HHS Public Access

Author manuscript

Free Radic Biol Med. Author manuscript; available in PMC 2017 September 01.

Published in final edited form as:

Free Radic Biol Med. 2016 September ; 98: 103–112. doi:10.1016/j.freeradbiomed.2016.05.010.

Redox regulation of autophagy in skeletal muscle

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Abstract

Autophagy is a cellular degradative pathway that involves the delivery of cytoplasmic components, including proteins and organelles, to the lysosome for degradation. Autophagy is implicated in the maintenance of skeletal muscle; increased autophagy leads to muscle atrophy while decreased autophagy leads to degeneration and weakness. A growing body of work suggests that reactive oxygen species (ROS) are important cellular signal transducers controlling autophagy. Nicotinamide adenine dinucleotide phosphate (NADPH) oxidases and mitochondria are major sources of ROS generation in skeletal muscle that are likely regulating autophagy through different signaling cascades based on localization of the ROS signals. This review aims to provide insight into the redox control of autophagy in skeletal muscle. Understanding the mechanisms by which ROS regulate autophagy will provide novel therapeutic targets for skeletal muscle diseases.

Keywords

reactive oxygen species; free radicals; autophagy; skeletal muscle

Introduction

Cellular homeostasis, essential for tissue development and cell survival, is maintained by a balance of protein synthesis and degradation. Skeletal muscle is a highly plastic tissue, effectively adapting to changes in metabolic demand. There are three major pathways regulating proteolysis is skeletal muscle: 1) the ubiquitin proteasome pathway (UPP); 2) the caspase-3 and calpain (calcium dependent protease) pathway; and 3) the autophagy-lysosomal pathway. Recently, mitochondrial specific proteases (i.e. Lon protease) have been shown to be upregulated in skeletal muscle in response to acute oxidative stress (1); however, its role in regulation of autophagy has not been investigated. Oxidative stress has been shown to increase protein breakdown through increased gene expression of key atrophy related protein such as atrogins and MuRF-1 (2, 3), as well as increase the activity of calpain

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and caspase-3 (4, 5). Oxidative modification of proteins also causes partial unfolding, promoting the exposure of hidden recognition sequences that facilitate their proteolytic degradation. Oxidation of myofibrillar proteins promotes proteolytic cleavage by calpain and caspase-3 (4, 5), which is required to facilitate degradation by UPP (6–8). While oxidized proteins are cleared by UPP and the calpain/caspase-3 pathways, large protein aggregates and damaged organelles are degraded by the autophagy-lysosomal pathway.

Autophagy is a homeostatic process that clears protein aggregates and damaged organelles through the autophagosome-lysosome system. Autophagy has recently gained immense attention for its role in metabolic homeostasis and disease progression of skeletal muscle. Alterations in autophagic flux are commonly observed in response to stress and have been shown to increase in skeletal muscle in response to starvation, denervation, disuse atrophy, hypoxia, and exercise (9–12). A number of factors and signaling pathways have been shown to contribute to the regulation of autophagic flux. Among them, reactive oxygen species (ROS) have been implicated in the control of autophagic flux.

Oxidative stress may occur through an increase in ROS levels or a decrease in the cellular antioxidant capacity. While a certain level of ROS is essential for the regulation of cell growth and various biological functions, a disrupted ROS balance has negative implications. For example, oxidative stress has been associated with a number of pathological conditions, including neurodegenerative disorders (13–18), skeletal muscle disorders (19–23), lysosomal storage disorders (24, 25), cardiomyopathy (26, 27), carcinogenesis (28, 29), atherosclerosis (30, 31), diabetes (32, 33), and aging (34, 35). While the involvement of oxidative stress is firmly demonstrated in these pathological conditions, the specific source of ROS generation and the mechanisms by which each disease is regulated by ROS has yet to be elucidated. While ROS and autophagy were first described a number of years ago; the precise mechanisms of ROS-regulated autophagy and effective therapeutic strategies still remain to be discovered. Due to the compelling recent evidence associating autophagy with skeletal muscle homeostasis, we focus this review on summarizing the identified molecular mechanisms of ROS-regulated autophagy and their relevance to skeletal muscle health and disease.

Overview of Autophagy Signaling

Autophagy is an evolutionarily conserved cellular degradation pathway that involves breakdown of cytoplasmic components by the lysosome. In general, autophagy is categorized by three main types: microautophagy, chaperone-mediated autophagy (CMA), and macroautophagy (36, 37).

Microautophagy

Microautophagy is a non-selective lysosomal degradative process which directly engulfs the cytoplasmic cargo and eliminates them by both invagination and vesicle scission (38, 39). While microautophagy is unresponsive to amino-acid deprivation (39), little else is known regarding the mechanisms regulating miroautophagy in mammalian cells.

Chaperone-mediate autophagy (CMA)

During CMA, cytoplasmic cargo is targeted to the lysosome, where it is degraded by lysosomal enzymes (40–42) (Figure 1). The pentapeptide motif of CMA substrates contains a glutamine (Q) residue at the beginning or end of the sequence, one or two of the positive charged amino acids lysine (K) or arginine (R), one of the hydrophobic amino acids, phenylalanine (F), valine (V), leucine (L) or isoleucine (I) and one of the negatively charged amino acids, glutamic (E) or aspartic acid (D) (40, 43, 44). In the cytosol, a constitutive chaperone, heat shock cognate protein of 70 kDa (Hsc70), along with other co-chaperones (Bag1, Hip, Hop and Hsp40), bind to the substrate on the pentapeptide motif KFERQ, which is present in the amino acid sequence of all CMA substrates, consequently transporting it to the surface of the lysosomal membrane (40, 43, 45).

Once the substrate complex is targeted to the lysosomal surface, it interacts with the cytosolic tail of lysosomal-associated membrane protein type 2A (LAMP-2A). The monomeric LAMP-2A forms multi-protein complex structures, along with many other proteins, promoting the translocation of CMA substrates. CMA substrates can be introduced to this multi-protein complex in the folded or unfolded state; however, translocation of the substrates can only be carried out in the unfolded form (46, 47). The folding and unfolding of CMA substrates are tightly regulated by Hsc70 and the other co-chaperones. Once the CMA substrates are internalized into the lysosomes, they are degraded by lysosomal hydrolases. Subsequently, LAMP-2A dissociates from the multi-protein complex to form monomers, where another CMA substrate can bind, and thus this dynamic process maintains the homeostasis of CMA (48). Alterations in redox balance and subsequent oxidative stress is one of the major factors that regulate the levels of LAMP-2A (40, 48–50). The role of CMA in skeletal muscle has not been widely studied. Increased LAMP2A has been reported in mouse skeletal muscle after a single bout of exercise (51). Additionally, abnormalities of CMA have been observed in sporadic inclusion-body myositis muscle fibers (52).

Macroautophagy

Macroautophagy, referred to here as autophagy, is the most investigated form of autophagy and is characterized by the formation of double-membrane structures, called autophagosomes, which sequester cytoplasmic substrates and fuse with lysosomes to eliminate damaged components or recycle end products for production of energy that regulates cellular homeostasis (53, 54) (Figure 2). Substrates of autophagy include damaged proteins, organelles, inclusion bodies, and superfluous and invasive bacteria (36, 53, 55). Precise regulation of autophagy is a highly selective process, as it critically depends on engulfment of specific substrates within autophagosomes, while preventing engulfment of undamaged cytoplasmic contents (55). Due to the vast range of substrate selectivity, autophagic pathways can be impaired through a wide range of mechanisms that vary in each disease. Therefore, understanding the key regulators of autophagy in mammalian cells and how they are altered under different pathological conditions has gained immense attention in recent years.

Control and regulation of autophagy

Low basal levels of autophagy allow cells to break down long-lived and large cytosolic protein aggregates and organelles, which has been shown to be necessary for cell survival. The regulatory process of autophagy is divided into two distinct forms, selective and nonselective autophagy. Selective autophagy is mainly regulated under homeostatic conditions; while, nonselective autophagy is induced upon starvation or in response to external or internal stress related conditions (56). Both selective and nonselective autophagy are regulated by core autophagic machinery structured by a number of autophagy-related (ATG) genes that have been identified by large-scale genetic screening in yeast almost three decades ago (57). Most of the ATGs identified in yeast have mammalian counterparts, where they are actively involved in regulating autophagy by highly-conserved mechanisms in the initiation of double-membrane autophagosome formation (54, 56–58).

Initiation of autophagosome formation

In mammalian cells, formation of the autophagosome is initiated by a complex consisting of the serine/threonine protein kinase unc-51-like kinase-1 (ULK1) and -2 (ULK2), FIP200, and Atg13 (53, 56–58). The classical paradigm of autophagosome formation is controlled by two master regulators of ULK, mammalian target of rapamycin (mTOR) complex1 and AMP-activated protein kinase (AMPK) (59–63). mTOR is a serine/threonine kinase which acts as a central inhibitor of autophagy by inhibiting ULK1 activity through phosphorylation at S757, thereby disrupting its interaction with AMPK. Under nutrient starvation, mTORC1 is inhibited, resulting in its dissociation from the ULK1 complex with subsequent dephosphorylation and activation of ULK1. Recent studies have identified the association between AMPK and ULK1. Bioinformatics approaches have screened several possible AMPK-phosphorylation sites in ULK1 (S555, T574, S637, and S467). However, all the phosphorylation sites have not been confirmed *in vivo*. Recently, using systematic mutagenesis, two major AMPK-phosphorylation sites in ULK1 (S317 and S777) were identified and later confirmed by cell based assays (62, 63). AMPK-dependent phosphorylation of ULK1 increases ULK1 activity and promotes autophagy (63). In addition to ULK1 phosphorylation, AMPK can directly phosphorylate the Tuberous sclerosis complex2 (TSC2), leading to the inactivation of the GTPase Rheb, which directly binds to and activates mTORC1 kinase activity (62). AMPK-mediated inactivation of mTORC1 increases ULK1 activity and promotes autophagy.

Nucleation of the phagophore

The nucleation and assembly of the initial phagophore membrane is a major determinant of mature autophagosome formation. This process is centrally regulated by a complex which consists of class III phosphatidylinositol 3-kinase (PI3K or hVps34), its regulatory subunits p150 or hVps15, Beclin1, and Atg14L, the relatively recent discovered mammalian homology of Atg14 (56, 57, 64, 65). The activity of this complex is tightly controlled by several positive and negative regulators, and is often dysregulated in various pathological conditions. Recent studies have implicated an mTORC1/AMPK-independent regulation of autophagy, which is directly dependent on the interaction between Beclin1 and hVps34 (66).

However, the precise mechanisms by which ULK:Atg13:FIP200 complex connects with beclin1:hVps34:Atg14L complex has not been clearly established.

Elongation of the phagophore, autophagosome formation, and fusion

Elongation of the autophagophore is critical for the completion of the autophagosome. Atg12 conjugates with Atg5, and the conjugated Atg12:Atg5 complex interacts with Atg16L to form a multimeric complex Atg12:Atg5:Atg16L. This multimeric complex associates with the microtubule-associated protein-light chain 3 (LC3) conjugation system, which is recruited by the beclin1:hVps34:Atg14L complex to form the mature autophagosome (56, 57, 67–69). While mammalian cells express three variants of LC3 (LC3A, LC3B, LC3C), LC3B is expressed in nearly all tissues and is the most widely used marker of autophagic flux (70). Conjugation of phosphatidylethanolamine (PE) to soluble LC3B (LC3B-I) is mediated by the protease Atg4 followed by Atg3 and Atg7. The lipidated form of LC3B (LC3B-II) is associated with the outer and inner membranes of the autophagosome for the induction and maturation of the autophagosome (71–73). Atg4 also acts to delipidate LC3B-II present on the cytoplasmic face of the autophagosome, recycling it back to LC3B-I, thereby ensuring elongation of the autophagosome. Autophagosomes move along microtubules in a dynein/kinesin dependent manner to the lysosome and fuse with the lysosome to form the autolysosome. Lysosomal acid hydrolases then degrade the autohagic cargo.

Redox balance, oxidative stress and redox control of autophagy in skeletal muscle

ROS are produced at relatively low rates under physiological conditions in skeletal muscle fibers and exert positive effects on gene expression, regulation of cell signaling, and modulation of contractile force. In contrast, high levels of ROS result in damage to cellular components such as proteins and organelles, leading to muscle dysfunction. The role of ROS and oxidative stress in the regulation of skeletal muscle has been extensively reviewed elsewhere (74–81) as well as in this Special Issue.

Indeed, autophagic flux has been shown to participate in pro-atrophic stimuli (11, 12, 82–90), fasting (91, 92), high fat diet/insulin resistance (93, 94), hypoxia (95), and exercise (9, 96–101). Conversely, impaired autophagy has been reported in several myopathies (23, 102–108). While autophagy and oxidative stress have been studied individually, little is known about the molecular regulation of autophagy by ROS. A number of studies, as reviewed below, report that ROS induces autophagy and, vice-versa, autophagy serves to reduce oxidative stress.

Much of the work that has reported on autophagy and oxidative stress in skeletal muscle merely hypothesize that ROS are crucial for induction of autophagy (11, 82–84, 86, 87, 91, 95), as direct cause and effect was not established. More direct evidence that ROS regulates autophagic flux comes from Dobrowolny *et al* (109), who have shown that skeletal muscle expressing a mutant form of superoxide dismutase 1 (SOD1G93A) increases oxidative stress and triggers activation of autophagy, leading to muscle atrophy and weakness. In addition,

pharmacological application of H_2O_2 has been shown to induce autophagy in C_2C_{12} myotubes (85, 110, 111). Concomitantly, antioxidant treatment has been shown to inhibit the induction of autophagy (92, 94, 110, 112). In a mouse model of muscular dystrophy, we have shown that blocking Nox2-dependent ROS production relieves inhibition of autophagy and improves muscle function (23). On the contrary, skeletal muscle specific genetic knockout of Atg7 showed an altered metabolic profile, defective mitochondrial respiration, and increased steady state ROS production (113–115), suggesting that decreased autophagy results in increased production of ROS. It is clear that ROS and autophagy play a role in skeletal muscle homeostasis; however, it is unclear how up or down regulation of these processes induce a negative or beneficial response. The emerging theme is that the amount of ROS generated and its sub-cellular localization are major determinants of ROS-mediated autophagy regulation in skeletal muscle (Figure 3).

The source of ROS in regulation of not only autophagy, but many skeletal muscle cell signaling cascades is an area of active research. There are a number of potential sources of ROS production in skeletal muscle. These include mitochondria, NADPH oxidase (Nox), xanthine oxidase, and phospholipase A2 (reviewed in (74, 75)). However, mitochondria and Nox isoform 2 (Nox2) have emerged as the two main sources of ROS production. Mitochondria have been proposed as the primary source of ROS to regulate autophagy in many cell types (116–120), including skeletal muscle (86, 91, 109, 110). The role of Nox2 in regulation of autophagy is less clear. In macrophages, Nox2-dependent ROS has been shown to induce autophagy upon bacterial infection (121, 122), functioning as an innate immune-defense mechanism. In a cellular model of neurodegeneration we have shown that rotenone, a prototypical mitochondrial complex I inhibitor, increases Nox2-dependent ROS production (18), resulting in inhibition of autophagy. To our knowledge, we are the only group to show that Nox2-generated ROS regulates autophagy in skeletal muscle. We found that exuberant Nox2-dependent ROS production impairs autophagic flux in skeletal muscle (23).

While many studies show that ROS are a signal to induce or impair autophagy, we still know very little about the mechanisms of action. Some studies have shown that ROS activate autophagy by regulating the activation of the PI3K/Akt/mTORC1-signaling pathway. In malignant glioma, ROS promoted autophagy by inhibiting Akt/mTOR signaling (123, 124). In a hindlimb casting model of disuse atrophy, Talbert *et al* (125) have shown that mitochondrial ROS promote inhibition of Akt/mTOR and subsequent induction of autophagy. In our recent study, we have demonstrated that ROS generated from Nox2 induces activation of mTORC1 through activation of a Src/PI3K/Akt pathway, and thus ROS-mediated activation of mTORC1 inhibits autophagy in a dystrophic mouse model (23).

Another potential pathway for ROS dependent regulation of autophagy is through p38 MAPK/p53. Mitochondrial ROS was shown to induce autophagy through a p38/p53 dependent path in A375 cells (126). In skeletal muscle, ROS induced autophagy in a p38 MAPK dependent manner (85). Interestingly, Yuan *et al* (127) have shown that the p38/p53 pathway appears to not only activate autophagy, but to be involved in a positive feed-back response, as both p38 and p53 were shown to increase ROS production in cardiomyocytes. Inhibition of the p53-target gene TIGAR (TP53-induced glycolysis and apoptosis regular)

results in increased ROS production and activation of autophagy (mitophagy), (128) while TIGAR overexpression results in decreased ROS levels and inhibition of autophagy (129).

AMPK, a widely established sensor of cellular energy levels, is an essential regulator of muscle metabolism during exercise, as well as in skeletal muscle adaptation to exercise training (reviewed in (130)). Alterations in redox balance have been shown to regulate AMPK activity. Exposure of C_2C_{12} cells to pharmacological H_2O_2 concentrations resulted in activation of AMPK (110, 111), with a subsequent increase in autophagy (110).

The tumor suppressor gene PTEN (phosphatase and tensin homolog deleted on chromosome 10) is inhibited by oxidative stress (131–135). Inactivation of PTEN results in an increase in cellular PIP3 levels, activation of PI3K/Akt, and subsequent activation of autophagy. PTEN can also regulate ROS production, providing a feedback loop in which Nox may be intimately poised to regulate this signaling (131). While ROS has been shown to activate Akt through inhibition of PTEN in C_2C_{12} myotubules (135), its role in regulating autophagy in skeletal muscle has not been directly assessed.

In Chinese Hamster Ovary (CHO) cells, nutrient deprivation resulted in increased ROS production, specifically mitochondrial H_2O_2, oxidation and inactivation of Atg4, thus preventing its delipidation of LC3B-II and ensuring elongation of the autophagosome (120). REDD1 (regulated in development and DNA damage responses 1), is a hypoxia-inducible factor-1 target gene and plays a crucial role in inhibiting mTORC1 (136). Ellisen and colleagues (137) have shown that hypoxia and exercise increase ROS production through a REDD1/TXNIP pro-oxidant complex, inhibiting Atg4 activity and promoting autophagy. Mice lacking REDD1 displayed impaired oxidative phosphorylation and reduced exercise capacity, presumably due to altered Atg4 activity and decreased mitophagy.

The Forkhead box O (FoxO) transcription factors play essential roles in regulation of muscle physiology (10, 12). They are phosphorylated and inactivated by Akt/PKB and predominantly localize in the cytosol. However, in response to Akt supression, FoxO translocates to the nucleus, inducing transcription of atrophy related genes (atrogin 1 and MuRF-1) and the autophagy related genes cathepsin L, Bnip3, and LC3B (10). While basal autophagy is essential for the maintenance of metabolic homeostasis, oxidative stress-dependent activation of FoxO3 and subsequent up-regulation of FoxO3-mediated autophagy have been shown to promote muscle atrophy and weakness (10, 138). Other studies have also demonstrated that ROS generation induces activation of Akt (139–142), an event that negatively regulates transcriptional activity of FoxO3. Therefore, the precise role of oxidative stress on FoxO-mediated autophagy in skeletal muscle remains unclear.

Regulation of redox balance by autophagy

Dysregulation in the homeostasis of autophagy promotes ROS generation and subsequent alterations in redox balance. Impairment of autophagy leads to cytosolic-accumulation of ubiquitinated proteins that induces mitochondrial damage and promotes ROS generation (143). In squamous cell carcinoma cells autophagy was shown to increases ROS generation from xanthine oxidase, leading to mitochondrial damage and exacerbating oxidative stress

(144). Keap1 (Kelch-like ECH- associated protein 1) binds Nrf2 (nuclear factor erythroid 2-related factor 2), sequestering Nrf2 in the cytoplasm and preventing transcriptional regulation of antioxidant genes. Autophagic degradation of Keap1 allows Nrf2 to translocate to the nucleus and bind the antioxidant-responsive elements (ARE) in the promoter region of antioxidant genes (145). Skeletal muscle specific knockout of Atg7 leads to dysfunctional mitochondria, oxidative stress, myofiber atrophy, and muscle weakness (102, 113–115). Although it is not clearly established whether autophagy is a major checkpoint for the control of redox balance, together, these studies suggest that alterations in redox balance coordinate with changes in autophagy.

Autophagy is differentially regulated in fast-twitch glycolytic and slow-twitch oxidative muscle

Several lines of evidence suggest that autophagy signaling is differentially regulated between muscles with distinct fiber type distribution and metabolic characteristics. Analysis of autophagsome formation in skeletal muscle in response to starvation has indicated that there is a significantly greater increase in glycolytic muscle (tibialis anterior, TA) compared to oxidative muscle like the diaphragm (105, 108, 146). After spontaneous wheel running for 3 months, TA muscle from mice, did not show any evidence of autophagy induction (LC3 lipidation) (9). Conversely, in plantaris muscle, composed of glycolic and oxidative fibers, from mice subjected to 4 weeks of voluntary running displayed increased LC3 lipidation, decreased p62 protein content, and increased expression of several autophagy-related proteins (i.e., Atg6, LC3, and Bnip3) (101, 147). Inactivation of mTORC1 signaling resulted in greater atrophy in glycolytic muscle fibers compared to oxidative muscle fibers (148, 149). In this regard, muscle specific ATG5 knockout mice showed increased p62 protein content and accumulation of cytoplasmic ubiquitinated proteins in glycolytic muscle fibers but not oxidative muscle fibers (150).

Autophagic flux also shows fiber-type variability in myopathic conditions. Autophagy is severely compromised in glycolytic TA compared to the more oxidative diaphragm muscle in both Collagen VI (105) and Duchenne muscular dystrophies (108, 146). Deficiency of the glycogen-degrading lysosomal enzyme acid-alpha glucosidase (Pompe disease) resulted in accumulation of p62, LAMP-1, and ubiquitinated proteins in fast glycolytic fiber of the gastrocnemius but not slow oxidative fibers of the soleus (150). In a mouse model of sepsis, LPS induced upregulation of autophagy was greater in the TA than either the diaphragm or soleus (86). Pessin and colleagues (151) have shown that a Fyn/STAT3/Vps34 pathway upregulates macroautophagy in glycolytic muscle, with less effect on oxidative muscle. Finally, in a rat model of myocardial infarction, autophagy-related genes (MAP1LC3B, GABARAPL1, BNIP3 and CTSL1) were upregulated in plantaris (glycolytic) muscle fibers but not soleus muscle fibers; even though both fiber types showed marked atrophy (152).

Taken together, there is sufficient data indicating that autophagy is differentially regulated in a fiber-type specific manner. However, the basis for the selectivity under different physiological or pathophysiological conditions and what role oxidative stress may play are important yet unresolved issues.

Conclusions

ROS play an important role in controlling a wide range of cell signal transduction pathways and modulation of skeletal muscle force. Autophagy is an important cell survival mechanism that is now recognized to be crucial in skeletal muscle health. Both ROS and autophagy likely have either beneficial or detrimental effects, depending on their balance. While ROS have been shown to promote autophagy in skeletal muscle, ROS have also been shown to impair autophagy. An important question is how ROS crosstalk with autophagic signaling. While we have begun to uncover the role of redox signaling in regulation of specific signaling cascades in autophagy, intricate details of this process have yet to be elucidated. It is likely that the amount of ROS generated and the specific sub-cellular localization of ROS are major determinants of ROS-mediated autophagy regulation in skeletal muscle. Future studies aimed at understanding the control of autophagy through micro-domain redox signaling will aid in our understanding of the control of autophagy, providing valuable information for the development of selective therapies for skeletal muscle dysfunction.

Acknowledgments

Research reported in this publication was supported by the National Institute of Arthritis and Musculoskeletal and Skin Diseases of the National Institutes of Health under Award Number R01 AR061370, the National Institute of Neurological Disorders and Stroke of the National Institutes of Health under Award Number R21 NS085208, and a Clifford Elder White Graham Endowed Fellowship to G.G.R.

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Highlights

- Autophagy regulates skeletal muscle homeostasis.
- Skeletal muscle atrophy occurs due to increased autophagy.
- Impaired autophagy leads skeletal muscle degeneration due to accumulation of damaged proteins and organelles.
- Regulation of skeletal muscle autophagy by reactive oxygen species is due to sub-cellular production of ROS.

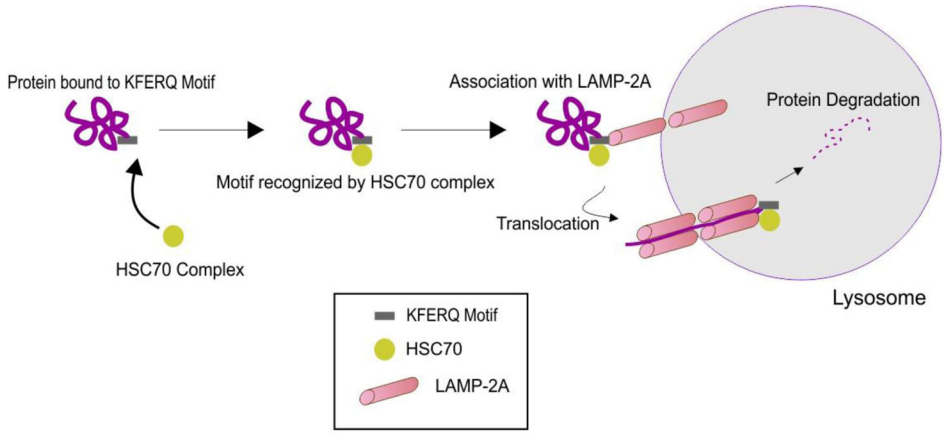

Figure 1. Schematic diagram of chaperone mediated autophagy

Chaperone mediated autophagy is involved in the breakdown of damaged cytosolic proteins. Chaperones recognize a KFERQ motif on the targeted protein and deliver the protein to LAMP-2A on the lysosomal membrane for degradation. See text for details.

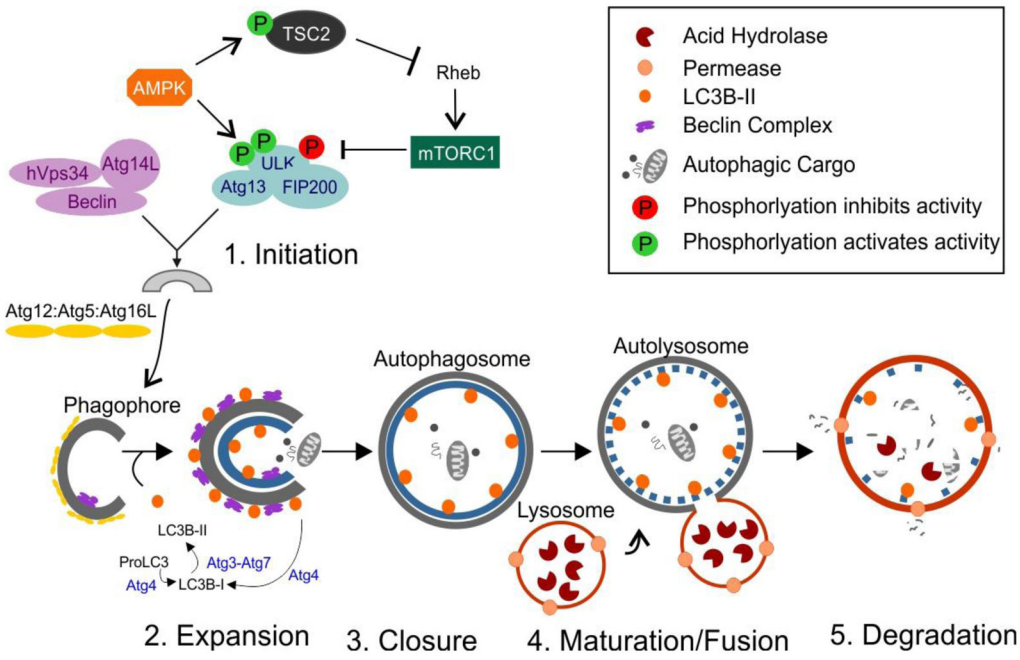

Figure 2. Schematic diagram of macroautophagy

Macroautophagy involves the formation of distinct complexes during five sequential stages: (1) initiation, (2) expansion and elongation, (3) closure, (4) maturation and fusion of autophagosomes with lysosomes, and (5) degradation of the autophagic cargo. See text for details.

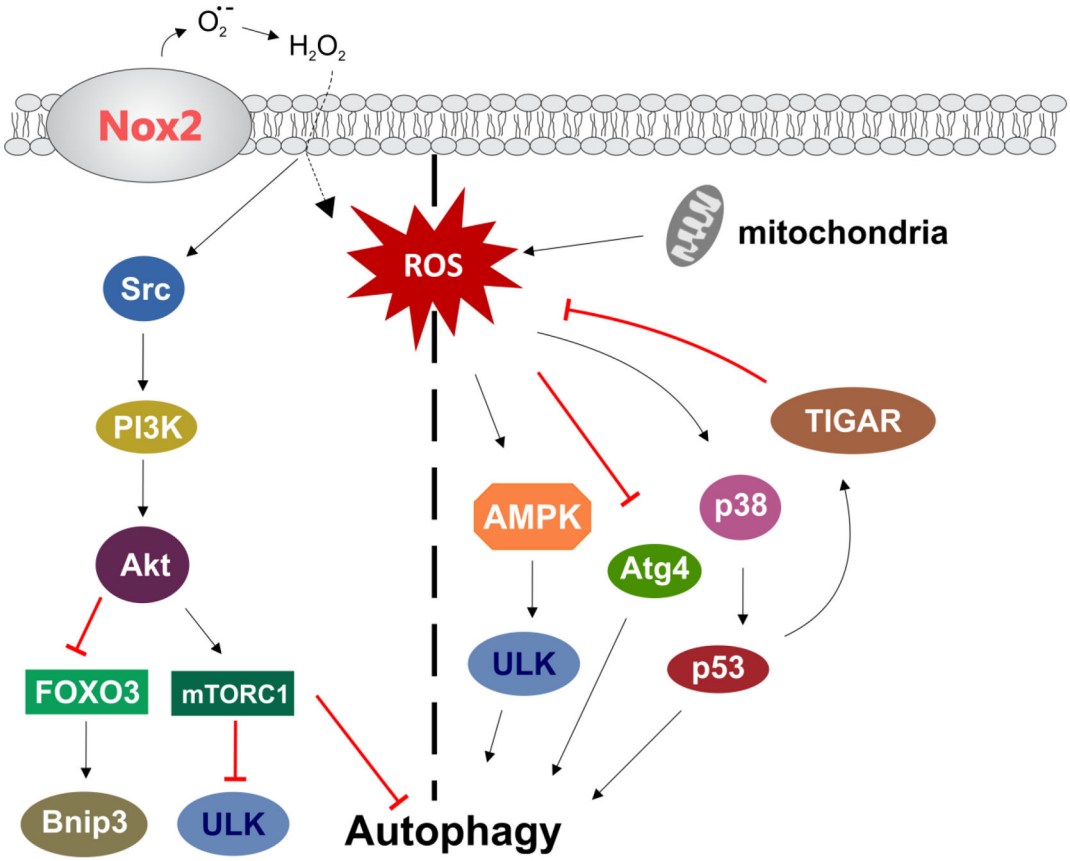

Figure 3. Regulation of autophagy by ROS

Nox2 and mitochondria are the main sources of ROS in skeletal muscle. Activation or inhibition of autophagy is likely governed by micro-domain redox signaling and the amount of ROS produced. See text for details.