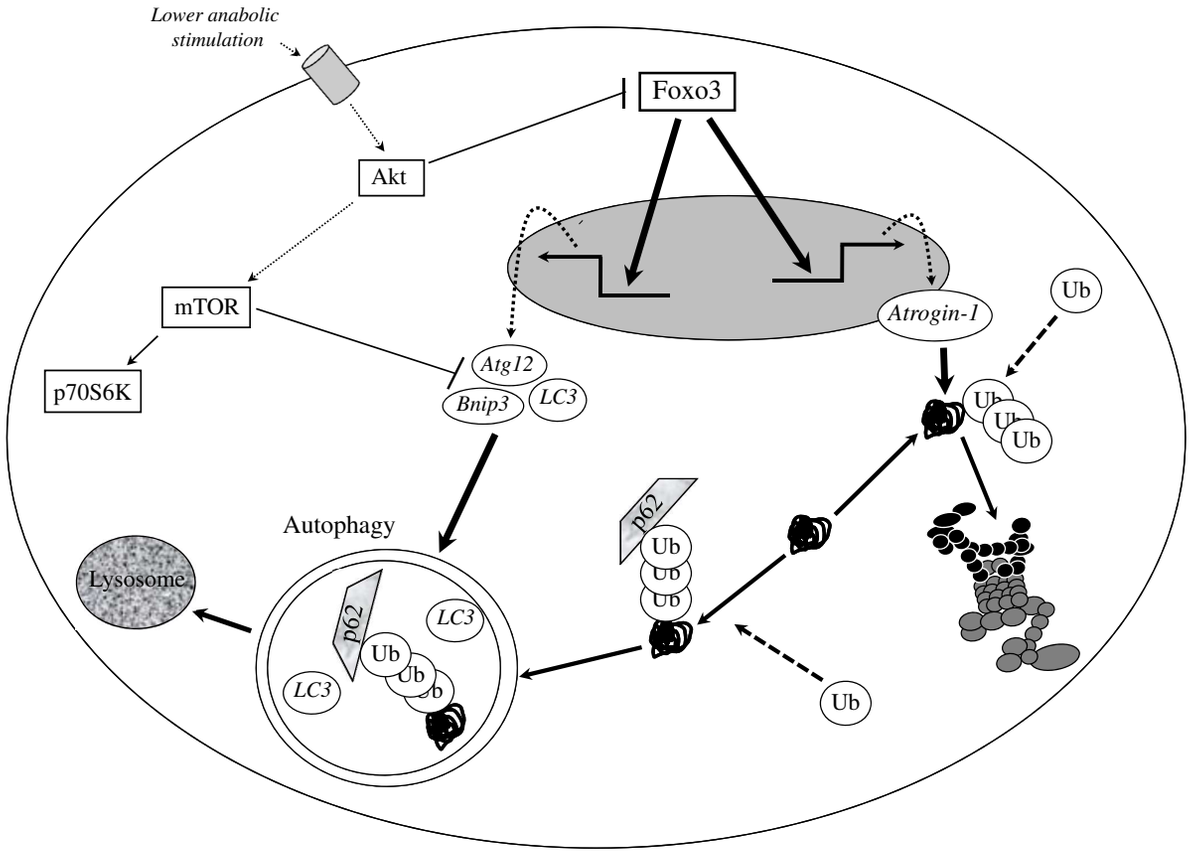

Figure 3. Contribution of the proteolytic pathways to muscle atrophy during catabolic conditions. In catabolic conditions such as denervation, cancer, and fasting, an atrophy program is induced to degrade muscle proteins and organelles. Proteins can have a double fate, being recognized and removed by the proteasome or docked to the autophagosome. In the latter case the chains of polyubiquitins are interacting with the p62. These proteins have also a domain for the interaction with LC3 therefore bringing the ubiquitinated proteins to the growing autophagosome. Less anabolic stimulation (IGF-I, mechanical loading, amino acids, etc.) reduces the amount of activated Akt, not promoting protein synthesis by activating the mTOR/p70S6K pathway. Lower Akt activity also does not block the nuclear translocation of FOXO3 to enhance the expression of autophagy-related genes (Bnip3, LC3, Atg12) and Atrogin-1 and the consequent protein degradation. FOXO: forkhead box O; IGF-I: insulin-like growth factor-I; LC3: microtubule-associated protein light chain; mTOR: mammalian target of rapamycin; p70S6K: 70 kDa ribosomal protein S6 kinase; Ub: ubiquitin. Data from Sakuma et al. [130]

with lung cancer [71, 104]. Furthermore, a few general observations suggested that autophagy can be activated in the muscle of animals bearing LLC or colon 26 (C26) tumor [105, 106]. More recently, Penna et al. [107] investigated whether autophagy signaling was elevated in muscle using three different models of cancer cachexia. They observed marked increases in the levels of beclin-1, p62/SQSTM1, and LC3B-II (the lipidated form; a reliable marker of autophagosome formation) in muscle in C26-bearing mice. In addition, Penna et al. [107] evaluated autophagic markers in the gastrocnemius muscle of rats bearing Yoshida AH-130 hepatoma or of mice transplanted with LLC. Several autophagic markers were upregulated in the muscle of these two cancer cachexia rodent models, although there was some difference in the adaptive manner. Furthermore, OP den Kamp et al. [70] indicated that the levels of both LC3B-I and -II proteins but not LC3B mRNA were significantly increased in the vastus lateralis muscle of

patients with lung cancer cachexia. Esophageal cancer patients also appear to exhibit higher LC3B-II/I ratios and levels of cathepsin B and L expression in muscle [72]. Since they did not detect a significant change of proteasome, calpain, or caspase 3 activity in the muscle of these patients, they considered that the autophagic-lysosomal pathway is the main proteolytic system in the muscle in esophageal cancer cachexia

The functional importance of autophagy in the pathogenesis of lung disease in COPD patients has recently been demonstrated by Chen et al. [108] who described significant increases of autophagy in clinical lung samples taken from COPD patients. LC3B, beclin-1, Atg7, and Atg5 were all upregulated, and autophagosome formation was visualized using electron microscopy. In addition, Ryter et al. [109] have also described increased autophagy in clinical specimens of the lung from patients with COPD. They showed the increased expression and activation of autophagic regulator proteins (i.e., LC3B, beclin-1, Atg5, Atg7) in lung. Similar evidence of increased autophagy was observed in mice subjected to chronic inhalation of cigarette smoke [108] and in lung epithelial cells exposed to aqueous cigarette smoke extracts [110]. Taking these findings together, autophagy seems to be activated in the lungs as a stress response. To date, little research has been completed on the contribution of the autophagy system to protein degradation and loss of skeletal muscle mass in COPD patients. Using muscle biopsy samples obtained from severe COPD patients with marked atrophy [forced expiratory volume in 1 s (FEV1) value of 35±2% of predicted], Plant et al. [111] demonstrated that there was no difference in the levels of beclin-1 and LC3 transcripts in the quadriceps muscle of patients with COPD compared with those in control individuals. On the basis of these results, Plant et al. [111] concluded that autophagy is not activated in muscles of COPD patients. However, they assessed the degree of autophagy by measuring mRNA levels only. More recently, Guo et al. [112] performed a pilot experiment using Western blot and real-time PCR mRNA measurements to evaluate autophagy-related gene expression of muscle biopsies obtained from cases of severe COPD. These experiments revealed significant increases in the intensity of LC3B-II protein in muscle of COPD patients compared with that in control subjects. In addition, they also observed significant increases in beclin-1 and p62/SQSTM1 protein levels in muscle biopsies of COPD patients indicating the activation of autophagy. More complete elucidation of the functional role of autophagy in muscle of COPD patients remains to be determined, but some research in this field has been undertaken. It is probable that the activation of autophagy in the muscle of COPD patients is modulated by several factors, such as oxidative stress, inflammation, malnutrition, and therapeutic medication, as proposed in an excellent systematic review by Hussain and Sandri [113].

One original study investigated the relationship between CHF and autophagy signaling in skeletal muscle [114]. It was suggested that there is a difference in the manner of autophagic adaptation between soleus (slow-type) and plantaris (fast-type) muscles by using rats with myocardial infarction. In fact, the transcription levels of GABARAPL-1 and Atg7 were increased in the plantaris but not the soleus muscle. However, the expression levels of other autophagic markers (beclin-1 and Atg12) did not change significantly. In addition, an autophagy-activating marker (LC3B-II/I) also did not increase in both muscles. However, there have been no studies examining the autophagy in muscle in cases of CHF. It remains to be elucidated

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whether CHF includes autophagic activation in skeletal muscle similar to muscle in cancer cachexia and COPD.

A possible contribution of autophagic signaling to sarcopenia

Autophagic defect has been described for invertebrates and higher organisms during normal aging. Inefficient autophagy has been attributed a major role in the age-dependent accumulation of damaged cellular components, such as undegradable lysosome-bound lipofuscin, protein aggregates, and damaged mitochondria [115]. The function of the autophagy/lysosome system of protein degradation seems to decline during aging in the *Drosophila* skeletal muscle [116]. Senescent *Drosophila* muscle exhibits the progressive accumulation of the aggregates of poly-ubiquitin protein. Intriguingly, overexpression of the FOXO upregulates the many autophagy-related genes, preserves the function of the autophagy pathway, and prevents the accumulation of poly-ubiquitin protein aggregates in sarcopenic *Drosophila* muscle [116]. Several investigators reported autophagic changes in aged mammalian skeletal muscle [101, 117, 118]. Compared with those in young male Fischer 344 rats, amounts of beclin-1 were significantly increased in the plantaris muscles of senescent rats [117]. Using Western blot of fractionated homogenates and immunofluorescence microscopy, we recently demonstrated the selective induction of p62/SQSTM1 and beclin-1 but not LC3 in the cytosol of sarcopenic muscle fibers in mice [119]. In addition, we also observed a significant smaller p62/SQSTM1-positive muscle fibers in aged muscle compared to the surrounding p62/SQSTM1-negative fibers [119]. In contrast, aging did not influence the amounts of Atg7 and Atg9 proteins in rat plantaris muscle [117]. More recently, Wohlgemuth et al. [117] clearly showed a marked increase in the amount of LC3 in muscle during aging using analysis of Western blot. However, they failed to detect an aging-related increase of the ratio of LC3-II to LC3-I, a better biochemical marker of ongoing autophagy. In addition, we failed to detect marked increases in LC3-I and LC3-II (active form) proteins in aged quadriceps muscle [119]. In contrast, a significant increase in the ratio of LC3-II to LC3-I during aging has been demonstrated in the biceps femoris muscle of wild-type mice [101]. None of the studies determining the mRNA expression level of autophagy-linked molecules found a significant increase with age [117, 118]. Not all contributors to autophagy signaling seem to change similarly at both mRNA and protein levels in senescent skeletal muscle. Therefore, sarcopenia may include a partial defect of autophagy signaling, although more exhaustive investigation is needed in this field. Intriguingly, more recent study [120] using biopsy samples of young and aged human volunteers clearly showed the age-dependent autophagic defect such as the decrease in the amount of Atg7 protein and in the ratio of LC3-II/LC3-I protein. Figure 4 summarizes a possible adaptation of autophagy-linked molecules (LC3 and p62/SQSTM1) in sarcopenic muscle.

Autophagic signaling in muscular dystrophy

Inhibition/alteration of autophagy contributes to myofiber degeneration leading to accumulation of abnormal (dysfunctional) organelles and of unfolded and aggregation-prone proteins [94, 99], which are typical features of several myopathies [121, 122]. Generation of Atg5 and Atg7 muscle-specific knockout mice confirmed the physiological importance of the autophagy system in muscle mass maintenance [99, 123]. The muscle-specific Atg7 knockout mice are characterized by the presence of mitochondrial abnormality, accumulation of polyubiquiti-

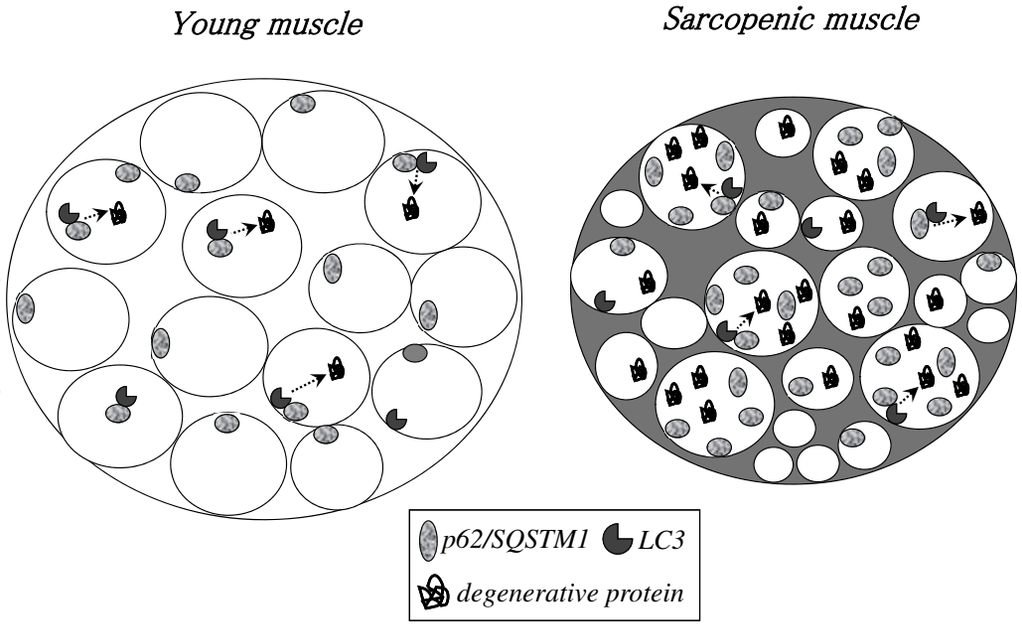

Figure 4. The comparison of an autophagy-dependent system between young and sarcopenic muscle. In contrast to young muscle, sarcopenic muscle exhibits abundant p62/SQSTM1 proteins with no activation of LC3, showing apparent autophagy defects, which cannot destroy the degenerative proteins.

nated proteins, and sarcomere disorganization [99]. In addition, the central role of the autophagy-lysosome system in muscle homeostasis is highlighted by lysosomal storage diseases (Pompe disease, Danon disease, and X-linked myopathy). These diseases are a group of debilitating muscle disorders characterized by alterations in lysosomal proteins and autophagosome buildup [124]. Intriguingly, the accumulation of autophagic vacuoles inside myofibers is recognized in all of these myopathies because of defects in their clearance.

Various muscular dystrophies also exhibit the apparent defect of autophagy-dependent signaling. The first evidence of impaired autophagy in these models was provided by studies in mice and patients with mutations in collagen VI [125]. Mutations that inactivate Jumpy, a phosphatase that counteracts the activation of VPS34 for autophagosome formation and reduces autophagy, are associated with centronuclear myopathy [126]. De Palma et al. [127] have described a decreased expression of autophagic regulator proteins (i.e., LC3 II, Atg12, GABARAPL-1, Bnip3) in dystrophin-deficient mdx mice and DMD patients. In addition, starvation and treatment with chloroquine, potent inducers of autophagy, did not activate autophagy-dependent signaling in both tibialis anterior and diaphragm muscles of mdx mice [127]. Furthermore, mdx mice and DMD patients exhibited an unnecessary accumulation of p62/SQSTM1 protein, which was lost after prolonged autophagy induction by a low-protein diet [127]. A similar block in autophagy progression was described in lamin A/C null mice [128]. LGMD2A muscles showed up-regulation of p62/SQSTM1 (2.1-fold) and Bnip3 (3-fold) mRNA and slightly increased LC3-II/LC3-I protein ratio and p62/SQSTM1 [87]. Conversely, laminin-mutated (*dy*/*dy*) animals displayed excessive levels of autophagy, which is equally detrimental [129]. These findings suggest that the defect of autophagy signaling has a central role in the degenerative symptoms in various types of muscular dystrophy.

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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References

[1] Staron RS, Leonardi MJ, Karapondo DL, Malicky ES, Falkel JE, Hagerman FC, Hikida RS (1991) Strength and skeletal muscle adaptations in heavy-resistance-trained women after detraining and retraining. J. Appl. Physiol. 70: 631-640.

[2] Allen RE, Goll DE (2003) Cellular and developmental biology of skeletal muscle as related to muscle growth. Biology of Growth of Domestic Animals, 148-193, ed: Scanes CG. Iowa State Press, Iowa.

[3] McCormick KM, Schultz E (1992) Mechanisms of nascent fiber formation during avian skeletal muscle hypertrophy. Dev. Biol. 150: 319-334.

[4] Schiaffino S, Bormioli SP, Aloisi M (1973) The fate of newly formed satellite cells during compensatory muscle hypertrophy. Virchows Arch. B Cell Pathol. 21: 113-118.

[5] Rosenblatt JD, Parry DJ (1992) Adaptation of rat extensor digitorum longus muscle to gamma irradiation and overload. J. Appl. Physiol. 73: 255-264.

[6] McCarthy JJ, Esser KA (2007) Counterpoint: satellite cell addition is not obligatory for skeletal muscle hypertrophy. J. Appl. Physiol. 103: 1100-1102.

[7] Hikida RS (2007) In response to point: Counterpoint: satellite cell addition is/is not obligatory for skeletal muscle hypertrophy. J. Appl. Physiol. 103, 1104-1105.

[8] Glass DJ (2010) PI3 kinase regulation of skeletal muscle hypertrophy and atrophy. Curr. Top. Microbiol. Immunol. 346: 267-278.

[9] Egerman MA, Glass DJ (2014) Signaling pathways controlling skeletal muscle mass. Crit. Rev. Biochem. Mol. Biol. 49: 59-68.

[10] Gordon SE, Flück M, Booth FW (2001) Selected contribution: Skeletal muscle focal adhesion kinase, paxillin, and serum response factor are loading dependent. J. Appl. Physiol. 90: 1174-1183.

[11] Sakuma K, Yamaguchi A (2011) Serum response factor (SRF)-dependent pathway: potential mediators of growth, regeneration, and hypertrophy of skeletal muscle. Recent. Res. Devel. Life Sci. 13-37, 5th edn, Research Signpost, Kerala, India.

[12] Cheema U, Brown R, Mudera V, Yang SY, McGrouther G, Goldspink G (2005) Mechanical signals and IGF-I gene splicing in vitro in relation to development of skeletal muscle. J. Cell. Physiol. 202: 67-75.

[13] Furuno K, Goodman MN, Goldberg AL (1990) Role of different proteolytic systems in the degradation of muscle proteins during denervation atrophy. J. Biol. Chem. 265: 8550-8557.

[14] Levine B, Kroemer G (2008) Autophagy in the pathogenesis of disease. Cell 132: 27-42.

[15] Mammucari C, Milan G, Romanello V, Masiero E, Rudolf R, Del Piccolo P, Burden SJ, Di Lisi R, Sandri C, Zhao J, Goldberg AL, Schiaffino S, Sandri M (2007) FoxO3 controls autophagy in skeletal muscle in vivo. Cell Metab. 6: 458-471.

[16] Zhao J, Brault JJ, Schild A, Cao P, Sandri M, Schiaffino S, Lecker SH, Goldberg AL (2007) FoxO3 coordinately activates protein degradation by the autophagic/ lysosomal and proteasomal pathways in atrophying muscle cells. Cell Metab. 6: 472-483.

[17] Dobrowolny G, Aucello M, Rizzuto E, Beccafico S, Mammucari C, Boncompagni S, Belia S, Wannenes F, Nicoletti C, Del Prete Z, Rosenthal N, Molinaro M, Protasi F, Fanò G, Sandri M, Musarò A (2008) Skeletal muscle is a primary target of SOD1G93A-mediated toxicity. Cell Metab. 8: 425-436.

[18] Jefferson LS, Fabian JR, Kimball SR (1999) Glycogen synthase kinase-3 is the predominant insulin-regulated eukaryotic initiation factor 2B kinase in skeletal muscle. Int. J. Biochem. Cell Biol. 31: 191-200.

[19] Chen WS, Xu PZ, Gottlob K, Chen ML, Sokol K, Shiyanova T, Roninson I, Weng W, Suzuki R, Tobe K, Kadowaki T, Hay N (2001) Growth retardation and increased apoptosis in mice with homozygous disruption of the Akt1 gene. Genes Dev. 15: 2203-2208.

[20] Peng XD, Xu PZ, Chen ML, Hahn-Windgassen A, Skeen J, Jacobs J, Sundararajan D, Chen WS, Crawford SE, Coleman KG, Hay N (2003) Dwarfism, impaired skin development, skeletal muscle atrophy, delayed bone development, and impeded adipogenesis in mice lacking Akt1 and Akt2. Genes Dev. 17: 1352-1365.

[21] Blaauw B, Canato M, Agatea L, Toniolo L, Mammucari C, Masiero E, Abraham R, Sandri M, Schiaffino S, Reggiani C (2009) Inducible activation of Akt increases skeletal muscle mass and force without satellite cell activation. FASEB J. 23: 3896-3905.

[22] Sartori R, Milan G, Patron M, Mammucari C, Blaauw B, Abraham R, Sandri M (2009) Smad2 and 3 transcription factors control muscle mass in adulthood. Am. J. Physiol. Cell Physiol. 296: C1248-C1257.

[23] Zoncu R, Efeyan A, Sabatini DM (2011) mTOR: from growth signal integration to cancer, diabetes and ageing. Nat. Rev. Mol. Cell Biol. 12: 21-36.

[24] Drummond MJ, Fry CS, Glynn EL, Dreyer HC, Dhanani S, Timmerman KL, Volpi E, Rasmussen BB (2009) Rapamycin administration in humans blocks the contraction-induced increase in skeletal muscle protein synthesis. J. Physiol. 587: 1535-1546.

[25] Kline WO, Panaro FJ, Yang H, Bodine SC (2007) Rapamycin inhibits the growth and muscle-sparing effects of clenbuterol. J. Appl. Physiol. 102: 740-747.

[26] Bodine SC, Stitt TN, Gonzalez M, Kline WO, Stover GL, Bauerlein R, Zlotchenko E, Scrimgeour A, Lawrence JC, Glass DJ, Yancopoulos GD (2001) Akt/mTOR pathway is a crucial regulator of skeletal muscle hypertrophy and can prevent muscle atrophy in vivo. Nat. Cell Biol. 3: 1014-1019.

[27] Goodman CA, Miu MH, Frey JW, Mabrey DM, Lincoln HC, Ge Y, Chen J, Hornberger TA (2010) A phosphatidylinositol 3-kinase/protein kinase B-independent activa-

tion of mammalian target of rapamycin signaling is sufficient to induce skeletal muscle hypertrophy. Mol. Biol. Cell 21: 3258-3268.

[28] Hornberger TA, Stuppard R, Conley KE, Fedele MJ, Fiorotto ML, Chin ER, Esser KA (2004) Mechanical stimuli regulate rapamycin-sensitive signalling by a phosphoinositide 3-kinase-, protein kinase B- and growth factor-independent mechanism. Biochem. J. 380: 795-804.

[29] Gan B, Yoo Y, Guan JL (2006) Association of focal adhesion kinase with tuberous sclerosis complex 2 in the regulation of s6 kinase activation and cell growth. J. Biol. Chem. 281: 37321-37329.

[30] O'Neil TK, Duffy LR, Frey JW, Hornberger TA (2009) The role of phosphoinositide 3-kinase and phosphatidic acid in the regulation of mammalian target of rapamycin following eccentric contractions. J. Physiol. 587: 3691-3701.

[31] MacKenzie MG, Hamilton DL, Murray JT, Taylor PM, Baar K (2009) mVps34 is activated following high-resistance contractions. J. Physiol. 587: 253-260.

[32] Kim E, Goraksha-Hicks P, Li L, Neufeld TP, Guan KL (2008) Regulation of TORC1 by Rag GTPases in nutrient response. Nat. Cell Biol. 10: 935-945.

[33] Pipes GC, Creemers EE, Olson EN (2006) The myocardin family of transcriptional coactivators: versatile regulators of cell growth, migration, and myogenesis. Genes Dev. 20: 1545-1556.

[34] Charvet C, Houbron C, Parlakian A, Giordani J, Lahoute C, Bertrand A, Sotiropoulos A, Renou L, Schmitt A, Melki J, Li Z, Daegelen D, Tuil D (2006) New role for serum response factor in postnatal skeletal muscle growth and regeneration via the interleukin 4 and insulin-like growth factor 1 pathways. Mol. Cell. Biol. 26: 6664-6674.

[35] Mokalled MH, Johnson AN, Creemers EE, Olson EN (2012) MASTR directs MyoD-dependent satellite cell differentiation during skeletal muscle regeneration. Genes Dev. 26: 190-202.

[36] Lange S, Xiang F, Yakovenko A, Vihola A, Hackman P, Rostkova E, Kristensen J, Brandmeier B, Franzen G, Hedberg B, Gunnarsson LG, Hughes SM, Marchand S, Sejersen T, Richard I, Edström L, Ehler E, Udd B, Gautel M (2005) The kinase domain of titin controls muscle gene expression and protein turnover. Science 308: 1599-1603.

[37] Kuwahara K, Barrientos T, Pipes GC, Li S, Olson EN (2005) Muscle-specific signaling mechanism that links actin dynamics to serum response factor. Mol. Cell. Biol. 25: 3173-3181.

[38] Miralles F, Posern G, Zaromytidou AI, Treisman R (2003) Actin dynamics control SRF activity by regulation of its coactivator MAL. Cell 113: 329-342.

[39] Kuwahara K, Teg Pipes GC, McAnally J, Richardson JA, Hill JA, Bassel-Duby R, Olson EN (2007) Modulation of adverse cardiac remodeling by STARS, a mediator of MEF2 signaling and SRF activity. J. Clin. Invest. 117: 1324-1334.

[40] Flück M, Carson JA, Schwartz RJ, Booth FW (1999) SRF protein is upregulated during stretch-induced hypertrophy of rooster ALD muscle. J. Appl. Physiol. 86: 1793-1799.

[41] Lamon S, Wallace MA, Léger B, Russell AP (2009) Regulation of STARS and its downstream targets suggest a novel pathway involved in human skeletal muscle hypertrophy and atrophy. J. Physiol. 587: 1795-1803.

[42] Sakuma K, Nishikawa J, Nakao R, Nakano H, Sano M, Watanabe K, Totsuka T (2003) Serum response factor plays an important role in the mechanically overloaded plantaris muscle of rats. Histochem. Cell Biol. 119: 149-160.

[43] Lee WJ, Thompson RW, McClung JM, Carson JA (2003) Regulation of androgen receptor expression at the onset of functional overload in rat plantaris muscle. Am. J. Physiol. Regul. Integr. Comp. Physiol. 285: R1076-R1085.

[44] Vlahopoulos S, Zimmer WE, Jenster G, Belaguli NS, Balk SP, Brinkmann AO, Lanz RB, Zoumpourlis VC, Schwartz RJ (2005) Regulation of androgen receptor expression at the onset of functional overload in rat plantaris muscle. J. Biol. Chem. 260: 7786-7792.

[45] Guerci A, Lahoute C, Hébrard S, Collard L, Graindorge D, Favier M, Cagnard N, Batonnet-Pichon S, Précigout G, Garcia L, Tuil D, Daegelen D, Sotiropoulos A (2012) Srf-dependent paracrine signals produced by myofibers control satellite cell-mediated skeletal muscle hypertrophy. Cell Metab. 15: 25-37.

[46] Bruusgaard JC, Johansen IB, Egner IM, Rana ZA, Gundersen K (2010) Myonuclei acquired by overload exercise precede hypertrophy and are not lost on detraining. Proc. Natl. Acad. Sci. U. S. A. 107: 15111-15116.

[47] O'Connor RS, Pavlath GK, McCarthy JJ, Esser KA (2007) Last word on point: Counterpoint: satellite cell addition is/is not obligatory for skeletal muscle hypertrophy. J. Appl. Physiol. 103: 1107.

[48] McCarthy JJ, Mula J, Miyazaki M, Erfani R, Garrison K, Farooqui AB, Srikuea R, Lawson BA, Grimes B, Keller C, Van Zant G, Campbell KS, Esser KA, Dupont-Versteegden EE, Peterson CA (2011) Effective fiber hypertrophy in satellite cell-depleted skeletal muscle. Development 138: 3657-3666.

[49] Short KR, Vittone JL, Bigelow ML, Proctor DN, Nair KS (2004) Age and aerobic exercise training effects on whole body and muscle protein metabolism. Am. J. Physiol. Endocrinol. Metab. 286: E92-E101.

[50] Sakuma K, Aoi W, Yamaguchi A (2015) Current understanding of sarcopenia: possible candidates modulating muscle mass. Pflügers Arch. 467: 213-229.

[51] Sakuma K, Aoi W, Yamaguchi A (2015) The intriguing regulators of muscle mass in sarcopenia and muscular dystrophy. Front. Aging Neurosci. 6: 230.

[52] Sakuma K, Akiho M, Nakashima H, Akima H, Yasuhara M (2008) Age-related reductions in expression of serum response factor and myocardin-related transcription factor A in mouse skeletal muscles. Biochim. Biophys. Acta Mol. Basis Dis. 1782: 453-461.

[53] Lahoute C, Sotiropoulos A, Favier M, Guillet-Deniau I, Charvet C, Ferry A, Butler-Browne G, Metzger D, Tuil D, Daegelen D (2008) Premature aging in skeletal muscle lacking serum response factor. PLoS One 3: e3910.

[54] Dubé J, Goodpaster BH (2006) Assessment of intramuscular triglycerides: contribution to metabolic abnormalities. Curr. Opin. Clin. Nutr. Metab. Care. 9: 553-559.

[55] Shefer G, Van de Mark DP, Richardson JB, Yablonka-Reuveni Z (2006) Satellite-cell pool size does matter: defining the myogenic potency of aging skeletal muscle. Dev. Biol. 294: 50-66.

[56] Sakuma K, Nakao R, Inashima S, Hirata M, Kubo T, Yasuhara M (2004) Marked reduction of focal adhesion kinase, serum response factor and myocyte enhancer factor 2C, but increase in RhoA and myostatin in the hindlimb dy mouse muscles. Acta Neuropathol. (Berl.) 108: 241-249.

[57] Davis FJ, Gupta M, Pogwizd SM, Jeevanandam V, Gupta MP (2002) Increased expression of alternatively spliced dominant-negative isoform of SRF in human failing hearts. Am. J. Physiol. Heart Circ. Physiol. 282: H1521-H1533.

[58] Chang J, Wei L, Otani T, Youker KA, Entman ML, Schwartz RJ (2003) Inhibitory cardiac transcription factor, SRF-N, is generated by caspase 3 cleavage in human heart failure and attenuated by ventricular unloading. Circulation 108: 407-413.

[59] Miano JM (2010) Role of serum response factor in the pathogenesis of disease. Lab. Invest. 90: 1274-1284.

[60] Bodine SC, Baehr LM (2014) Skeletal muscle atrophy and the E3 ubiquitin ligases MuRF1 and MAFbx/atrogin-1. Am. J. Physiol. Endocrinol. Metab. 307: E469-E484.

[61] Lagirand-Cantaloube J, Offner N, Csibi A, Leibovitch MP, Batonnet-Pichon S, Tintignac LA, Segura CT and Leibovitch SA (2008) The initiation factor eIF3-f is a major target for atrogin1/MAFbx function in skeletal muscle atrophy. EMBO J. 27: 1266-1276.

[62] Lagirand-Cantaloube J, Cornille K, Csibi A, Batonet-Pichon S, Leibovitch MP, Leibovitch SA (2009) Inhibition of atrogin-1/MAFbx mediated MyoD proteolysis prevents skeletal muscle atrophy in vivo. PLoS One. 4: e4973.

[63] Jogo M, Shiraishi S, Tamura TA (2009) Identification of MAFbx as a myogenin-engaged F-box protein in SCF ubiquitin ligase. FEBS Lett. 583: 2715-2719.

[64] Cohen S, Brault JJ, Gygi SP, Glass DJ, Valenzuela DM, Gartner C, Latres E, Goldberg AL (2009) During muscle atrophy, thick, but not thin, filament components are degraded by MuRF1-dependent ubiquitylation. J. Cell Biol. 185: 1083-1095.

[65] Temparis S, Asensi M, Taillandier D, Aurousseau E, Larbaud D, Obled A, Béchet D, Ferrara M, Estrela JM, Attaix D (1994) Increased ATP-ubiquitin-dependent proteolysis in skeletal muscle of tumor-bearing rats. Cancer Res. 54: 5568-5573.

[66] Khal J, Wyke SM, Russell ST, Hine AV, Tisdale MJ (2005) Expression of the ubiquitin-proteasome pathway and muscle loss in experimental cancer cachexia. Br. J. Cancer. 93: 774-780.

[67] Costelli P, Muscaritoli M, Bossola M, Penna F, Reffo P, Bonetto A, Busquets S, Bonelli G, Lopez-Soriano FJ, Doglietto GB, Argilés JM, Baccino FM, Rossi Fanelli F (2006) IGF-I is downregulated in experimental cancer cachexia. Am. J. Physiol. Regul. Integr. Comp. Physiol. 291: R674-R683.

[68] Khal J, Hine AV, Fearon KCH, Dejong CHC, Tisdale MJ (2005) Increased expression of proteasome subunits in skeletal muscle of cancer patients with weight loss. Int. J. Biochem. Cell Biol. 37: 2196-2206.

[69] Bossola M, Muscaritoli M, Costelli P, Grieco G, Bonelli G, Pacelli F, Rossi Fanelli F, Doglietto GB, Baccino FM (2003) Increased muscle proteasome activity correlates with disease severity in gastric cancer patients. Ann. Surg. 237: 384-389.

[70] Op den Kamp C, Langen RC, Snepvangers FJ, De Theije CC, Schellekens JM, Laugs F, Dingemans AMC, Schols AM (2013) Nuclear transcription factor κB activation and protein turnover adaptations in skeletal muscle of patients with progressive stages of lung cancer cachexia. Am. J. Clin. Nutr. 98: 738-748.

[71] Jagoe RT, Redfern CP, Roberts RG, Gibson GJ, Goodship TH (2002) Skeletal muscle mRNA levels for cathepsin B, but not components of the ubiquitin-proteasome pathway, are increased in patients with lung cancer referred for thoracotomy. Clin. Sci. 102: 353-361.

[72] Tardif N, Klaude M, Lundell L, Thorell A, Rooyackers O (2013) Autophagic-lysosomal pathway is the main proteolytic system modified in the skeletal muscle of esophageal cancer patients. Am. J. Clin. Nutr. 98: 1485-1492.

[73] Doucet M, Russell AP, Léger B, Debigaré R, Joanisse DR, Caron MA, LeBranc P, Maltais F (2007) Muscle atrophy and hypertrophy signaling in patients with chronic obstructive pulmonary disease. Am. J. Respir. Crit. Care Med. 176: 261-269.

[74] Natanek SA, Riddoch-Contreras J, Marsh GS, Hopkinson NS, Moxham J, Man WDC, Kemp PR, Polkey MI (2013) MuRF-1 and atrogin-1 protein expression and quadriceps fiber size and muscle mass in stable patients with COPD. COPD. 10: 618-624.

[75] Höllriegel R, Beck EB, Linke A, Adams V, Möbius-Winkler S, Mangner N, Sandri M, Gielen S, Gutberlet M, Hambrecht R, Schuler G, Erbs S (2013) Anabolic effects of ex-

ercise training in patients with advanced chronic heart failure (NYHA IIIb): impact on ubiquitin-protein ligases expression and skeletal muscle size. Int. J. Cardiol. 167: 975-980.

[76] Li P, Waters RE, Redfern SI, Zhang M, Mao L, Annex BH, Yan Z (2007) Oxidative phenotype protects myofibers from pathological insults induced by chronic heart failure in mice. Am. J. Pathol. 170: 599-608.

[77] Foletta VC, White LJ, Larsen AE, Léger B, Russell AP (2011) The role and regulation of MAFbx/atrogin-1 and MuRF1 in skeletal muscle atrophy. Pflügers Arch. 461: 325-335.

[78] Baehr LM, Tunzi M, Bodine SC (2014) Muscle hypertrophy is associated with increases in proteasome activity that is independent of MuRF1 and MAFbx expression. Front. Physiol. 5: 69.

[79] Sakuma K, Yamaguchi A (2011) Sarcopenia: molecular mechanisms and current therapeutic strategy. Cell Aging, 93-152, ed: Perloft JW & Wong AH. Nova Science Publisher, NY.

[80] Edström E, Altun M, Hägglund M, Ulfhake B (2006) Atrogin-1/MAFbx and MuRF1 are downregulated in ageing-related loss of skeletal muscle. J. Gerontol. Series A Biol. Sci. Med. Sci. 61: 663-674.

[81] Léger B, Derave W, De Bock K, Hespel P, Russell AP (2008) Human sarcopenia reveals an increase in SOCS-3 and myostatin and a reduced efficiency of Akt phosphorylation. Rejuvenation Res. 11: 163-175.

[82] Sandri M, Barberi L, Bijlsma AY, Blaauw B, Dyar KA, Milan G, Mammucari C, Meskers CG, Pallafacchina G, Paoli A, Pion D, Roceri M, Romanello V, Serrano AL, Toniolo L, Larsson L, Maier AB, Muñoz-Cánoves P, Musarò A, Pende M, Reggiani C, Rizzuto R, Schiaffino S (2013) Signaling pathways regulating muscle mass in ageing skeletal muscle. The role of IGF-1-Akt-mTOR-FoxO pathway. Biogerontology 14: 303-323.

[83] Hwee DT, Baehr LM, Philp A, Baar K, Bodine SC (2014) Maintenance of muscle mass and load-induced growth in Muscle RING Finger 1 null mice with age. Aging Cell 13: 92-101.

[84] Keira Y, Noguchi S, Kurokawa R, Fujita M, Minami N, Hayashi YK, Kato T, Nishino I (2007) Characterization of lobulated fibers in limb girdle muscular dystrophy type 2A by gene expression profiling. Neurosci. Res. 57: 513-521.

[85] Sáenz A, Azpitarte M, Armananzas R, Leturcq F, Alzualde A, Inza I, García-Bragado F, De la Herran G, Corcuera J, Cabello A, Navarro C, De la Torre C, Gallardo E, Illa I, López de Munain A (2008) Gene expression profiling in limb girdle muscular dystrophy 2A. PLoS One 3: e3750.

[86] Laure L, Suel L, Roudaut C, Bourg N, Ouali A, Bartoli M, Richard I, Danièle N (2009) Cardiac ankyrin repeat protein is a marker of skeletal muscle pathological remodeling. FEBS J. 276: 669-684.

[87] Fanin M, Nascimbeni AC, Angelini C (2013) Muscle atrophy in limb girdle muscular dystrophy 2A: a morphometric and molecular study. Neuropath. Appl. Neurobiol. 39: 762-771.

[88] Bansal D, Miyake K, Vogel SS, Groh S, Chen CC, Williamson R, McNeil PL, Campbell KP (2003) Defective membrane repair in dysferlin-deficient muscular dystrophy. Nature 423: 168-172.

[89] Fanin M, Nascimbeni AC, Angelini C (2014) Muscle atrophy, ubiquitin-proteasome, and autophagic pathways in dysferlinopathy. Muscle Nerve 50: 340-347.

[90] Azakir BA, Di Fulvio S, Kinter J, Sinnreich M (2012) Proteasomal inhibition restores biological function of missense mutated dysferlin in patient-derived muscle cells. J. Biol. Chem. 287: 10344-10354.

[91] Paco S, Ferrer I, Jou C, Cusi V, Corbera J, Torner F, Gualandi F, Sabatelli P, Orozco A, Gómez-Foix AM, Colomer J, Nascimento A, Jimenez-Mallebrera C (2012) Muscle fiber atrophy and regeneration coexist in collagen VI-deficient human muscle: role of calpain-3 and nuclear factor-κB signaling. J. Neuropathol. Exp. Neurol. 71: 894-906.

[92] Bonuccelli G, Sotgia F, Capozza F, Gazzerro E, Minetti C, Lisanti MP (2007) Localized treatment with a novel FDA-approved proteasome inhibitor blocks the degradation of dystrophin and dystrophin-associated proteins in mdx mice. Cell Cycle 6: 1242-1248.

[93] Gazzerro E, Assereto S, Bonetto A, Sotgia F, Scarfi S, Pistorio A, Bonuccelli G, Cilli M, Bruno C, Zara F, Lisanti MP, Minetti C. (2010) Therapeutic potential of proteasome inhibition in Duchenne and Becker muscular dystrophies. Am. J. Pathol. 176: 1863-1877.

[94] Sandri M (2010) Autophagy in health and disease. 3. Involvement of autophagy in muscle atrophy. Am. J. Physiol. Cell Physiol. 298: C1291-C1297.

[95] Sandri M (2011) New findings of lysosomal proteolysis in skeletal muscle. Curr. Opin. Clin. Nutr. Metab. Care 14: 223-229.

[96] Cuervo AM (2004) Autophagy: many paths to the same end. Mol. Cell Biochem. 263: 55-72.

[97] Park C, Cuervo AM (2013) Selective autophagy: talking with the UPS. Cell Biochem. Biophys. 67: 3-13.

[98] Shaid S, Brandts CH, Serve H, Dikic I (2013) Ubiquitination and selective autophagy. Cell Death Differ. 20: 21-30.

[99] Masiero E, Agatea L, Mammucari C, Blaauw B, Loro E, Komatsu M, Metzger D, Reggiani C, Schiaffino S, Sandri M (2009) Autophagy is required to maintain muscle mass. Cell Metab. 10: 507-515.

[100] Paul PK, Gupta SK, Bhatnagar S, Panguluri SK, Darnay BG, Choi Y, Kumar A (2010) Targeted ablation of TRAF6 inhibits skeletal muscle wasting in mice. J. Cell Biol. 191: 1395-1411.

[101] Wenz T, Rossi SG, Rotundo RL, Spiegelman BM, Moraes CT (2009) Increased muscle PGC-1alpha expression protects from sarcopenia and metabolic disease during aging. Proc. Natl. Acad. Sci. U. S. A. 106: 20405-20410.

[102] Baracos VE, DeVivo C, Hoyle DH, Goldberg AL (1995) Activation of the ATP ubiquitin-proteasome pathway in skeletal muscle of cachectic rats bearing a hepatoma. Am. J. Physiol. 268: E996-E1006.

[103] Tessitore L, Costelli P, Baccino FM (1993) Cancer cachexia, malnutrition, and tissue protein turnover in experimental animals. Arch. Biochem. Biophys. 306: 52-58.

[104] Deval C, Mordier S, Obled C, Bechet D, Combaret L, Attaix D, Ferrara M (2001) Identification of cathepsin L as a differentially expressed message associated with skeletal muscle wasting. Biochem. J. 360: 143-150.

[105] Asp ML, Tian M, Wendel AA, Belury MA (2010) Evidence for the contribution of insulin resistance to the development of cachexia in tumor-bearing mice. Int. J. Cancer 126: 756-763.

[106] Lokireddy S, Wijesoma JW, Bonala S, Wei M, Sze SK, McFarlane C, Kambadur R, Sharma M (2012) Myostatin is a novel tumoral factor that induces cancer cachexia. Biochem. J. 446: 23-36.

[107] Penna F, Costamagna D, Pin F, Camperi A, Fanzani A, Chiarpotto EM, Cavallini G, Bonelli G, Baccino FM, Costelli P (2013) Autophagic degradation contributes to muscle wasting in cancer cachexia. Am. J. Pathol. 182: 1367-1378.

[108] Chen ZH, Kim HP, Sciurba FC, Lee SJ, Feghali-Bostwick C, Stolz DB, Dhir R, Landreneau RJ, Schuchert MJ, Yousem SA, Nakahira K, Pilewski JM, Lee JS, Zhang Y, Ryter SW, Choi AM (2008) Egr-1 regulates autophagy in cigarette smoke-induced chronic obstructive pulmonary disease. PLoS One 3: e3316.

[109] Ryter SW, Chen ZH, Kim HP, Choi AMK (2009) Autophagy in chronic obstructive pulmonary disease. Autophagy 5: 235-237.

[110] Kim HP, Wang X, Chen ZH, Lee SJ, Huang MH, Wang Y, Ryter SW, Choi AM (2008) Autophagic proteins regulate cigarette smoke-induced apoptosis: protective role of heme oxygenase-1. Autophagy 4: 887-895.

[111] Plant PJ, Brooks D, Faughnan M, Bayley T, Bain J, Singer L, Correa J, Pearce D, Binnie M, Batt J (2010) Cellular markers of muscle atrophy in chronic obstructive pulmonary disease. Am. J. Respir. Cell Mol. Biol. 42: 461-471.

[112] Guo Y, Gosker HR, Schols AM, Kapchinsky S, Bourbeau J, Sandri M, Jagoe RT, Debigaré R, Maltais F, Taivassalo T, Hussain SN (2013) Autophagy in locomoter muscles of patients with chronic obstructive pulmonary disease. Am. J. Respir. Crit. Care Med. 188: 1313-1320.

[113] Hussain SNA, Sandri M (2013) Muscle dysfunction in COPD. Role of autophagy in COPD skeletal muscle dysfunction. J. Appl. Physiol. 114: 1273-1281.

[114] Jannig PR, Moreira JBN, Bechara LRG, Bozi LHM, Bacurau AV, Monteiro AWA, Dourado PM, Wisløff U, Brum PC (2014) Autophagy signaling in skeletal muscle of infarcted rats. PLoS One 9: e85829.

[115] Terman A, Brunk UT (2006) Oxidative stress, accumulation of biological 'garbage', and aging. Antioxid. Redox Signal. 8: 197-204.

[116] Demontis F, Perrimon N (2010) FOXO/4E-BP signaling in Drosophila muscles regulates organism-wide proteostasis during aging. Cell 143: 813-825.

[117] Wohlgemuth SE, Seo AY, Marzetti E, Lees HA, Leeuwenburgh C (2010) Skeletal muscle autophagy and apoptosis during aging: effects of calorie restriction and lifelong exercise. Exp. Gerontol. 45: 138-148.

[118] McMullen CA, Ferry AL, Gamboa JL, Andrade FH, Dupont-Versteegden EE (2009) Age-related changes of cell death pathways in rat extraocular muscle. Exp. Gerontol. 44: 420-425.

[119] Sakuma K, Kinoshita M, Ito Y, Aizawa M, Aoi W, Yamaguchi A (2015) p62/SQSTM1 but not LC3 is accumulated in sarcopenic muscle of mice. J. Cachexia Sarcopenia Muscle (in press) DOI: 10.1002/jcsm.12045

[120] Carnio S, LoVerso F, Baraibar MA, Longa E, Khan MM, Maffei M, Reischl M, Canepari M, Loefler S, Kern H, Blaauw B, Friguet B, Bottinelli R, Rudolf R, Sandri M (2014) Autophagy impairment in muscle induces neuromuscular junction degeneration and precocious aging. Cell Reports 8: 1509-1521.

[121] Grumati P, Coletto L, Sabatelli P, Cescon M, Angelin A, Bertaggia E, Blaauw B, Urciuolo A, Tiepolo T, Merlini L, Maraldi NM, Bernardi P, Sandri M, Bonaldo P (2010) Autophagy is defective in collagen VI muscular dystrophies, and its reactivation rescues myofiber degeneration. Nat. Med. 16: 1313-1320.

[122] Nogalska A, D'Agostino C, Terracciano C, Engel WK, Askanas V (2010) Impaired autophagy in sporadic inclusion-body myositis and in endoplasmic reticulum stress-provoked cultured human muscle fibers. Am. J. Pathol. 177: 1377-1387.

[123] Raben N, Hill V, Shea L, Takikita S, Baum R, Mizushima N, Ralston E, Plotz P (2008) Supression of autophagy in skeletal muscle uncovers the accumulation of ubiquiti-

nated proteins and their potential role in muscle damage in Pompe disease. Hum. Mol. Genet. 17: 3897-3908.

[124] Vainshtein A, Grumati P, Sandri M, Bonaldo P (2014) Sakeletal muscle, autophagy, and physical activity: the ménage á trois of metabolic regulation in health and disease. J. Mol. Med. 92: 127-137.

[125] Irwin WA, Bergamin N, Sabatelli P, Reggiani C, Megighian A, Merlini L, Braghetta P, Columbaro M, Volpin D, Bressan GM, Bernardi P, Bonaldo P (2003). Mitochondrial dysfunction and apoptosis in myopathic mice with collagen VI deficiency. Nat. Genet. 35: 361-371.

[126] Vergne I, Roberts E, Elmaoued RA, Tosch V, Delgado MA, Proikas-Cezanne T, Laporte J, Deretic V (2009) Control of autophagy initiation by phosphoinositide 3-phosphatase Jumpy. EMBO J. 28: 2244-2258.

[127] De Palma C, Morisi F, Cheli S, Pambianco S, Cappello V, Vezzoli M, Rovere-Querini P, Moggio M, Ripolone M, Francolini M, Sandri M, Clementi E (2012) Autophagy as a new therapeutic target in Duchenne muscular dystrophy. Cell Death Dis. 3: e418.

[128] Ramos FJ, Chen SC, Garelick MG, Dai DF, Liao CY, Schreiber KH, MacKay VL, An EH, Strong R, Ladiges WC, Rabinovitch PS, Kaeberlein M, Kennedy BK (2012) Rapamycin reverses elevated mTORC1 signaling in lamin A/C-deficient mice, rescues cardiac and skeletal muscle function, and extends survival. Sci. Transl. Med. 4: 144ra103.

[129] Carmignac V, Svensson M, Körner Z, Elowsson L, Matsumura C, Gawlick KI, Allamand V, Durbeej M (2011) Autophagy is increased in laminin α2 chain-deficient muscle and its inhibition improves muscle morphology in a mouse model of MDC1A. Hum. Mol. Genet. 20: 4891-4902.

[130] Sakuma K, Yamaguchi A (2012) Cellular and molecular mechanism regulating hypertrophy and atrophy of skeletal muscle. Skeletal Muscle: Physiology, Classification and Disease, 141-193, ed: Willems M. Nova Science Publisher, NY.

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