

Review

Fine-Tuning Autophagy in Skeletal Muscle: From Homeostasis to Muscle Wasting Disorders

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ABSTRACT: Skeletal muscle homeostasis and regenerative capacity depend on efficient protein turnover, organelle quality control, and metabolic adaptation. Disruption of these processes contributes to muscle atrophy and functional decline during aging and various pathological conditions. Autophagy, a lysosome-dependent degradative pathway, maintains muscle integrity by clearing damaged proteins and organelles, preserving mitochondrial quality, and supporting muscle stem cell (MuSC) function. Both insufficient and excessive autophagy are detrimental: reduced flux impairs proteostasis, mitochondrial function, and regeneration, whereas hyperactivation drives excessive protein degradation, mitochondrial loss, and muscle wasting under stress. This review discusses molecular mechanisms regulating autophagy in skeletal muscle, including nutrient- and energy-sensing pathways (AMPK and mTORC1), transcriptional control of autophagy and lysosomal genes, and mitochondrial modulators. Evidence from genetic models and disease contexts indicates that both insufficient and excessive autophagy are associated with muscle degeneration, highlighting the need for balanced autophagic control rather than simple activation or inhibition. Together, these observations support a conceptual framework in which skeletal muscle health depends on maintaining autophagic activity within a context-dependent functional range, although this range is not yet quantitatively defined. This framework provides a useful basis for considering therapeutic strategies targeting muscle wasting.

Keywords: Autophagy, muscle aging, muscle stem cell, muscle diseases

1. Introduction

Skeletal muscle is a highly plastic and metabolically active tissue, comprising nearly 40% of adult body mass and playing essential roles in locomotion, posture, glucose homeostasis, and systemic energy metabolism [1, 2]. Loss of muscle mass and function—whether during aging, cancer cachexia, or muscular dystrophies—leads to impaired mobility, metabolic dysfunction, increased frailty, and elevated mortality risk [3-5]. Given its central role in health, understanding the molecular processes that preserve muscle integrity and regenerative capacity is therefore of major physiological and clinical importance.

Autophagy, a lysosome-dependent degradative pathway, plays a central role in maintaining skeletal muscle integrity and metabolic homeostasis. By selectively removing damaged proteins and dysfunctional

organelles, autophagy sustains proteostasis, mitochondrial quality, and metabolic flexibility in long-lived, post-mitotic myofibers [6]. Autophagy also supports muscle adaptation to physiological stressors such as fasting and exercise and is essential for muscle stem cell (MuSC) maintenance and regeneration [7-12].

Autophagy exists in three primary forms: chaperone-mediated autophagy (CMA), microautophagy, and macroautophagy. CMA mediates the selective lysosomal degradation of proteins containing a KFERQ-like pentapeptide motif, which are recognized by HSC70 (heat shock cognate 70 kDa protein) and delivered to lysosomes for degradation [13]. Microautophagy refers to the direct engulfment of cytoplasmic components by the lysosome, a process that involves lysosomal membrane invagination forming inward tubular protrusions, followed by vesicle formation, expansion, scission, and degradation [14]. In

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macroautophagy, the double-membrane phagophore expands to sequester cytoplasmic components, forming an autophagosome that encloses intracellular materials [15-18]. The autophagosome then fuses with lysosomes, leading to degradation of its contents [19]. This process includes initiation, vesicle nucleation, elongation, maturation, and fusion [14, 20].

Autophagy in skeletal muscle is dynamically regulated by physiological stimuli, such as exercise, starvation, and hypoxia, as well as by pathological stressors, including aging, diabetes, and muscular dystrophies [11, 21-26]. Proper autophagic activity is essential for muscle integrity, regeneration, and functional maintenance, whereas impaired autophagy contributes to muscle atrophy and aging through multiple signaling pathways involving AMPK, ULK1, TP53/INP2, and FOXO [27-37].

Importantly, autophagy is context-dependent. Basal autophagy maintains mitochondrial quality and prevents muscle loss, whereas excessive autophagic activity contributes to cancer or inflammation-induced muscle wasting [38-42]. Together, these observations support a conceptual framework in which skeletal muscle health depends not on maximal or minimal autophagic activity,

but on maintaining autophagy within a context-dependent functional range. Importantly, this framework should be viewed as a theoretical model derived from multiple experimental observations rather than a quantitatively defined threshold. In this review, we discuss the regulation of autophagy in skeletal muscle and its dual roles in maintaining muscle homeostasis and driving muscle wasting.

2. Autophagy is essential for skeletal muscle homeostasis and regeneration

2.1 Basal autophagy safeguards myofiber integrity and muscle homeostasis

Skeletal muscle fibers are long-lived, post-mitotic cells that cannot dilute damaged proteins or organelles through cell division; therefore, maintenance of muscle integrity relies critically on intracellular quality control systems that ensure continuous cytoplasmic turnover. Accumulating evidence indicates that basal autophagy is indispensable for maintaining skeletal muscle mass, structural integrity, and regenerative capacity [32, 33, 43] (Fig. 1).

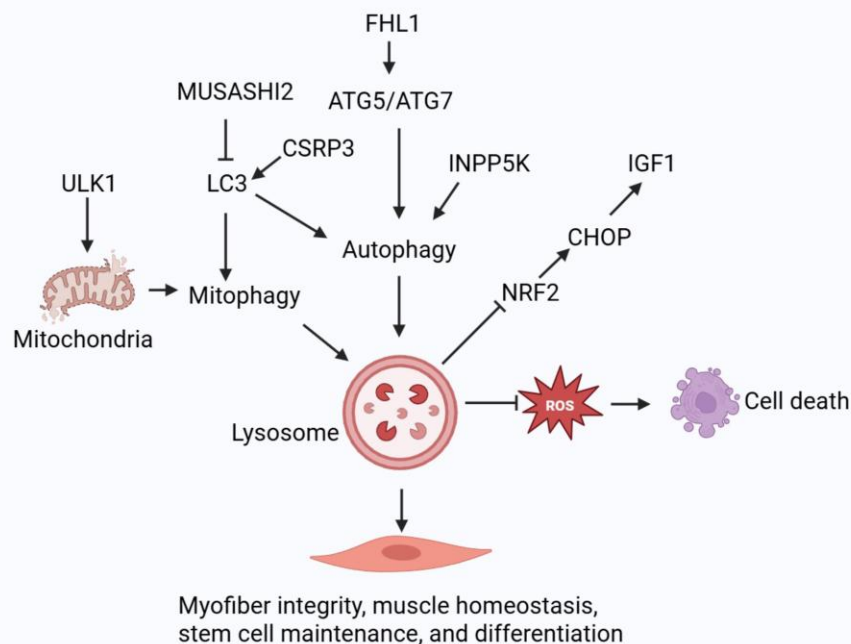


Figure 1. Autophagy is essential for skeletal muscle homeostasis and regeneration. Basal autophagy safeguards skeletal muscle integrity through the ULK1 kinase and core autophagy machinery (ATG5/ATG7), which drive autophagosome formation and mitophagy to ensure mitochondrial quality control and cytoplasmic turnover in post-mitotic myofibers. Disruption of these pathways, including INPP5K-mediated autophagic lysosome reformation, precipitates muscular dystrophy-like phenotypes and contractile dysfunction. In muscle stem cells, autophagy regulates myogenic differentiation via the NRF2-CHOP-IGF1 signaling axis and LC3-dependent autophagosome formation. Specifically, FHL1 and CSRNP3 promote myoblast differentiation by enhancing ATG5/ATG7 expression and LC3 interaction, whereas MUSASHI2 suppresses LC3 to inhibit autophagy and drive atrophy. Collectively, these molecular circuits constitute a critical regulatory network coordinating myofiber maintenance, stem cell survival, and regenerative capacity.

Genetic studies using conditional knockout models provide strong evidence that basal autophagy is required for skeletal muscle maintenance. ULK1, a key kinase that initiates autophagosome formation [44], is essential for mitochondrial quality control in muscle [45]. Muscle-specific deletion of *Ulk1* impairs mitochondrial network remodeling and force recovery following acute injury [45], while lifelong *Ulk1* deficiency results in mitochondrial dysfunction and reduced contractile performance [46]. Similarly, the core autophagy genes *Atg5* and *Atg7* are indispensable for autophagosome biogenesis [47, 48]. Muscle-specific deletion of *Atg7* or *Atg5* results in profound skeletal muscle atrophy accompanied by a marked decline in muscle strength [33, 49]. In addition, deletion of *Inpp5k*, a regulator of autophagic lysosome reformation, suppresses autophagy and promotes progressive muscular dystrophy-like phenotypes [32]. Collectively, these studies establish basal autophagy as a central mechanism safeguarding skeletal muscle integrity, survival, and functional maintenance.

2.2 Autophagy regulates muscle stem cell maintenance and myogenic differentiation

Beyond its role in mature myofibers, autophagy is equally critical for muscle stem cell (MuSC) maintenance and myogenic differentiation. Genetic ablation of *Atg7* in muscle progenitor cells blocks autophagy, activates NRF2 and CHOP signaling, suppresses IGF1 production, and ultimately leads to defective neonatal myogenesis characterized by reduced muscle mass and impaired myofiber maturation [34]. Consistently, in L6 skeletal muscle cells, *Atg7* deficiency impaired autophagic flux and markedly exacerbated iron-induced oxidative stress and apoptotic cell death [35]. In contrast, activation of autophagy promotes myogenic differentiation and muscle regeneration. Four and a half LIM domain protein 1 (FHL1) enhances myoblast differentiation by inducing *Atg5* and *Atg7* expression and stimulating autophagic activity [36]. Mechanistically, LC3-dependent autophagosome formation is required for proper myogenic progression. MUSASHI2 suppresses LC3 expression and autophagy, thereby inhibiting myoblast differentiation and promoting muscle atrophy [50]. In contrast, CSRP3 directly interacts with LC3 to enhance autophagosome formation and autophagic flux, supporting muscle remodeling and structural maintenance [51]. These findings indicate that autophagy functions as a critical regulatory axis coordinating myogenic differentiation, muscle stem cell survival, and regenerative capacity. Impairment of this pathway disrupts developmental myogenesis and compromises long-term muscle maintenance.

3. Molecular regulation of autophagy signaling in skeletal muscle

The essential role of basal autophagy in maintaining muscle integrity raises a key question: how is autophagy dynamically tuned under physiological and pathological conditions? In skeletal muscle, autophagy is primarily regulated by nutrient- and energy-sensing signaling networks, with the AMPK–mTORC1 axis functioning as the central regulatory hub that balances catabolic and anabolic processes (Fig. 2).

3.1 AMPK signaling axis links energy stress to autophagy

AMPK functions as a master cellular energy sensor that activates autophagy in response to energetic stress. Upon activation, AMPK directly phosphorylates ULK1, initiating autophagosome formation and promoting autophagic flux [52]. Consistent with this mechanism, studies in human and mouse skeletal muscle have shown that exercise activates AMPK signaling in parallel with enhanced autophagy [53], and that AMPK-mediated ULK1 phosphorylation is required for exercise-induced mitophagy [54]. Loss of AMPK in skeletal muscle impairs fasting-induced autophagy and results in myopathic phenotypes, highlighting its essential role in adaptive autophagy [55, 56]. Activation of the AMPK–ULK1 pathway preserves mitochondrial quality and protects against muscle atrophy [29, 52, 57].

Beyond activation of ULK1, AMPK also regulates transcriptional programs controlling lysosomal biogenesis and autophagy gene expression. Upon energetic stress, AMPK promotes nuclear relocalization and activation of FOXO3a in skeletal muscle, driving the expression of autophagy-related genes such as *LC3B*, *Gabapll1*, and *Beclin1* in primary myotubes and *in vivo* skeletal muscle [55, 56]. AMPK has also been linked to lysosomal and autophagy-related transcription through CARM1-related mechanisms [58], further supporting adaptive autophagy under energetic stress. Collectively, these findings suggest that AMPK coordinates both autophagy initiation and sustained transcriptional reinforcement of the autophagic machinery.

In metabolic disease contexts, including obesity and diabetes, impairment of AMPK–ULK1 signaling contributes to defective autophagy and accelerated muscle degeneration. Restoration of AMPK signaling—through exercise or pharmacological intervention—partially rescues autophagic defects and improves muscle function [57, 59]. Together, these findings establish AMPK as a key driver of adaptive autophagy during metabolic and energetic stress.

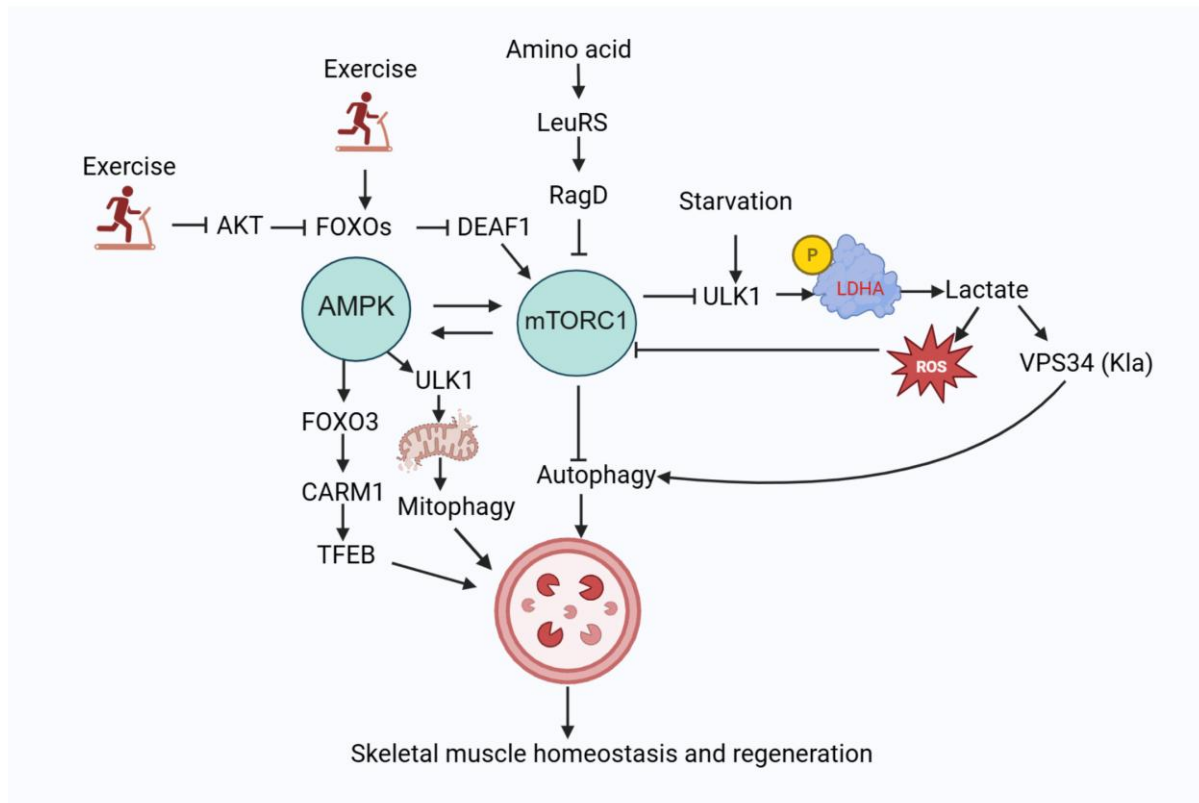


Figure 2. Molecular regulation of autophagy signaling in skeletal muscle. In skeletal muscle, the AMPK–ULK1 axis functions as a pivotal energy-sensing pathway that activates autophagosome formation and mitochondrial quality control, while concurrently engaging the transcriptional programs that enhance autophagy and lysosomal function to drive lysosomal biogenesis. Conversely, mTORC1 integrates growth factor and amino acid signals to antagonize autophagy through dual phosphorylation of ULK1 and TFEB, thereby suppressing autophagosome initiation and lysosomal gene expression. Upon metabolic stress, suppression of mTORC1 relieves this inhibition, triggering a feed-forward loop wherein ULK1-mediated lactate production promotes VPS34 lactylation to amplify autophagic flux. This signaling balance is further shaped by transcriptional and kinase-dependent regulatory mechanisms, ensuring coordinated control of anabolic and catabolic programs.

3.2 mTORC1 antagonizes autophagy activation in muscle

In contrast to AMPK, mTORC1 integrates growth factor and amino acid signals to promote anabolic metabolism while suppressing autophagy [60–63]. mTORC1 represses autophagy through coordinated inhibition of both autophagosome initiation and lysosomal biogenesis [64, 65]. Mechanistically, mTORC1 phosphorylates TFEB, preventing its nuclear translocation and transcriptional activation of lysosomal and autophagy-related genes [66, 67]. Simultaneously, mTORC1 phosphorylates ULK1, directly inhibiting autophagosome initiation [68]. Together, these mechanisms restrict both lysosomal biogenesis and autophagosome formation, thereby reducing autophagic activity.

Under metabolic stress conditions, suppression of mTORC1 activity permits ULK1-dependent autophagy activation. During starvation, ULK1 phosphorylates

lactate dehydrogenase A (LDHA), increasing lactate production and secretion. Lactate subsequently promotes VPS34 lactylation, which enhances autophagosome formation and reinforces autophagy induction [69]. In differentiated myotubes, lactate-induced ROS generation further stimulates autophagy while suppressing mTOR signaling, forming a metabolic feed-forward loop that amplifies autophagic responses during energetic stress [70].

Physiological inhibition of mTORC1, such as during exercise, promotes autophagy and supports muscle remodeling. Exercise suppresses AKT–mTORC1 signaling, facilitating autophagy activation and fiber-type adaptation [24, 71]. In aging muscle, chronic mTORC1 hyperactivation contributes to autophagy suppression and sarcopenia. This pathogenic link is supported by skeletal muscle-specific TSC1 deletion, where sustained mTORC1 activation inhibits constitutive and starvation-induced autophagy via ULK1 despite FOXO3 activation,

leading to a late-onset myopathy that is ameliorated by rapamycin [72, 73]. Additionally, 4EBP1 activation restores autophagy flux and lysosomal protease activity in TSC1-deficient muscle without relieving mTORC1-mediated ULK1 inhibition, suggesting that chronic mTORC1 hyperactivity impairs not only autophagosome initiation but also downstream lysosomal degradative capacity [74]. Exercise restores autophagy partly by inhibiting AKT–mTOR signaling and improving muscle function [24]. Together with the established inhibition of FOXO3 by AKT signaling [30], these observations support bidirectional crosstalk between anabolic signaling and autophagy-related transcription in skeletal muscle. Recent work suggests that exercise-responsive FOXO signaling may modulate mTORC1 activity through FOXO-dependent repression of DEAF1, a transcriptional regulator of mTOR expression [11].

In addition to growth factor signaling, dysregulated amino acid sensing can pathologically activate mTORC1. For example, activation of mTORC1 via the LeuRS–RagD pathway suppresses autophagic flux and promotes muscular dystrophy. Pharmacological disruption of the LeuRS–RagD interaction using the LeuRS inhibitor BC-LI-0186 restores autophagy and improves muscle pathology in mdx mice [75]. Collectively, these findings highlight that precise regulation of mTORC1 activity is essential for balancing anabolic signaling and autophagic degradation in skeletal muscle.

3.3 Interpreting autophagy flux in skeletal muscle

Autophagy is a multistep process encompassing initiation, autophagosome formation, autophagosome–lysosome fusion, and lysosomal degradation [76, 77]. Effective autophagic flux therefore depends not only on autophagosome biogenesis but also on intact lysosomal function and completion of cargo clearance [78].

Experimentally, autophagy is commonly assessed by measuring LC3 lipidation (LC3-II levels or the LC3-II/LC3-I ratio) together with cargo adaptors such as p62/SQSTM1 [79]. However, these static markers primarily reflect autophagosome abundance and cannot distinguish enhanced initiation from impaired degradation; importantly, autophagy induction does not necessarily equate to successful completion of the degradative process [78]. Interpretation is further complicated by transcriptional regulation of autophagy-related genes, whereby increased LC3 or p62 levels may arise from elevated synthesis rather than enhanced degradative throughput [80]. Moreover, autophagic flux ultimately requires intact lysosomal competence. Defects in autophagosome–lysosome fusion or lysosomal proteolysis may lead to accumulation of autophagic structures despite reduced cargo clearance [81, 82].

These methodological considerations are particularly relevant in aging contexts. While reduced autophagic efficiency is widely reported in aged muscle [83–85], LC3-II accumulation or increased expression of autophagy-related genes has also been observed [86, 87]. Aging is frequently accompanied by lysosomal dysfunction—including impaired acidification and reduced proteolytic capacity—which may impair cargo clearance and promote persistence of autophagic structures [88–90]. Thus, increased autophagosome markers do not necessarily contradict the concept of functional autophagy decline.

In addition, skeletal muscle heterogeneity and experimental model differences further influence interpretation. Distinct fiber types exhibit divergent metabolic profiles and basal autophagy levels, which may confer differential sensitivity to aging or stress [89, 91, 92]. Moreover, although chronic suppression of autophagic flux contributes to age-associated degeneration, genetic inhibition of autophagy in certain acute stress models, such as sepsis, may exacerbate muscle injury [93]. These findings underscore the context-dependent and stage-specific roles of autophagy. Thus, accurate interpretation of autophagy dynamics requires integrated assessment of autophagic flux along with careful consideration of methodological and biological context. These limitations also indicate that the “optimal autophagic range” discussed in this review should currently be regarded as a conceptual framework rather than a quantitatively measurable threshold.

4. Decline in autophagy drives skeletal muscle atrophy

4.1 Age-associated autophagy decline drives skeletal muscle atrophy

Autophagy is a conserved process responsible for degrading intracellular components and recycling nutrients, particularly under conditions of stress or nutrient deprivation. Increasing evidence indicates that autophagy is impaired during aging, contributing to skeletal muscle atrophy and mitochondrial dysfunction [24, 27, 29, 71, 94]. SIRT1, a key regulator of autophagic flux, exhibits reduced activity with age, and muscle-specific deletion of *Sirt1* markedly suppresses autophagy, resulting in tibialis anterior (TA) muscle atrophy and functional decline [95]. Consistently, pharmacological or nutritional interventions that restore autophagic activity demonstrate protective effects against muscle aging [21–23]. For example, resveratrol enhances SIRT1 activity, restores autophagic flux, and attenuates age-related motor dysfunction and TA muscle atrophy [95]. Similarly, urolithin A improves muscle function in aged mice via mitophagy induction, despite minimal effects on muscle

mass [96]. Collectively, these findings indicate that age-associated autophagy insufficiency contributes to skeletal muscle functional decline.

Among selective autophagy pathways, mitophagy is particularly critical in skeletal muscle aging. It selectively eliminates damaged mitochondria, thereby preserving mitochondrial integrity [97]. Disruption of mitophagy leads to accumulation of dysfunctional mitochondria, increased oxidative stress, impaired energy production, and ultimately progressive muscle atrophy [24, 27, 29, 94]. Multiple studies indicate that mitophagy capacity declines with age, directly contributing to mitochondrial defects and muscle degeneration. Mechanistically, age-associated reduction of MFN2 promotes ROS-mediated activation of HIF1 α , which suppresses mitophagy and exacerbates mitochondrial defects [87], while loss of the mitochondrial fission protein DRP1 similarly disrupts mitophagy and induces severe muscle atrophy [98]. Importantly, mitophagy defects in aged muscle are at least partially reversible: exercise training restores mitophagy via AMPK activation and improves mitochondrial quality [24, 59, 71], and pharmacological intervention with reversine enhances mitophagy and attenuates muscle aging [27].

While mitophagy represents a central mechanism of mitochondrial surveillance in skeletal muscle, aging-related proteostatic imbalance is not restricted to mitochondrial turnover. Aggrephagy, mediated by SQSTM1 and NBR1, governs the selective clearance of misfolded and damaged ubiquitinated protein aggregates that progressively accumulate in aged myofibers [99, 100]. In parallel, chaperone-mediated autophagy (CMA), dependent on LAMP2A, is reduced in aging muscle, and its decline has been mechanistically linked to defective Ca²⁺ homeostasis and diminished muscle force generation [83]. These findings suggest that impaired selective autophagy broadly contributes to functional decline in aging skeletal muscle.

4.2 Autophagy insufficiency drives muscle degeneration in disease conditions

Reduced autophagic activity also contributes to muscle degeneration under pathological conditions, including Duchenne muscular dystrophy (DMD), diabetes, and obesity-associated metabolic disorders. In dystrophic muscle, particularly in the mdx mouse model of DMD, restoration of autophagic flux via low-energy light therapy (LEDT), idebenone, betaine, or sodium butyrate attenuates myofiber degeneration and improves muscle strength through activation of distinct autophagy-regulatory pathways, such as METTL21C-p97/VCP-mediated proteostasis and GPR109A-PPAR γ signaling [21-23]. In metabolic disease-associated muscle atrophy,

exosomes derived from human umbilical cord mesenchymal stem cells (hucMSCs) alleviate skeletal muscle atrophy by activating AMPK-ULK1-dependent autophagy [57]. In diabetic muscle, reduced TP53INP2 expression suppresses autophagy and accelerates muscle degeneration, whereas TP53INP2 upregulation enhances autophagy and improves muscle atrophy [31, 101].

4.3 Autophagy decline impairs muscle stem cell function and regenerative capacity

Muscle stem cells (MuSCs) are essential for muscle regeneration and repair, and their activity is regulated by autophagy [102, 103]. Importantly, basal autophagy preserves MuSC quiescence and stem cell integrity, whereas its decline during aging promotes senescence through impaired proteostasis, mitochondrial dysfunction, and oxidative stress, thereby compromising regenerative capacity [104]. Autophagy is also induced during MuSC activation to support bioenergetic demands, and its inhibition suppresses ATP increase and delays activation [105]. Mechanistically, PINK1-dependent mitophagy helps maintain MuSC quiescence and self-renewal, and its disruption drives premature activation and commitment, progressively impairing regenerative capacity [106]. Activation of AMPK inhibits p27^{kip1}-mediated MuSC apoptosis and senescence, restoring MuSC activity [102]. Similarly, SIRT1-mediated autophagy induction facilitates MuSC activation [105]. In response to IL-6, STAT3 activation promotes muscle wasting and inhibits muscle repair, as observed in cancer cachexia or muscle injury models [107, 108]. In aged MuSCs, STAT3 activation suppresses autophagy, impairing MuSC function and muscle regeneration, which can be reversed by STAT3 inhibition [9]. Additional evidence suggests that proper regulation of autophagy is also required during muscle regeneration, as disruption of autophagic balance impairs MuSC survival and differentiation [28, 45, 104, 109-111]. Consistent with this, regeneration-associated autophagy is required for satellite cell activation, whereas in dystrophic muscle autophagy is transiently induced during early compensatory stages but progressively declines with disease progression, coinciding with satellite cell-mediated regenerative exhaustion and fibrosis [112]. Moreover, hypercapnia disrupts satellite cell autophagy flux and impairs activation, replication, and myogenic capacity, whereas rapamycin improves autophagy flux and post-transplantation myogenic capacity [110]. Overall, impaired autophagy disrupts MuSC quiescence, activation, and differentiation, thereby compromising regenerative capacity and underscoring the importance of proper autophagy regulation for muscle regeneration (Fig. 3).

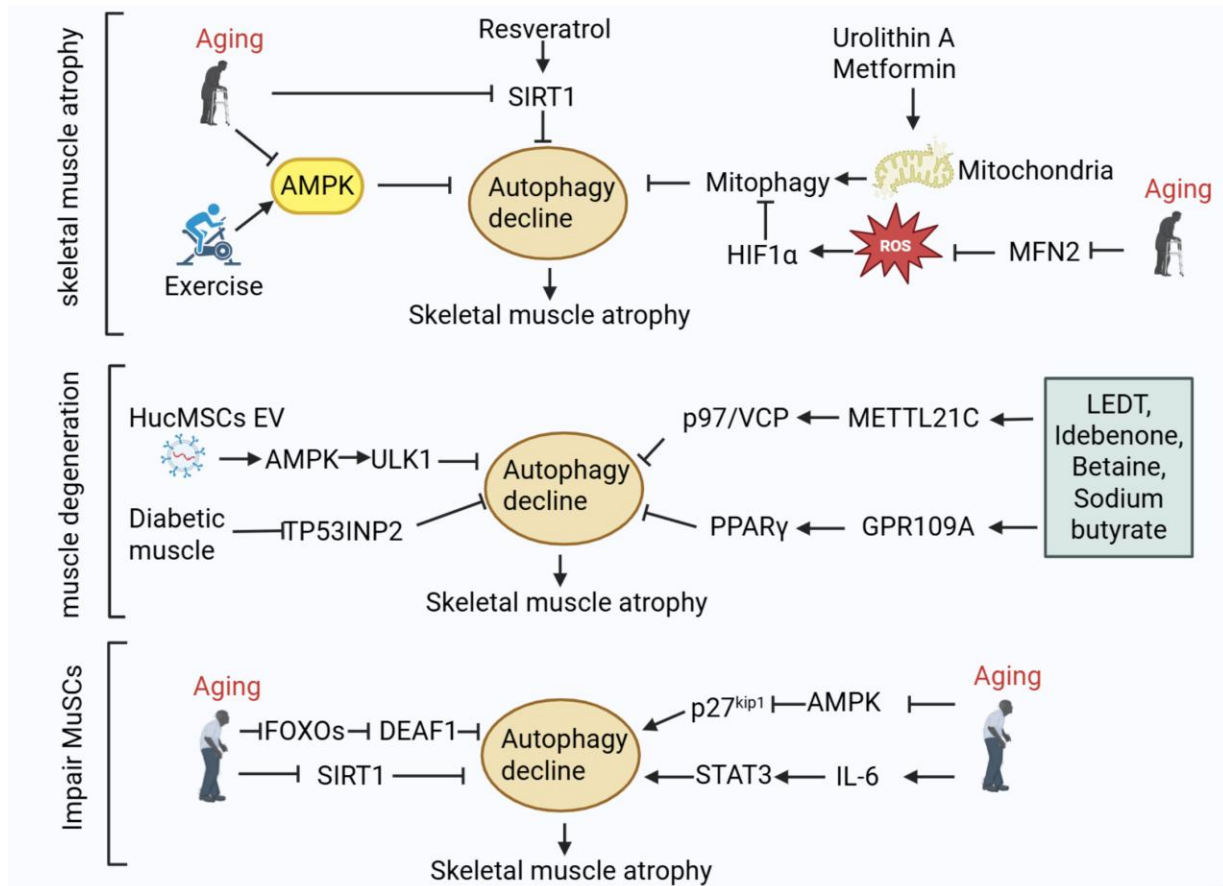


Figure 3. Decline in autophagy drives skeletal muscle atrophy. Age-associated decline in SIRT1 activity and AMPK signaling impairs autophagic flux, while reduced MFN2 expression activates ROS-mediated HIF1 α suppression of mitophagy, collectively driving muscle atrophy. In disease contexts, defective TP53INP2-mediated mitophagy and disrupted AMPK–ULK1 signaling accelerate muscle wasting through distinct pathways including METTL21C–p97/VCP and GPR109A–PPAR γ dysregulation. In muscle stem cells, STAT3 activation suppresses autophagy and promotes senescence, whereas AMPK–p27^{Kip1} signaling and other regulatory inputs help maintain the autophagic balance required for regenerative capacity.

5. Hyperautophagy contributes to muscle wasting

Although basal autophagy is indispensable for skeletal muscle homeostasis, excessive or sustained activation of autophagy, hereafter referred to as hyperautophagy, can become maladaptive and drive muscle degeneration. In this review, the term “hyperautophagy” refers specifically to a condition characterized by persistently elevated autophagic flux leading to net loss of cellular components and pathological tissue remodeling. Importantly, hyperautophagy does not simply denote increased autophagosome formation or elevated LC3-II levels, nor does it include compensatory or transient activation that supports cellular adaptation. Rather, it implies sustained enhancement of functional cargo degradation exceeding physiological requirements.

Experimentally, distinguishing hyperautophagy from compensatory activation requires flux-based assessment. Increased autophagosome markers without proportional

lysosomal degradation, or accumulation due to impaired completion, should not be equated with hyperautophagy. Instead, pathological hyperautophagy is inferred from evidence of increased autophagic flux coupled with progressive muscle mass loss, excessive mitochondrial clearance, or impaired regenerative capacity. Across diverse pathological contexts, such sustained autophagic flux promotes excessive protein and organelle degradation, mitochondrial dysfunction, impaired regenerative capacity, and ultimately muscle wasting (Fig. 4).

5.1 Hyperautophagy driven by metabolic, oxidative, and inflammatory stress

In metabolic and degenerative myopathies, hyperautophagy is frequently triggered by redox imbalance and mitochondrial dysfunction. In type 1 diabetic mice, chronic metabolic stress induces sustained

autophagy activation in skeletal muscle, resulting in progressive muscle atrophy; pharmacological inhibition of autophagy with niclosamide ethanolamine effectively mitigates muscle loss, underscoring a causal role for hyperautophagy in disease progression [113]. Similarly, in a rat model of knee osteoarthritis, excessive reactive oxygen species (ROS) accumulation induces aberrant

autophagy activation and mitochondrial damage in quadriceps muscle, thereby accelerating muscle atrophy. Partial suppression of autophagy alleviates muscle loss, supporting the notion that uncontrolled autophagy acts downstream of oxidative and mitochondrial stress to exacerbate muscle degeneration [38].

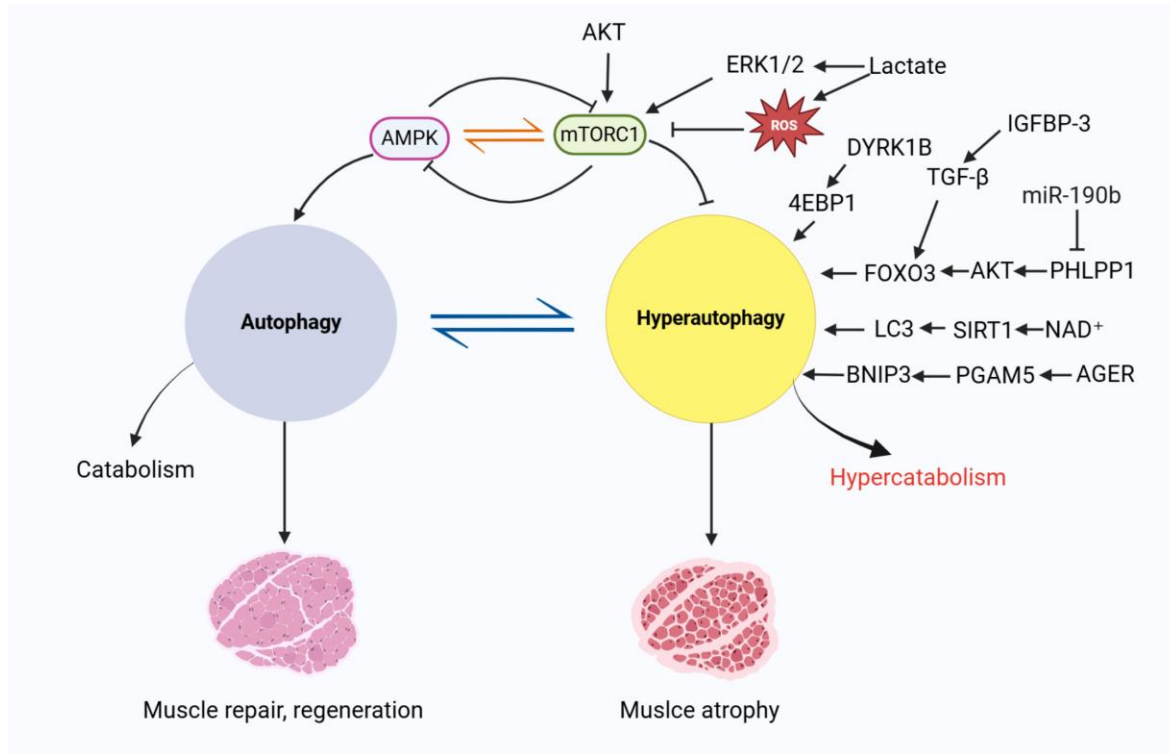


Figure 4. Hyperautophagy contributes to muscle wasting. Pathological hyperautophagy drives muscle wasting through distinct signaling cascades, including inflammatory suppression of AKT/mTOR anabolic signaling that disrupts proteostatic balance. Excessive autophagy impairs myogenic commitment via DYRK1B-mediated 4EBP1 overexpression and MBNL1 deficiency-associated suppression of mTOR signaling, compromising satellite cell proliferative capacity. Endogenous feedback mechanisms, including the miR-190b/PHLPP1/AKT/FOXO3a axis and lactate-induced ERK1/2–mTOR–p70S6K signaling, provide critical checkpoints to constrain autophagic overactivation. In cancer cachexia, tumor-derived signals activate diverse hyperautophagic pathways including IGFBP-3/TGF- β receptor/FOXO, AGER/PGAM5/BNIP3, and NAD⁺–SIRT1-mediated LC3, leading to persistent mitochondrial clearance and metabolic impairment. Blue circle indicates physiological autophagy, yellow circle indicates pathological hyperautophagy, green circle denotes mTOR signaling, and red circle represents stress-related inputs. Solid arrows indicate activation, and blunt-ended lines indicate inhibition.

Systemic inflammatory stress represents another potent driver of hyperautophagy-mediated muscle wasting. During sepsis, autophagy is robustly induced and has been associated with muscle atrophy in certain models [114]. Notably, its functional impact appears stage-dependent, as autophagy ablation can worsen outcomes in some settings [93, 114], suggesting protective roles during acute stress. Conversely, inhibition of autophagy alleviates sepsis-induced muscle wasting through reactivation of AKT/mTOR signaling, restoring anabolic balance and cell survival [39]. Together, these findings suggest that the impact of inflammatory stress on muscle is context-dependent, with excessive or sustained

autophagy promoting atrophy, whereas transient activation may be protective.

5.2 Hyperautophagy impairs muscle regeneration and stem cell competence

Beyond its catabolic effects on mature myofibers, hyperautophagy compromises muscle regenerative capacity by impairing the proliferation and differentiation of MuSCs, which are essential for muscle repair. MBNL1 promotes MuSC proliferation by inhibiting autophagy through mTOR activation [115]. Conversely, while DYRK1B-mediated induction of 4EBP1 supports physiological autophagy during myogenesis, the

DYRK1B(R102C) mutation causes aberrant 4EBP1 overexpression, leading to hyperautophagy and defective muscle differentiation [116]. These studies highlight that excessive autophagic activity disrupts the balance between self-renewal and differentiation in muscle progenitor cells, thereby limiting regenerative potential.

5.3 Endogenous feedback and energy-sensing pathways modulating hyperautophagy

Multiple endogenous feedback mechanisms act to buffer autophagic activity and prevent uncontrolled degradation. MicroRNA-mediated regulation plays an important role in this fine-tuning process. In burn injury models, reduced miR-190b expression is associated with hyperautophagy and severe muscle wasting, whereas restoration of miR-190b suppresses PHLPP1 expression, activates AKT/FOXO3a signaling, and restrains excessive autophagy, thereby protecting against muscle loss [117].

Metabolic feedback loops further constrain autophagy during nutrient stress. During starvation, ULK1-dependent phosphorylation of LDHA promotes lactate release and autophagy activation [69]. However, downstream metabolic and redox signals can reactivate mTOR-related pathways, thereby providing negative feedback to limit autophagic overactivation [70]. These buffering systems highlight the necessity of precise temporal control to maintain adaptive, rather than destructive, autophagy in skeletal muscle.

Chronic activation of AMPK represents a critical node linking redox stress to pathological autophagy and muscle aging. While transient AMPK activation supports adaptive autophagy and muscle maintenance, sustained AMPK signaling drives hyperautophagy [118, 119]. In NRF2-deficient skeletal muscle, elevated ROS chronically activates AMPK, triggering excessive autophagy and accelerating muscle loss [118]. Conversely, calycosin attenuates oxidative stress and suppresses AMPK-driven autophagy, thereby alleviating muscle atrophy [119]. Together, these feedback mechanisms indicate that hyperautophagy arises from the convergence of metabolic, redox, and inflammatory stress signals rather than from a single linear pathway.

5.4 Hyperautophagy as a catabolic driver of cancer cachexia

In many forms of cancer cachexia, sustained activation of autophagy and mitophagy contributes to progressive skeletal muscle wasting across multiple malignancies [120-122]. In pancreatic ductal adenocarcinoma (PDAC)-associated cachexia, muscle atrophy is associated with increased ULK1 and LC3B-II levels and activation of FOXO-dependent catabolic programs. This process is

driven in part by tumor-derived IGFBP-3 acting through a non-canonical TGF- β receptor-FOXO axis that coordinately activates autophagy-lysosome and ubiquitin-proteasome pathways [123].

Similarly, in cachexia associated with multiple solid tumors, inflammatory mediators activate mitophagy-associated signaling pathways, leading to excessive mitochondrial clearance, mitochondrial dysfunction, and muscle atrophy; partial suppression of mitophagy alleviates muscle loss [124]. In IDH-mutant acute myeloid leukemia-associated cachexia, metabolic reprogramming enhances autophagic flux through NAD⁺-SIRT1-dependent mechanisms, independent of AMPK-mTOR signaling, resulting in metabolic impairment and muscle wasting [125]. Collectively, these findings highlight a critical distinction between pathological hyperautophagy and age-associated impairment of autophagy flux. Excessive or sustained autophagy activation drives muscle wasting by promoting uncontrolled catabolism under conditions such as metabolic stress, inflammation, and cancer cachexia. In contrast, aging and sarcopenia are commonly associated with defective or inefficient autophagic flux, leading to the accumulation of damaged proteins and organelles and progressive loss of muscle function.

Conclusion and Perspective

Autophagy is a lysosome-dependent catabolic process that maintains skeletal muscle homeostasis by recycling intracellular components and regulating nutrient availability. Released metabolites, such as amino acids, activate mTORC1, thereby providing negative feedback on autophagy and highlighting the bidirectional crosstalk between degradation and anabolic signaling [65, 68, 126]. The dynamic crosstalk between autophagy activators (e.g., AMPK) and inhibitors (e.g., mTORC1) coordinates protein anabolism and catabolism in skeletal muscle, maintaining homeostasis [71, 126]. However, the precise temporal and quantitative relationship between mTORC1 signaling and autophagic flux remains complex and requires further investigation, as understanding this interplay is critical for preventing muscle degeneration.

Accumulating evidence supports the concept of an “optimal autophagic range” as a useful framework for understanding skeletal muscle homeostasis, within which muscle integrity, mitochondrial quality, and regenerative capacity are more likely to be preserved [8, 46, 56, 95, 123]. However, this concept should not be interpreted as a quantitatively defined threshold. Rather, it represents a theoretical framework derived from convergent observations across genetic, physiological, and disease contexts. Deviation from this functional range, whether

due to insufficient autophagic flux or hyperautophagy, is associated with progressive muscle degeneration.

Translating this framework into therapy remains challenging. Since autophagy is essential for homeostasis across multiple organs, systemic modulation entails inherent trade-offs: chronic mTOR inhibition may enhance autophagy but suppress protein synthesis and immune function whereas sustained suppression of autophagic flux may aggravate mitochondrial dysfunction and proteotoxic stress [127, 128]. Achieving skeletal muscle-specific benefit without unintended systemic consequences therefore remains difficult. Moreover, autophagic requirements vary not only between organs but also within skeletal muscle [129], where post-mitotic myofibers and proliferative muscle stem cells exhibit distinct demands. Temporal regulation adds further complexity, as transient activation during acute stress may be adaptive, whereas persistent activation under chronic inflammation or cachexia can drive net proteolysis and muscle wasting [120–122].

Autophagy also functions within an integrated proteostasis network that includes the ubiquitin–proteasome system (UPS) [130]. In many atrophic states, coordinated activation of both pathways under FOXO-dependent programs drives global protein degradation, suggesting that targeting autophagy alone may be insufficient to restore overall proteostatic balance [30, 131, 132].

Although emerging approaches—including mTOR modulators and mitophagy-enhancing compounds such as urolithin A—have shown improvements in mitochondrial function and muscle performance in preclinical and early clinical studies [133], robust evidence for reversing sarcopenia or cachexia remains limited. To date, no autophagy-targeting therapy has been approved for these conditions, and reliable biomarkers to quantify autophagic flux in human skeletal muscle are still lacking. Future progress will depend on defining stage-specific intervention windows, developing quantitative biomarkers of autophagic flux, and designing muscle-targeted strategies capable of restoring autophagy within a physiological, context-dependent range. In this regard, therapeutic modulation of autophagy represents a problem of precise regulation rather than simple pathway activation, requiring integration of mechanistic insight with clinical specificity.

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Disclosure statement

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