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Review

Role of autophagy in the pathogenesis of amyotrophic lateral sclerosis

Jae Keun Lee [a], Jin Hee Shin [b], Ji Eun Lee [c,d,*], Eui-Ju Choi [a,*]

[a] Laboratory of Cell Death and Human Diseases, Department of Life Sciences, Korea University, Seoul, South Korea
[b] Department of Microbiology, Ajou University School of Medicine, 206 World cup-ro, Yeongtong-gu, Suwon 443–749, South Korea
[c] Department of Health Sciences and Technology, Samsung Advanced Institute for Health Sciences & Technology (SAIHST), Sungkyunkwan University, South Korea
[d] Samsung Genome Institute (SGI), Samsung Medical Center, #81 Irwon-Dong Gangnam-Gu, Seoul 135–710, South Korea

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ABSTRACT

Amyotrophic lateral sclerosis (ALS) is a late-onset neurodegenerative disease characterized by the selective degeneration of upper and lower motor neurons associated with the abnormal aggregation of ubiquitinated proteins. The molecular mechanisms underlying the pathogenesis of ALS remain unclear, however. Autophagy is a major pathway for the elimination of protein aggregates and damaged organelles and therefore contributes to cellular homeostasis. This catabolic process begins with the formation of the double membrane-bound autophagosome that engulfs portions of the cytoplasm and subsequently fuses with a lysosome to form an autolysosome, in which lysosomal enzymes digest autophagic substrates. Defects at various stages of autophagy have been associated with pathological mutations of several ALS-linked genes including SOD1, p62, TDP-43, and optineurin, suggesting that such defects may play a causative role in the pathogenesis of this condition. In this review, we summarize the dysregulation of autophagy associated with ALS as well as potential therapeutic strategies based on modulation of the autophagic process.

1. Introduction

Amyotrophic lateral sclerosis (ALS)[1] is an adult-onset neurological disorder that is characterized by muscle weakness and atrophy, paralysis, and eventual death by respiratory failure and which results from the selective degeneration of upper and lower motor neurons that project from the spinal cord, brain stem, and motor cortex [1]. Most cases of ALS are sporadic, with ~10% of patients experiencing a familial form of the disease [1]. Both sporadic and familial cases share similar clinical characteristics.

A pathological hallmark of ALS is the presence of cytoplasmic inclusions or protein aggregates in affected motor neurons [2], suggesting that impairment of protein degradation plays a role in the disease process. Unlike mitotic cells, which are able to clear aggregates of intracellular proteins through their dilution or asymmetric distribution during cell division [3], postmitotic neurons rely on two major pathways of protein degradation for aggregate removal: the ubiquitin-proteasome system (UPS) and autophagy-associated lysosomal degradation. Whereas the UPS mostly mediates the degradation of short-lived proteins conjugated with ubiquitin, the autophagy-based system preferentially targets long-lived proteins and damaged organelles [4]. Dysfunction of these two pathways has been implicated in the pathogenesis of various neurodegenerative diseases including ALS [4].

Although the precise role of autophagy in the pathogenesis of ALS is still under controversy, emerging evidence supports the notion that defects in autophagic flux may contribute to the demise of motor neurons and disease progression in ALS [5]. Various stages of the autophagy-dependent lysosomal degradation of protein aggregates may be impaired in individuals with this disease. In this review, we summarize the case for a potential role of autophagic dysfunction in the pathogenesis of ALS.

2. Autophagic processing

Autophagy is a catabolic process that is highly conserved from yeast and fungi to plants and mammals and which is responsible for the lysosomal degradation of proteins and damaged organelles [6]. Autophagy has been classified into three subtypes on the basis of how cargo is delivered to lysosomes: chaperone-mediated autophagy, microautophagy, and macroautophagy [7]. In chaperone-mediated autophagy, substrate proteins interact with lysosome-associated membrane protein type 2 (LAMP2) and are subsequently transported into the lysosomal lumen for degradation [8]. Such substrates contain a consensus pentapeptide motif (KFERQ) that is recognized by a cytosolic chaperone, heat shock cognate 70 (HSC70) [9]. Microautophagy refers to the direct engulfment of cytoplasmic cargo by an autophagic tube, which forms by invagination of the lysosomal membrane and

* Corresponding authors.
E-mail addresses: jieun.lee@skku.edu (J.E. Lee), ejchoi@korea.ac.kr (E.-J. Choi).

[1] Abbreviations: ALS, amyotrophic lateral sclerosis; LAMP2, lysosome-associated membrane protein type 2; PAS, pre-autophagosomal structure; UPS, ubiquitin-proteasome system.

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undergoes vesicle scission into the lysosomal lumen [10]. Macroautophagy (hereafter referred to as autophagy) is mediated by a rearrangement of subcellular membranes that results in the envelopment of cytosol or organelles for delivery into lysosomes, where the enveloped cargo is digested and recycled [6].

Autophagy is initiated by the formation of a phagophore (or isolation membrane) in a manner dependent on multiple signaling molecules (Fig. 1). The phagophore undergoes elongation and is transformed into a double membrane-bound autophagosome [7]. The autophagosome is transported along a microtubule track toward the microtubule-organizing center, around which lysosomes are enriched [11]. During this trafficking process, the autophagosome undergoes fusion first with endosomal vesicles or multivesicular bodies (also known as amphisomes) and then with a lysosome, resulting in formation of an autolysosome. Finally, the contents of the autophagosome are digested by lysosomal acidic hydrolases, yielding basic metabolites that can be used for new synthetic processes or as an energy source. Many key regulators of autophagy, termed autophagy-related (Atg) proteins, were first identified in yeast but are evolutionarily conserved from yeast to mammals [12].

The autophagic process may be divided into three main stages: initiation, maturation, and degradation. Defects at any of these stages may give rise to neurodegeneration including that associated with ALS [5,13,14]. We will now focus on each stage to shed light on the potential role of autophagic defects in the pathogenesis of ALS.

3. ALS-associated defects at different stages of autophagy

3.1. Initiation stage: substrate recognition and autophagosome formation

Initiation of autophagy involves the rearrangement of subcellular membranes to allow the sequestration of cargo as well as the consecutive formation of a protein-kinase autophagy regulatory complex and a lipid–kinase signaling complex. The rearrangement of subcellular membranes requires recruitment of Atg proteins to the phagophore and leads to autophagosome formation. The initial event, referred to as vesicle nucleation, is induced by phosphorylation (activation) of the Unc51-like kinase 1 (ULK1)–Atg13–FIP200 complex under the control of mammalian target of rapamycin (mTOR) complex 1 (mTORC1) or AMP-activated protein kinase (AMPK) [15,16]. The activated ULK1–Atg13–FIP200 complex promotes movement of a multiprotein complex containing Beclin-1 (mammalian ortholog of yeast Atg6) and class III phosphoinositide 3-kinase (PI3K CIII, also known as Vps34) to the pre-autophagosomal structure (PAS), thereby triggering autophagosome formation [17] (Fig. 1A). Elongation of the PAS and its

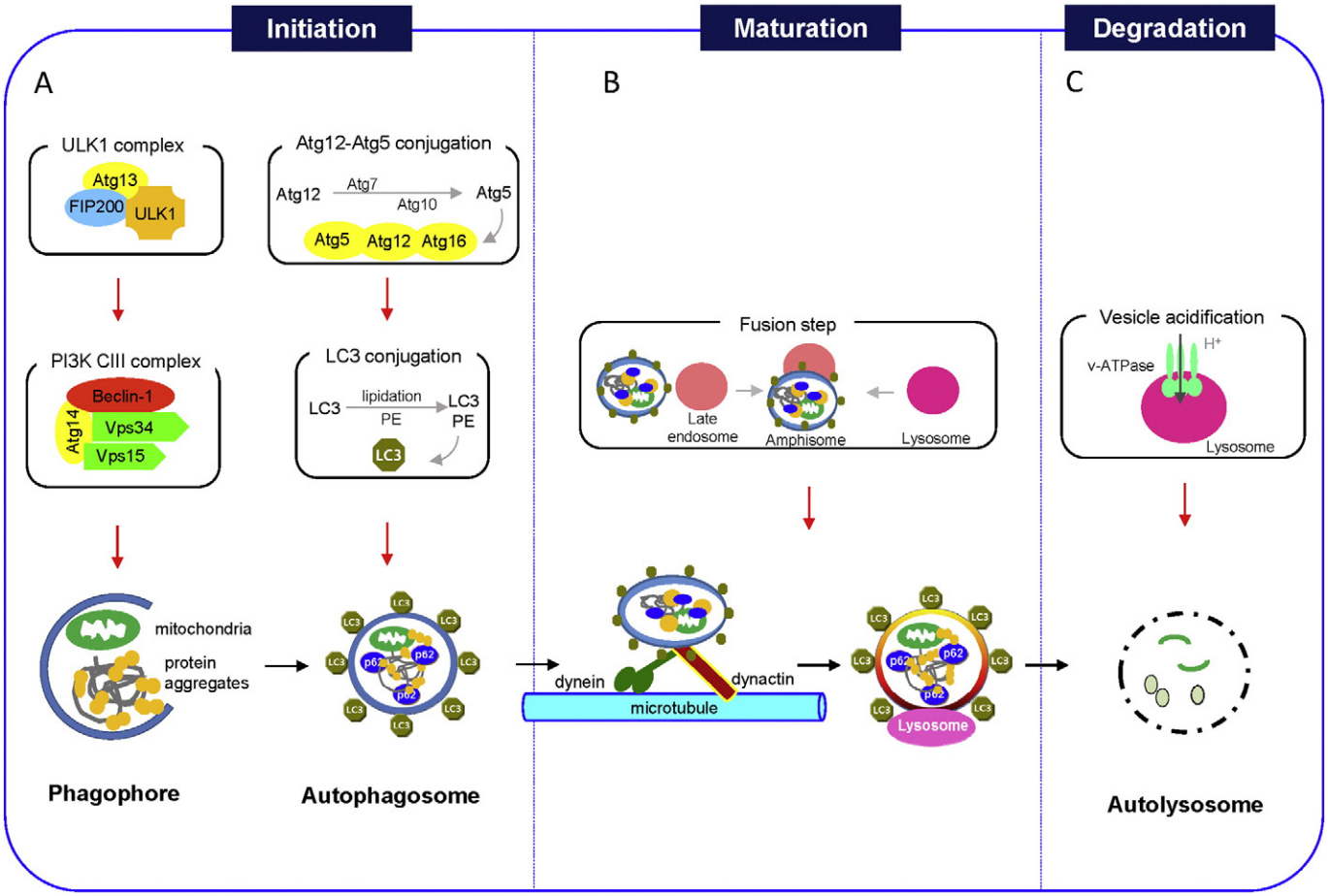

Fig. 1. Three key stages in the process of autophagy. A. The initiation stage of autophagy includes vesicle nucleation for a specific membrane structure known as the phagophore, elongation and closure of this structure to form a double membrane–bound vacuole, and formation of the autophagosome. Inhibition of mTOR or activation of AMPK triggers vesicle nucleation in a manner dependent on regulation by the ULK1 complex (ULK1, Atg13, FIP200) and the PI3K CIII complex (Vps34, Vps15, Atg14, Beclin-1), both of which come together at the phagophore assembly site. Elongation of the phagophore is regulated by two types of ubiquitination-like reaction. In the first reaction, Atg12 is covalently conjugated with Atg5 by the sequential actions of Atg7, Atg10, and Atg16. Docking of the conjugate on the phagophore promotes the second ubiquitination-like reaction, the covalent conjugation of phosphatidylethanolamine (PE) to LC3. This conjugation facilitates closure of the inner and outer bilayers of the phagophore. B. The maturation stage of autophagy involves the consecutive fusion of the autophagosome with endocytic compartments (late endosomes and amphisomes) and a lysosome to form the autolysosome. This stage begins with movement of the cargo-loaded autophagosome along a microtubule track toward the microtubule-organizing center in a manner dependent on the dynein–dynactin complex. C. The degradation stage includes the digestion of engulfed material in the autolysosome by acidic hydrolases originally present in the lysosome. Acidification of the lysosome is highly dependent on v-ATPase, a multimeric proton-pumping enzyme.