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Redox regulation of autophagy in skeletal muscle

George G. Rodney [a,b,*], Rituraj Pal [a], Reem Abo-Zahrah [a]

[a] Department of Molecular Physiology and Biophysics, Baylor College of Medicine, Houston, TX, USA
[b] Cardiovascular Research Institute, Baylor College of Medicine, Houston, TX, USA

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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.

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1. 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 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

* Corresponding author at: Department of Molecular Physiology and Biophysics, Cardiovascular Research Institute, Baylor College of Medicine, One Baylor Plaza, Mail Stop BCM335, Houston TX, 77030, USA.
E-mail address: rodney@bcm.edu (G.G. Rodney).

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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.

2. 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].

2.1. 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 microautophagy in mammalian cells.

2.2. Chaperone-mediate autophagy (CMA)

During CMA, cytoplasmic cargo is targeted to the lysosome, where it is degraded by lysosomal enzymes [40–42] (Fig. 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].

2.3. 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] (Fig. 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.

3. 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

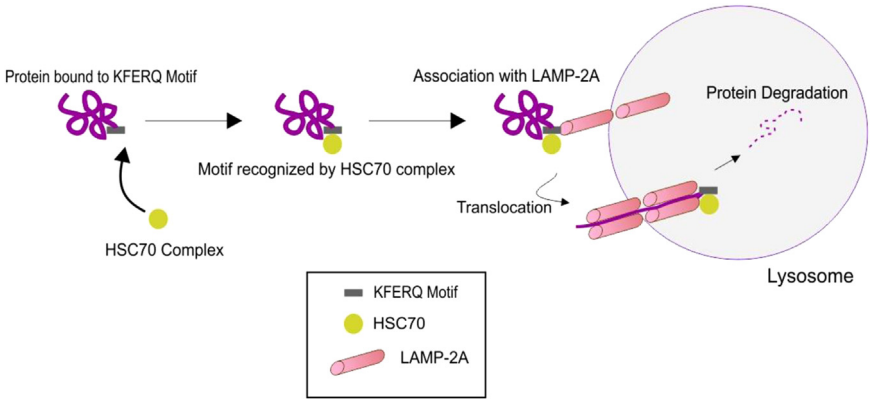

Fig. 1. Schematic diagram of chaperone mediated autophagy. Chaperone mediated autophagy is involved in the breakdown of damaged cytosolic proteins. Chaperones recognize a KFERQ motif on the targeted protein and deliver the protein to LAMP-2A on the lysosomal membrane for degradation. See text for details.

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