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Skeletal Muscle Autophagy: A New Metabolic Regulator

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Abstract

Autophagy classically functions as a physiological process to degrade cytoplasmic components, protein aggregates, and/or organelles, as a mechanism for nutrient breakdown, and as a regulator of cellular architecture. Proper autophagic flux is vital for both functional skeletal muscle, which controls support and movement of the skeleton, and muscle metabolism. The role of autophagy as a metabolic regulator in muscle has been previously studied; however, the underlying molecular mechanisms that control autophagy in skeletal muscle have only just begun to emerge. Here, we review recent literature on the molecular pathways controlling skeletal muscle autophagy, and discuss how they connect autophagy to metabolic regulation. We also focus on the implications these studies hold for understanding metabolic and muscle wasting diseases.

Skeletal Muscle Autophagy

Skeletal muscle is comprised of highly organized myofibers containing aligned contractile units called sarcomeres. Through the rhythmic activity of the actin filaments and myosin motor proteins within the sarcomeres, skeletal muscle provides the force for movement and support required by the body [1]. Daily movements, accentuated during physical activity, produce high amounts of reactive oxygen species, which can damage cellular components [2]. Moreover, skeletal muscle comprises roughly 40% of whole body lean mass, thereby providing a tissue source for amino acids that can be used in times of stress or starvation. Thus, skeletal muscle needs an efficient method of not only recycling damaged or aged organelles and accumulated protein aggregates, but also breaking down protein to meet the energy demands of the body. Macroautophagy (herein autophagy) represents the physiological process skeletal muscle utilizes to transport cytoplasm, organelles, and proteins to the lysosome for degradation (see Glossary) [3,4]. Autophagy is vital for removing old and damaged cellular components, breaking down undedicated nutrient stores,

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and remodeling cellular architecture. Recently, examination of various skeletal muscle diseases causing atrophy and dystrophy has discovered an interesting common feature; the buildup of autophagosomes within myofibers [5]. This striking feature of diseased skeletal muscle underlies the importance of autophagy in proper skeletal muscle function.

The importance of autophagy is demonstrated by the postnatal lethality of mice with a whole body knockout of the E3 ubiquitin ligase, autophagy protein 5 (Atg5), which is required for autophagy [6]. Fortunately, with the use of conditional knockouts, researchers have uncovered many interesting insights into the role of autophagy in the regulation of muscle mass and energy metabolism. Multiple excellent reviews have independently covered the mechanisms of skeletal muscle autophagy and how autophagy interplays with systemic metabolism [1,7]. This review will discuss how skeletal muscle autophagy regulates metabolism in physiological and pathophysiological states.

Autophagy Signal Transduction

Mammalian Target of Rapamycin (mTOR)-dependent pathways

The family of evolutionary conserved Atg proteins controls the major steps of autophagy: autophagy initiation, nucleation, and lysosomal fusion/degradation. Box 1 reviews the canonical signaling pathway involving these proteins. Another important protein involved in skeletal muscle autophagy is mTOR, a highly conserved serine/threonine kinase required for numerous aspects of cellular homeostasis [8]. mTOR is the major metabolic sensor in the myocyte and can accordingly regulate physiological processes depending on nutritional conditions. Canonically, mTOR regulates autophagy based on the nutritional state via a trimeric protein complex containing unc51-like kinase-1/FAK family kinase-interacting protein of 200 kDa/Atg13 (ULK-1/FIP200/Atg13) (Figure 1) [9]. However, studies employing the mTOR inhibitor, rapamycin, or RNAi against mTOR have shown that inhibition of mTOR itself is not sufficient to alter autophagic flux in muscle. Furthermore, skeletal muscle mTOR or regulatory-associated protein of mTOR ((raptor) a mTOR Complex 1 (mTORC1) component), knockout mice present with muscular dystrophy as opposed to an atrophy phenotype [1,10–12]. However, knockout of the mTORC2 component, rapamycin-insensitive companion of mTOR (rictor), in skeletal muscle, results in increased autophagy due to the translocation and activation of forkhead box O3 (FoxO3), a key transcription factor that promotes the expression of autophagy and proteosomal-related genes in muscle [10]. On the other hand, constitutively activating mTOR via the skeletal muscle knockout of tuberous sclerosis 1 (TSC1) causes a late onset myopathy specific to white muscle, presumably due to autophagy inhibition via ULK1 [13] (Box 2). These studies outline the role of mTOR in skeletal muscle autophagy control and highlight the complex interaction between mTOR, autophagy, and muscle wasting. However, studies are still needed to delineate which downstream actions and targets of mTOR are the culprits in muscle wasting phenotypes.

Together, these studies have cumulatively led to the conclusion that mTOR only regulates 10% of skeletal muscle autophagy. Interestingly, the kinase, Akt, that lies upstream of mTOR seems to play a much more important role; it has been reported that Akt controls roughly 50% of skeletal muscle autophagy (Figure 1) [14]. Consequently, the current model of autophagy regulation includes two pathways; a transcriptionally independent pathway via the mTORC1/ULK1 interaction, and a second transcriptionally dependent pathway via Akt/FoxO3-dependent gene expression.

FoxO3-dependent pathways

FoxO3 is a member of the forkhead family of transcription factors that play a vital role in connecting growth factor signaling to degradative processes in the myofiber by regulating

expression of proteasome and autophagy-related genes. Akt controls FoxO3 activity via phosphorylation, preventing the protein from entering the nucleus and thus blocking transcription of FoxO3-dependent gene expression [15]. Studies manipulating mTOR activity found that Akt is altered as well; both the Raptor and Rictor skeletal muscle knockout mice show hyperactivation of Akt, which would be hypothesized to inhibit FoxO3 target gene expression and thus decrease autophagy [12]. However, other studies have shown that ablating Rictor drives FoxO3 nuclear translocation and activation, demonstrating our incomplete understanding of the signal transduction pathways regulating FoxO3-dependent gene expression [10,16]. Furthermore, diabetic patients display marked impairment in skeletal muscle insulin sensitivity due to reduced insulin signal transduction and Akt phosphorylation [17,18]. In response, it would be hypothesized that these individuals may have increased FoxO3 activity, thus assigning potential clinical significance to FoxO3 signaling. Studies are needed to address this and whether FoxO3 is one of the mechanisms that result in enhanced skeletal muscle autophagy, sufficient to drive muscle wasting in diabetic patients.

FoxO3 has been implicated in the control of both proteasomal and autophagic degradation pathways in skeletal muscle. Roughly 90% of single protein degradation in a cell is controlled via the proteasome pathway by protein ubiquitination. Ubiquitination is regulated by the FoxO3-dependent ubiquitin ligases, muscle atrophy F-box protein (MAFbx)/atrogin1 and muscle specific ring finger protein 1 (MuRF1), and many studies have demonstrated a role for these proteins in muscle atrophy [19]. As discussed above, FoxO3 drives the expression of key autophagic genes such as microtubule-associated protein 1 light chain 3 (LC3), Bcl2/adenovirus E1B 19kda interacting protein 3 (Bnip3), vacuolar protein sorting 34 (Vps34), Atg12, and GABA(A) receptor-associated protein (GABARAP) (Box 1, Fig. 1). These genes drive atrophy in skeletal muscle but also interact with the autophagy-mediated degradative pathway [14].

One regulator of autophagy brings together the mTOR and FoxO3 signaling pathways. AMP-activated protein kinase (AMPK) is a conserved serine/threonine kinase that activates in response to low cellular energy levels and controls many aspects of lipid and glucose metabolism. AMPK directly opposes mTOR mediated autophagy inhibition via phosphorylating a different residue on ULK1 and activating the autophagy initiation complex [9]. AMPK also functions as an autophagy activator by directly phosphorylating and activating FoxO3, thus promoting autophagy on two fronts [20,21]. Interestingly, AMPK is necessary for mitochondrial-dependent muscle wasting, and inhibition of AMPK can reverse the atrophy phenotype [22]. Taken together, mTOR, FoxO3, and AMPK are important regulators of skeletal muscle autophagy; however, the genetic manipulation of these players to activate or inhibit autophagy has similarly led to muscle wasting phenotypes (discussed further below). Further studies are needed to address these confounding results and elucidate the mechanisms at work in skeletal muscle that coordinate cellular cues to autophagic flux.

Emerging Players of Skeletal Muscle Autophagy

Recent studies investigating the molecular mechanisms of known signaling pathways of skeletal muscle autophagy have uncovered many novel regulators of autophagy (Fig 1). The beclin1/Vps34 complex mediates phagophore nucleation and is composed of many different proteins (Box 1) [23]. One such component is another member of the vacuolar protein sorting family, Vps15. Interestingly, Vps15 skeletal muscle knockout mice develop an excessive accumulation of autophagosomes due to unregulated autophagy and have a myopathy phenotype. This study demonstrates the role of Vps15 in autophagosome/lysosome fusion. Nevertheless, is this a Vps15 specific effect or does the beclin1 complex control not only autophagosome formation, but also autophagosome-lysosome fusion [24]?

The beclin1 complex is diversely regulated and one of these regulators is B-cell CLL/ Lymphoma 2 (Bcl-2), a protein with established roles in apoptosis and calcium flux regulation that has been shown to regulate autophagy as well. Binding of Bcl-2 to beclin-1 inhibits beclin-1 from interacting with Vps34, resulting in an inhibition of autophagic initiation [25]. The Bcl-2-mediated regulation of autophagy is partly mediated by the recently identified protein, nuclear assembly factor-1 (NAF-1), an ER localized protein shown to direct the action of Bcl-2 towards autophagy inhibition and away from its other functions. Interestingly, the full body Naf-1 knockout mouse develops a skeletal muscle phenotype, characterized by excessive autophagy, muscle wasting, and a fiber type switch [26] (Box 2). Why skeletal muscle is the main tissue affected by the knockout has yet to be addressed.

Vps34 functions in nucleation by generating phosphoinositide-3-phosphate (PI3P), a necessary lipid species for nucleating the forming phagophore membrane [17]. Myotubularin-related protein 14 (MTMR14), also known as Jumpy, has recently been identified as a lipid phosphatase that can specifically dephosphorylate PI3P to phosphatidylinositol (PI), therefore acting as a novel inhibitor of autophagy. MTMR14 gene mutations in humans cause centronuclear myopathy. Genetic studies using zebrafish uncovered that MTMR14 knockdown resulted in unregulated autophagy and a muscle wasting phenotype [27,28]. Intriguingly, a family member of MTMR14, myotubularin 1 (MTM1), has also been implicated in muscle wasting. MTM1 has the same lipid phosphatase activity as MTMR14, and the knockout mouse model presents with an activation of skeletal muscle autophagy [29,30]. The necessity of proper lipid species in autophagy is also exemplified by the identification of choline kinase β (Chk β), which generates phosphatidylcholine (PC). Loss of enzymatic activity in humans and the knockout mouse model both show congenital muscular dystrophy [31]. Interestingly, investigation of the mouse model determined the muscle wasting to occur from decreased oxidative metabolism due to excessive mitophagy, or the autophagic clearance of mitochondria [31]. These novel autophagy regulators specifically target skeletal muscle and regulate the balance of lipid species within the myofiber. Identifying how these lipid species affect membrane curvature or lipid-protein interactions is vital to understanding their regulation of skeletal muscle autophagy.

Proper levels of mitophagy are necessary for the function of oxidative metabolism and maintaining viable tissue [32]. This is demonstrated by the discovery of the mitochondrial E3 ubiquitin protein ligase 1 (Mul-1). Muscle wasting stimuli such as dexamethasone, myostatin, or serum starvation up-regulate Mul-1 in a FoxO1/3 dependent manner in skeletal muscle. Mul-1 ubiquitinates and promotes the degradation of the outer mitochondria membrane fusion protein, mitofusin-2. This results in an increase in mitophagy and ultimately leads to skeletal muscle wasting [33]. In addition to these novel regulatory proteins, histone deacetylase 1 and 2 (HDAC1/2) were shown to regulate skeletal muscle autophagy. HDAC1/2 were selectively knocked out in skeletal muscle, and the subset of mice that survived from birth went on to develop a progressive myopathy and impaired autophagy; however, the genes controlled by these HDACs are still unclear. [34]. Collectively, the field of skeletal muscle autophagy signal transduction is becoming more complicated with the identification of new players and the characterization of novel roles of old players. Yet, how all these fit into the larger picture of autophagic regulation and whether any hold pharmaceutical potential for combating muscle atrophy has yet to be addressed.

Features of Skeletal Muscle Autophagy

Skeletal muscle autophagy has many features that make it both unique and difficult to study. Autophagosomes in this tissue are the smallest among those studied, and upon autophagy activation they persist for up to 48 hours, compared to a few hours in other tissues such as liver [35]. Fortunately, the generation of the LC3-GFP mouse has provided a new tool to examine how autophagy is regulated in skeletal muscle [35]. LC3-II coats the surface of autophagosomes therefore adding a fluorescent tag to the protein allows one to visualize the presence of autophagic vacuoles. One conclusion made from studying autophagy is the intimate relationship between autophagy and lysosomes. Many of the lysosomal myopathies studied have features of dysregulated autophagy; however, the underlying factor in this phenotype is unknown [5]. Does lysosomal impairment cause dysregulated autophagy or does abnormal autophagy cause lysosomal dysfunction? Studies differentiating the two will be necessary to identify the core of the lesion and treat such myopathies.

Skeletal Muscle Autophagy: A Balancing Act

The skeletal muscle specific knockout of the required autophagy protein, Atg7, demonstrates the essential requirement of autophagy function in skeletal muscle [36]. However, the study of various myopathies begs the question: is autophagy protective or detrimental? Many studies have shown it is both, and a fine equilibrium of autophagic flux is needed to preserve muscle mass and prevent wasting. Figure 2 summarizes recent studies that have identified factors that play a role in skeletal muscle wasting. Interestingly, despite the very diverse functions of these proteins, genetic manipulation to activate or inhibit autophagy presents with similar underlying muscle wasting phenotypes. Upon comparing all these studies, it appears that muscle wasting from autophagy loss is a chronic process in which the buildup of damaged organelles and proteins takes time to elicit a phenotype. However, muscle atrophy from autophagy activation occurs within days to weeks due to a clearance of necessary organelles [37]. These studies reveal not only the necessity of autophagy, but also the importance of its proper regulation and response to appropriate stimuli.

Autophagy in Models of Muscular Dystrophic

Genetic studies of muscular dystrophy, a progressive, degenerative muscle disease, have revealed further insights into autophagy regulation. Examination of the collagen, type VI, $\alpha 1$ (Col6a1) knockout mouse uncovered defective autophagy, an accumulation of damaged organelles/proteins, loss of mitochondrial oxidative metabolism, and spontaneous apoptosis in skeletal muscle [38]. Mice also showed a decrease in beclin-1 and bnip3 levels, thus driving autophagy inhibition. On the other hand, restoration of beclin-1 levels re-activated autophagy and ameliorated the dystrophic phenotype. Low protein diet and rapamycin treatment were also effective in reversing the muscle dystrophy, lending to the physiological importance of mTOR in regulating skeletal muscle autophagy [38]. In another model of dystrophy, researchers found that dystrophin knockout (mdx) mice have damaged mitochondria leading to impaired oxidative metabolism, severe muscle weakness, and finally pulmonary arrest. Treatment with 5-aminoimidazole-4-carboxamide ribonucleotide (AICAR), an AMPK activator, resulted in the potent activation of autophagy, clearance of damaged mitochondria, and improvement of the dystrophic phenotype in the diaphragm [39]. These two critical studies also support that a delicate balance of autophagic flux is needed in the myocyte to ensure appropriate oxidative metabolism and muscle function.

Autophagy's Role in Exercise and Energy Metabolism

The connection between skeletal muscle autophagy and exercise was established decades ago, yet a few recent studies have furthered our understanding into how the two are linked

[40–42]. Nuclear receptor subfamily 1, group D member 1, Rev-erb- α (NR1D1) is a transcriptional repressor expressed in metabolic tissues and plays a role in lipid and glucose metabolism. The NR1D1 knockout mouse presents with excessive autophagy, impaired oxidative metabolism, and decreased mitochondrial content in skeletal muscle, compromising the exercise capacity of the mice. Conversely, overexpression of NR1D1 both *in vitro* and *in vivo* showed an increase in oxidative capacity and an increase in exercise capacity *in vivo* [41]. In another study, the molecular effects of the cytoprotective, anti-ischemic drug, trimetazidine (TMZ), was investigated. TMZ has previously been characterized to increase exercise capacity and in this current study, it was determined that TMZ activated the PI3K-Akt pathway and inhibited expression of the degradative proteins, MAFbx, MuRF1, and myostatin [43]. However, the inhibition of the PI3K-Akt pathway also resulted in an increase in autophagy, which was hypothesized to be beneficial for proper muscle mass maintenance and exercise capacity [40]. This study was performed in the C2C12 mouse derived myoblast cell line and thus *in vivo* studies are needed to fully understand the connection, yet the proposed link between skeletal muscle autophagy and exercise capacity is intriguing. Together, these studies provide insight into the regulation of exercise capacity by skeletal muscle autophagy, yet whether this is a direct or indirect effect is still unclear.

The connection of skeletal muscle autophagy to exercise capacity is interesting, yet the question remains whether autophagy can mediate the beneficial effects of exercise. Exercise has been found to induce Bcl-2 phosphorylation, providing a molecular link to autophagy regulation [44]. Bcl-2 mediated inhibition of beclin-1 is regulated by a variety of upstream kinases, including c-Jun N-terminal kinase 1 (JNK1) and p38 mitogen-activated protein kinase (p38 MAPK). These players phosphorylate Bcl-2 to promote its dissociation from beclin-1 and initiate autophagy [45,46]. Using knock-in techniques, a mouse model was developed with mutations in the phosphorylation sites of Bcl-2 that regulate exercise-induced autophagy without disrupting basal autophagy. These mice showed decreased exercise endurance and impaired exercise-induced glucose uptake due to a loss in glucose transporter 4 (GLUT4) translocation. Moreover, a high fat diet predisposed the mice to glucose intolerance. This study illustrates that skeletal muscle autophagy can play a role in the beneficial effects of exercise on glucose homeostasis. However, whether that metabolic role is a direct consequence of autophagy or an indirect result through other means has yet to be established. [44].

The study of a novel growth factor, fibroblast growth factor 21 (FGF21), revealed another layer in the complex relationship between autophagy and metabolism. The skeletal muscle Atg7 knockout model was found to have impaired oxidative metabolism, which was accompanied by the induction of FGF21. This factor promoted the browning of white adipose tissue (WAT), decreased WAT mass, and protected mice from high fat diet-induced obesity as well as insulin resistance [47]. These findings are indirect results from a loss of autophagy but will provide insights into the response of this genetic manipulation. For example, the increase in adipose oxidative metabolism is likely an adaptive response to the decreased oxidative metabolism in skeletal muscle; however, further studies are needed to determine the function of this response. In a larger picture, the direct role of autophagy in metabolic aspects such as insulin sensitivity and weight gain susceptibility remain unclear.

Nutrient Trafficking

Autophagy has classically been shown to take cytoplasm, protein aggregates, and organelles to the lysosome for degradation. However, more recently, a new appreciation has emerged for the role of autophagy in nutrient trafficking and the role of the lysosome in nutrient breakdown, a phenomenon illustrated by a number of human diseases. For example, the loss

of the lysosomal glucosidase, GAA, in Pompe's disease causes a severe skeletal muscle wasting. This is caused by the loss of functional lysosomes due to being swollen with glycogen and undergoing deacidification. Autophagy is also unregulated in the myofibers as an excessive accumulation of glycogen filled autophagosomes is present [48]. Likewise, patients with Wolman disease or cholesterol ester storage disease lack functional lysosomal lipase (LIPA) and have been characterized with muscle myopathies [49]. Even though not yet investigated, the buildup of triglycerides in autophagosomes and lysosomes could be the underlying culprit, much like that seen with glycogen in Pompe's disease. Other lysosomal storage diseases such as Tay-Sachs (hexosaminidase A deficiency), Gaucher (glucocerebrosidase deficiency), and Niemann-Pick (sphingomyelinase deficiency) disease all present with skeletal myopathies in one if not all of the clinical subtypes [4,20,50]. Similarly, glycogen storage diseases like Danon's (lysosome-associated membrane protein 2a [Lamp2a] deficiency), XMEA (vacuolar ATPase assembly integral membrane protein [VMA21] deficiency), and Pompe's disease show dysregulated autophagy and present with severe myopathy as well as a prominent pathology of excessive autophagosomes along the myofibers [5,51,52]. A functional lysosome is necessary for autophagosome fusion and activation of mTORC1 by amino acids, yet what connects a lysosomal defect to dysregulated autophagy is still under debate [53,54]. Collectively, these human diseases demonstrate the importance of having intact skeletal muscle autophagy and functional lysosomes in order to break down nutrients.

Despite the evident importance of this process, basic questions have yet to be addressed regarding how these physiological processes occur. How do lipids and carbohydrates like glycogen enter the autophagosome? How do the resulting free fatty acids and glucose exit the lysosome? Do these catabolic pathways have physiological significance with regards to systemic nutrient regulation? How important is GAA in comparison to glycogen phosphorylase; and similarly, how critical is LIPA in comparison to hormone sensitive lipase/adipocyte triglyceride lipase? Studies are needed to address these vital questions in order to fully understand the mechanisms at work in these lysosomal myopathies. The importance of autophagic trafficking of lipids has recently been further clarified with the discovery of lipophagy, the specific autophagy of lipids, but no studies have addressed if such a process occurs in skeletal muscle [55–58]. Moreover, the possibility of a role for the autophagic trafficking of glycogen in skeletal muscle is also unclear.

Concluding Remarks and Future Perspectives

Recent studies have vastly added to our understanding of the molecular mechanisms of skeletal muscle autophagy and the role it plays in muscle metabolism. New relationships have been uncovered that both elucidate and complicate the study of muscle autophagy. Many diseases exemplify the close connection between autophagy and the lysosome, yet the interplay between the two is still unclear. Despite our knowledge regarding the trafficking of a wide array of cellular components to the lysosome, including nutrients such as lipids and carbohydrates, its physiological importance is still unknown. Most importantly, understanding how autophagy is connected to muscle wasting and what factors define the dynamic balance between skeletal muscle hypertrophy and atrophy are critical to our ability to treat myopathic conditions (Box 3). Continued studies investigating the mechanisms of skeletal muscle autophagy and its relationship to muscle mass as well as energy metabolism will lead to discoveries of new signaling pathways and regulators. In time, these discoveries may identify new therapeutic targets for the various debilitating myopathic diseases we are confronted with today.

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Glossary

Autophagy-related gene (ATG)	a conserved family of over 30 autophagy-related proteins that function at various steps within the autophagic signal transduction pathway.
Forkhead box O3 (FoxO3)	a transcription factor and member of the O subclass of forkhead box proteins. It is regulated primarily by Akt via phosphorylation. Phosphorylated FoxO3 is retained in the cytoplasm and unable to activate target gene transcription. FoxO3 regulates the expression of vital degradative proteins in skeletal muscle, such as those that function in the proteasomal and autophagic pathways.
Lipophagy	a specific autophagic process used to traffic lipids to the lysosome. The acidic lipase, LIPA, then functions to degrade lipids to their free fatty acid components and the resulting nutrients are released from the lysosome.
Lysosome	an organelle specifically utilized to digest cellular components delivered to it via autophagy or endosomal trafficking. It is characterized by an acidic environment comprised of acid hydrolase enzymes used to digest incoming organelles, proteins, and cytoplasm.
Macroautophagy	a conserved physiological process by which the cell degrades cytoplasm, proteins, and/or organelles via transportation in an autophagosome to the lysosome. This pathway functions to degrade damaged or aged cellular components, break down undedicated nutrient stores, or alter cellular architecture/morphology.
Mammalian target of rapamycin (mTOR)	a conserved serine threonine kinase that is part of larger protein complexes (mTORC1/mTORC2). It functions as a nutrient sensor by sensing incoming signals from amino acids and growth factors. This is coupled to the regulation of downstream pathways controlling such processes as protein synthesis, autophagy, energy metabolism, lipid synthesis, and lysosome biogenesis.
Myodystrophy	a group of genetic diseases resulting in progressive muscle wasting, also called muscular dystrophy.
Myopathy	refers to a decline in muscle function leading to weakness, pain, and loss of movement due to a variety of conditions such as inactivity, denervation, and systemic diseases.
Skeletal Muscle	one of three types of muscle characterized by their connection to bone via tendons that enable voluntary bodily movements. Skeletal muscle is comprised of elongated, multinucleated cells termed myofibers that are made of organized, repeating cylinders of myofibrils. These contain the basic contractile unit called the sarcomere, which contains the filament, actin, and the motor protein, myosin. Skeletal muscle can be broken down into two

main subtypes: red, slow, oxidative, type I and white, fast, glycolytic, type II muscle.

Box 1: Brief Overview of Autophagy

Autophagy is controlled by many cellular pathways and the evolutionary conserved Atg proteins. This physiological process can fall into three general steps: i) initiation, ii) nucleation/autophagosome formation, and iii) lysosome fusion/degradation [3,31].

Initiation: Nutrients are the main physiological regulators of autophagy. The lack of nutrients and hormones during fasting like insulin and insulin-like growth factor 1 (IGF-1) are important inducers of skeletal muscle autophagy. During fasting, Akt, is inactive whereas AMPK is activated, resulting in activation and inactivation of FoxO3 and mTOR, respectively. FoxO3 induces transcription of Atg proteins and the E3 ubiquitin ligases MuRF1 and MAFbx [15]. On the other hand, the inactive mTOR complex cannot bind to and phosphorylate ULK1, thus allowing the active ULK1 complex to initiate nucleation [8,13]. Bcl-2 and other members of the BH3 protein family also regulate autophagy initiation by directly interacting with the beclin-1 nucleation complex. Bcl-2 resides on the endoplasmic/sarcoplasmic reticulum (ER/SR) membrane in a complex with NAF-1 and IP3R. Upstream kinases like JNK1 or p38MAPK can phosphorylate Bcl-2 and dissociate it from the beclin-1 complex, therefore acting as autophagy inducers [2,59].

Nucleation: The beclin-1 complex is necessary for autophagy as it initiates the nucleation of the phagophore. Beclin-1 complexes with a variety of proteins, including Atg14, Vps15, UVRAG, Rubicon, and the class III PI₃K, Vps34 [54]. Together, this complex can produce the nucleating lipid species, PI3P, and initiate the elongation of the nascent phagophore. The nucleation also necessitates the E1 and E2 ubiquitin ligases, Atg7 and Atg10, respectively. These facilitate the conjugation of Atg5 to the ubiquitin-like Atg12 and phosphatidylethanolamine to the ubiquitin-like Atg8/LC3 [60]. The forming autophagosome can then sequester cytoplasm, proteins, and organelles.

Lysosome fusion/degradation: The mature autophagosome is then trafficked to the lysosome where fusion occurs. The cargo of the autophagosome can then be degraded by specific lysosomal enzymes in a structure called an autolysosome. Lysosomal lipases or glucosidases break down lipids and carbohydrates to their respective components, and a variety of other hydrolases break down proteins into amino acids which can then pass out of the lysosome via undefined transporters or be exocytosed via the unclear method of lysosomal exocytosis [52].

Box 2: Fiber Type Differences

Type 1 skeletal muscle fibers can be categorized as red, slow twitch, or oxidative muscle. High in myoglobin and mitochondria, these fibers primarily undergo oxidative metabolism, and are resistant to fatigue. On the other hand, type II skeletal muscle fibers can be categorized as white, fast twitch, or glycolytic muscle. These fibers are relatively low in myoglobin and mitochondria, primarily undergo glycolytic metabolism, and are susceptible to fatigue [18]. A comparison of autophagy between muscle fibers found basal levels of autophagy similar to other tissues in white muscle, and nearly no basal autophagy in red muscle. Autophagic rates in white muscle can be moderately up regulated with starvation after 24 hours, whereas in red muscle, a slight induction was observed after a 24-hour fast and a moderate increase after 48 hours [35].

Studies have also found that there are fiber type differences in the response to stimuli that induce myopathy. For example, the myopathy seen in Pompe's disease primarily affects white muscle. A skeletal muscle specific transgenic mouse model of the non-receptor tyrosine kinase, Fyn, which inhibits AMPK via liver kinase B1 also exhibits selective white muscle wasting [61,62]. Furthermore, recent work has identified that Fyn has higher levels of endogenous activity in white muscle, leading to a Fyn/signal transducer and activator of transcription 3 (STAT3)/Vps34 autophagy signaling pathway that potentially explains the fiber type specific muscle wasting [63]. Aged skeletal muscle also presents with a selective white muscle wasting, termed sarcopenia; however, the role of autophagy in aging myopathy is unclear [64,65]. On the other hand, studies have elucidated that the red soleus muscle is susceptible to denervation- and microgravity-induced myopathy [66,67]. The underlying mechanisms controlling fiber type specific muscle atrophy are unknown, yet there are many targets that are being investigated [68].

A key discussion in the field remains whether the regulatory or autophagic machinery itself is different between fiber types, creating the selective phenotypes, or is it some other intrinsic aspect of the fibers that is responsible? In an attempt to understand this question, many investigations have examined players that control fiber type switching. Overexpression or activation of factors such as peroxisome proliferator-activated receptor gamma, co-activator 1 alpha, calcineurin, or peroxisome proliferator-activated receptor gamma, changes gene expression profiles in white muscle fibers to become more like red fibers; however, these studies have had very little success in completely reversing the fiber type selective phenotype [69–72].

BOX 3: Emerging questions and trends

Questions:

- What is the relationship between the lysosome and autophagy? Does lysosomal impairment dysregulate autophagy or does a lesion in autophagy lead to lysosomal abnormalities?
- What factors discern whether autophagy is protective or detrimental to the cell? What are the major cellular players that sway this equilibrium?
- How do lipids and carbohydrates traffic to the lysosome? How do FFAs and glucose get released from the lysosome?
- Does lysosomal breakdown via GAA and LIPA have a physiological effect on systemic nutrient availability?
- What are the molecular differences in autophagic regulation between white and red muscle fibers and why do they exist?
- Do any of the autophagy proteins have non-canonical roles that regulate energy metabolism?

Trends:

- Many metabolic regulators, like mTORC1 and FOXO3, classically control skeletal muscle autophagy. However, the current literature using knockout models and other techniques to analyze these components on autophagic regulation have confounding results. Studies are needed to further clarify the signaling pathways and interactions between these core components.
- In recent years many new players have been implicated in the regulation of skeletal muscle autophagy. They consist of a diverse set of proteins regulating various arms of autophagy. How they all fit into the larger picture of skeletal muscle autophagy and whether any have potential to be pharmaceutical targets has yet to be established.
- Recent studies have demonstrated that autophagy is not an on/off process. A fine equilibrium of skeletal muscle autophagy exists and swaying that balance in either direction leads to muscle wasting. What factors regulate this equilibrium and how that is achieved is an area of future interest.
- Classically, the breakdown of intracellular nutrient stores is controlled by proteins, glycogen phosphorylase (glycogen to glucose) and hormone sensitive lipase (triglycerides to free fatty acids). However, recent studies have identified a critical glycosidase (GAA) and lipase (LIPA) within the lysosomal lumen that potentially plays a role in nutrient breakdown via autophagy or endosomal trafficking. Many questions remain as to how this process occurs and how important it is for systemic regulation of energy metabolism.

Highlights

- The skeletal muscle autophagy signaling pathways contain many new, novel regulators.
- The benefits of exercise involve regulating skeletal muscle autophagy.
- Skeletal muscle autophagy requires a very fine balance for healthy muscle.
- Stored nutrients can be trafficked by autophagy and broken down in the lysosome.

Figure 1. Overview of signal transduction pathways controlling skeletal muscle autophagy Multiple inputs from various signaling cascades summate at the autophagosome nucleation step. The beclin1/Vps34 complex is the core component of nucleation and is positively regulated by the IP₃R/Bcl-2/Naf-1 complex and negatively regulated by the lipid phosphatase, MTMR14. Nucleation also responds to nutrients like insulin and IGFs via mTORC1. mTORC1 can phosphorylate Ulk-1, inhibiting its complex with Atg13 and FIP200. Atg7 catalyzes the ligation of Atg5 to Atg12, and phosphatidylethanolamine to LC3-I, now termed LC3-II. These processes are necessary for the maturation of the full autophagosome, which can then transport sequestered cellular components to the lysosome. FoxO3 upregulates the E3 ubiquitin ligases, MuRF1 and MAFb, Bnip3, and Mul-1, which all promote degradation via the proteasome or the lysosome. ChKβ functions to synthesize phosphatidylcholine, which can promote mitophagy. HDAC1/2 can promote autophagic flux via alterations in gene expression but the specific genes remain unknown.

Abbreviations: IP₃R, inositol-3-phosphate receptor; Bcl-2, B-cell lymphoma 2; Naf-1, nutrient-deprivation autophagy factor-1; Vps34/15, vacuolar protein sorting 34/15; Atg5/7/12/13/14, autophagy related protein 5/7/12/13/14; UVRAG, UV radiation resistance associated gene; LC3I/II, microtubule-associated protein 1 light chain 3I/II; MTMR14, myotubularin-related protein 14; Ulk-1, Unc51-like kinase 14; FIP200, FAK family kinase-interacting protein of 200kDa; mTORC1, mammalian target of rapamycin complex 1;

IGF-1, insulin-like growth factor 1; AMPK, AMP-activated kinase; FoxO3, forkhead box O3, Bnip3, Bcl-2/adenovirus E1B 19kDa interacting protein 3; MuRF1, muscle specific RING finger protein 1; MAFbx, muscle atrophy F-Box Protein; Mul-1, mitochondrial E3 ubiquitin protein ligase 1; Mfn2, mitofusin2; ChK β , choline kinase β ; PC, phosphatidylcholine; HDAC1/2, histone deacetylase 1/2; ER, endoplasmic reticulum;

Figure 2. A hypothetical diagram of the development of muscle wasting diseases. The equilibrium of skeletal muscle autophagy is important for maintaining muscle mass and maintaining healthy skeletal muscle. An imbalance due to a number of factors such as diet, physical activity, systemic disease, or genetics can cause a shift in the autophagic flux. Excessive autophagy will cause a quick loss in muscle mass (days to weeks) due to the continued clearance of necessary cellular components. Insufficient autophagy will cause a chronic loss in muscle mass (weeks to months) due to the buildup of damaged or aged cellular components. Despite these two different etiologies, the outcome remains the same. A loss of muscle mass will lead to myopathy with very similar phenotypes, both in mouse models and human diseases.