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Review

The mechanistic role of chemically diverse metal ions in the induction of autophagy

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ABSTRACT

Autophagy is an evolutionary conserved cellular catabolic degradation process in response to stress which involves lysosomal degradation of unnecessary or damaged organelles and misfolded proteins. This is primarily a pro-survival pathway providing the cell with essential nutrients during stressful conditions. There are number of essential metal ions, which are required for normal physiological functioning of cells. Studies have shown that autophagy can be regulated by cellular metal ion concentrations. On the other hand, autophagy is also shown to regulate intracellular levels of certain metal ions. This review discusses recent advances in the research examining the role of metal ions in the autophagic pathway.

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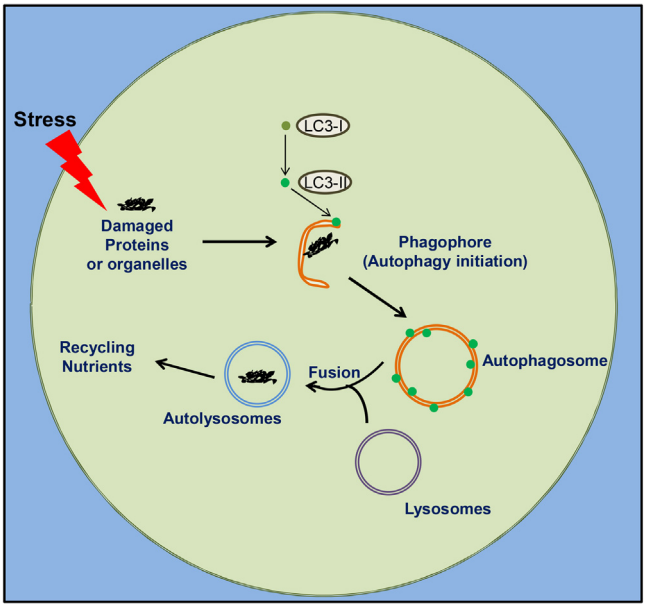

Fig. 1. The Autophagic Pathway: Cellular stress results in increased levels of damaged proteins and organelles (*i.e.*, autophagic cargo) in cells, which results in a trigger for induction of the autophagic pathway. Initially, a crescent-shaped structure shown as the phagophore is formed around the damaged autophagic cargo. This is followed by lipidation of the protein, LC3-I, to LC3-II, which is subsequently recruited onto the phagophore membrane. Following LC3-II recruitment, the phagophore membrane elongates and forms a closed double membranous structure known as the autophagosome. The autophagosome then fuses with the lysosome to form an autolysosome. The acidic hydrolases from the lysosomes digest the damaged autophagic cargo to recycle nutrients back into the cell for reuse.

1. Autophagy

Autophagy is a stress-induced catabolic pathway which involves intracellular breakdown of redundant or damaged organelles and misfolded proteins [1–3]. This process is crucial for maintenance of cellular homeostasis, quality control, defense against intra- and extracellular insults and sustaining energy balance in cells [1–3]. This is performed by providing essential macromolecules from degradation of intracellular components [1–3]. Autophagy can be non-selective, which leads to lysosomal processing of bulk cytoplasmic material, or can be selective by involving the targeted degradation of specific proteins and/or organelles such as mitochondria (mitophagy), ribosomes (ribophagy), or lipids (lipophagy) [4,5]. The autophagic process involves entrapment of the cytoplasm and/or organelles into a double membranous vesicle known as autophagosomes (Fig. 1) [1–3]. The autophagosome fuses with the lysosome to form a structure known as autolysosome (Fig. 1) [1–3]. Further, acidic hydrolases from lysosomes causes degradation of damaged proteins/organelle and recycle the products for cell biosynthesis (Fig. 1) [1–3]. Autophagy is also important in enabling cells to survive stressful conditions such as nutrient deprivation and infection by pathogens, as well as for engulfing apoptotic cells [5–7].

1.1. Types of autophagy

There are three major types of autophagy associated with specific functions: macroautophagy, microautophagy and chaperone-mediated autophagy. Macroautophagy is a process involving the formation of the membrane *de novo* in the cytosol [8]. As the vesicle elongates, it seals and sequesters whole cytosolic regions [8]. This form of autophagy is itself classified into mitophagy (autophagic digestion of the mitochondria) [9,10]; nucleophagy (selective digestion of portions of the nucleus) [9,11]; pexophagy (selective degradation of peroxisomes) [12–14]; aggrephagy (selective elimination of accumulated and aggregated ubiquinated proteins) [15]; and xenophagy (selective recognition and degradation of intracellular bacteria) [16]. Microautophagy is another autophagic process where a region of the cytosol is sequestered with the lysosomal membrane invaginating to encircle the cargo [8]. This cellular cargo is then internalized into the lumen of the lysosome in single membrane vesicles [8]. Chaperone-mediated autophagy involves controlling the translocation of single cytosolic proteins into the lysosomal lumen for degradation [8]. Macroautophagy is a major autophagic pathway in cells and for the purpose of this review, we will refer to macroautophagy as autophagy.

1.2. Regulation

Autophagy begins with the formation of a membranous structure known as a phagophore, which is believed to be derived from multiple intracellular sources [1,17]. Phagophore formation is controlled by the human autophagy initiation kinase unc-51-like kinase 1 (ULK1) and unc-51-like kinase 2 (ULK2) complexes (Fig. 2) [1,17]. The ULK1 kinase complex consists of ULK1 (human homologue of Atg1), Atg13 and FIP200 (human homologue of Atg17) (Fig. 2) [18]. This complex is itself controlled by nutrient-sensing kinase mammalian target of rapamycin complex 1 (mTORC1) from where it integrates stress signals [1,17]. Inhibition of mTORC1 kinase activity by adenosine monophosphate-activated protein kinase (AMPK) occurs when nutrients are limited, which allows autophagosome formation to proceed by nucleation of the phagophore [18–20]. This process is dependent on phosphatidylinositol 3-phosphate [PtdIns(3)P] which is converted from phosphatidylinositol (PtdIns) by a lipid complex containing the following proteins, namely vacuolar sorting protein 34 (Vps34; a class III phosphatidylinositol-3-kinase; PI3K), vacuolar protein sorting 15 homologue (Vps15; also known as p150) and Beclin-1 (Fig. 2) [17,18,21].

On the cellular membrane, PtdIns(3)P can recruit two ubiquitin-like protein conjugation systems resulting in the Atg12-Atg5-Atg16L complex being localized to the outer membrane (Fig. 2) [17,22]. The complex initiates the recruitment and conversion of the cytosolic protein light chain 3 (LC3) to the membrane-bound LC3-II [1,18]. The conversion between the different forms of LC3 occurs *via* the cleavage of LC3 by Atg4 protease to form LC3-I [1]. The exposed *C*-terminal glycine residue is activated by Atg7 and then transferred to Atg3 [1,23]. This is then lipidated by conjugation with phosphatidylethanolamine (PE) to form LC3-II [1,18]. The lipidation of LC3 is further controlled locally by Atg16 [1,24].

LC3-II is incorporated into the inner and outer surfaces of the autophagosome which depends on Atg5-Atg12 [1]. The autophagosome can recruit the cargo adaptor proteins: p62, neighbour of BRCA1 gene 1 (Nbr1), or Nip-like protein X (NIX) [22,25,26]. These proteins further recruit and regulate the packing and delivery of cargo (*i.e.*, ubiquinated proteins for p62, ubiquinated substrates for Nbr1 and damaged organelles for NIX) from the cytoplasm [17,22,25,27,28]. This process of autophagosome maturation is controlled by Ras-related protein 7A (RAB7A), which is activated by Beclin-1 recruited UV radiation associated gene (UVRAG) [22].

The autophagosomes can dock and fuse with lysosomes by involving membrane trafficking proteins such as lysosomal-associated membrane protein 2 (LAMP2) and the small guanosine triphosphatase (GTPase), RAB7A, to form autolysosomes (Fig. 2) [17,22]. The contents of the autolysosome are degraded by hydrolases and then exported from this organelle and recycled for processes involved in cellular biosynthesis [5]. The end products from this degradation process are basic molecular building blocks including nucleotides, fatty acids and amino acids, which are returned to the cytoplasm by the involvement of lysosomal