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Review Article

Molecular signaling toward mitophagy and its physiological significance

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ABSTRACT

Mitochondrial autophagy or mitophagy is a cellular metabolic pathway that mediates the selective elimination of dysfunctional or unwanted mitochondria. Considerable advancements have been made to elucidate the molecular mechanism behind mitophagy, particularly Parkin-mediated mitophagy. Several mitophagy receptors have been discovered in different physiological settings, including ATG32 in yeast as well as NIX, BNIP3, and FUNDC1 in mammalian cells. However, the signaling events that regulate these mitophagy receptors and their physiological significance in human diseases are poorly understood. In this paper, we review recent advancements in mitophagy at the cellular and molecular levels.

Contents

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Introduction

Mitochondria are the power houses of cells and the headquarters of programmed cell death. Mitochondria are also the centers for production of free radical oxygen species during oxidative phosphorylation. Thus, the accumulation of damaged mitochondria can be detrimental to cells. Mitochondrial quality and quantity should therefore be closely monitored for the well-being of cells. Damaged or unwanted mitochondria can be selectively removed by mitochondrial autophagy or mitophagy, a catabolic process for lysosome-dependent degradation. The molecular mechanism of mitophagy has begun to emerge. Several mitophagy receptors have been reported, including ATG32 in yeast [1,2], NIX/BNIP3L [3], BNIP3 [4], and the newly identified *f*un14 *d*omain-*c*ontaining *p*rotein 1 (FUNDC1) in mammalian cells [5]. These proteins interact with LC3 via their conserved *L*C3 *i*nteraction *r*egion (LIR) for mitophagy. Mitophagy receptors are regulated by post-translational modification such as phosphorylation in response to different stresses, highlighting that this important process is tightly controlled in the cell. E3 ubiquitin ligase Parkin and phosphatase and tensin homolog (PTEN)-induced putative protein kinase 1 (PINK1) have critical functions for the removal of depolarized mitochondria. When mitochondrial potential is lost, Pink1 is stabilized and recruits Parkin, which ubiquitinates a number of mitochondrial membrane proteins and leads to selective mitophagy [6,7]. These Parkin/pink1 and mitophagy receptor-dependent pathways for mitophagy are likely interrelated. In this paper, we review recent advances regarding the molecular regulations of mitophagy receptor-mediated and Parkin/pink1-dependent mitophagy.

Non-selective versus selective autophagy

Autophagy is a homeostatic process by which cellular components are sequestered within autophagosomes, which then fuse with lysosome/vacuole for degradation. Although autophagy was initially described in mammalian cells more than a half century ago [8], the molecular pathway of this process was only understood recently. Through the pioneering work of Ohsumi et al. [9], a number of autophagy-related genes (ATGs) have been cloned through elegant yeast genetics study. Around the same time, additional and partially overlapping ATGs have been found by Thumm and Klionsky [10,11]. These genes regulate the progression of autophagy, which includes induction, nucleation, vesicle expansion, completion, fusion with lysosome/vacuole, and degradation of the content that can be exported into the cytosol as biochemical building blocks for cell survival under stress conditions (Fig. 1) [12]. The membrane sources of the autophagosome might be the endoplasmic reticulum (ER) [13], mitochondria [14], plasma membrane [15], and Golgi [16,17].

Autophagosome biogenesis initiates from the appearance of a flat membrane sheet known as the phagophore in yeast or isolation membrane in mammals (Fig. 1). Briefly, in mammals, autophagosome assembly requires activation of the ULK1 (UNC-51-like kinase 1) complex (including ULK1, ATG13, focal adhesion kinase family interacting protein of 200 kDa (FIP200) and ATG101) and recruitment of the class III phosphoinositide 3-kinase (PI3K) Vps34 complex (including Beclin-1, Atg14, Ambra1, Vps34 and Vps15) for producing phosphatidylinositol 3-phosphate (PI3P). Formation of PI3P recruits the PI3P-binding proteins double FYVE domain-containing proteins (DFCP1) and

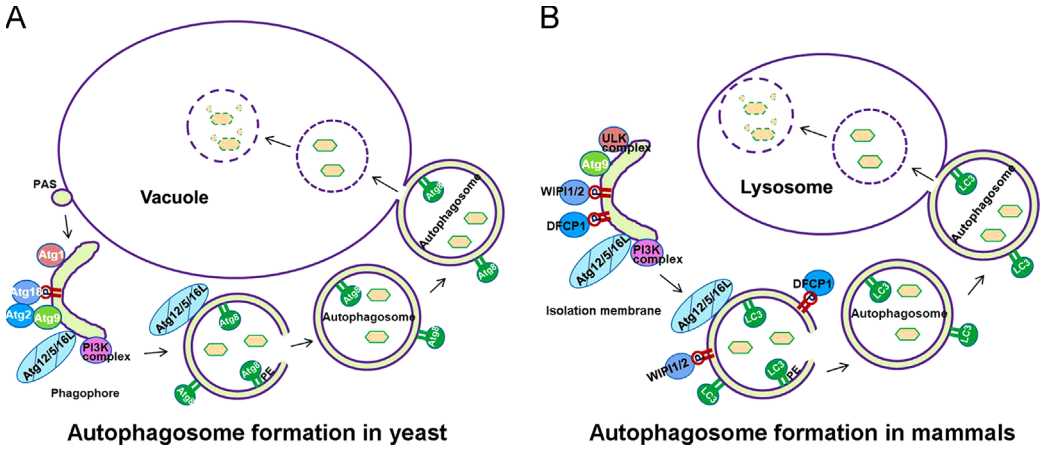

Fig. 1 – (A) Autophagosome formation in yeast. Atg1, a central member of a kinase complex, is a Ser/Thr kinase and its kinase activity is enhanced in autophagy induction. Atg9-containing vesicles shuttle between putative membrane sources and the phagophore assembly site (PAS) and may function in delivering membrane to the expanding phagophore. Both Atg8-PE conjugates and The Atg12–Atg5–Atg16 complex contribute to the elongation of the phagophore. Atg8 is incorporated into both sides of an autophagosome membrane. The single-membrane vacuole fuses with double-membrane autophagosomes to degrade the contents. (B) Autophagosome formation in mammals. Upon nutrient deprivation, ULK1 complex, including ULK1 (mammalian Atg1 orthologue), Atg13, Atg101 and FIP200 escapes from mTOR suppression and regulates the activity of the class III PI3K complex, including Beclin-1 (mammalian Atg6), Atg14, Ambra1, Vps34 and Vps15, to form PI3P, which further recruits the PI3P-binding proteins DFCP1 and WIPI1/2 to drive the formation of IM. The elongation and closure of the IM is regulated by the Atg5–Atg12–Atg16L1 complex and LC3-PE conjugates. The engulfed components of the cytoplasm in autophagosome are then delivered to lysosome for degradation.