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Review

Impairment of autophagy: From hereditary disorder to drug intoxication

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ABSTRACT

At first, the molecular mechanism of autophagy was unveiled in a unicellular organism *Saccharomyces cerevisiae* (budding yeast), followed by the discovery that the basic mechanism of autophagy is conserved in multicellular organisms including mammals. Although autophagy was considered to be a non-selective bulk protein degradation system to recycle amino acids during periods of nutrient starvation, it is also believed to be an essential mechanism for the selective elimination of proteins/organelles that are damaged under pathological conditions. Research advances made using autophagy-deficient animals have revealed that impairments of autophagy often underlie the pathogenesis of hereditary disorders such as Danon, Parkinson's, Alzheimer's, and Huntington's diseases, and amyotrophic lateral sclerosis. On the other hand, there are many reports that drugs and toxicants, including arsenic, cadmium, paraquat, methamphetamine, and ethanol, induce autophagy during the development of their toxicity on many organs including heart, brain, lung, kidney, and liver. Although the question as to whether autophagic machinery is involved in the execution of cell death or not remains controversial, the current view of the role of autophagy during cell/tissue injury is that it is an important, often essential, cytoprotective reaction; disturbances in cytoprotective autophagy aggravate cell/tissue injuries. The purpose of this review is to provide (1) a gross summarization of autophagy processes, which are becoming more important in the field of toxicology, and (2) examples of important studies reporting the involvement of perturbations in autophagy in cell/tissue injuries caused by acute as well as chronic intoxication.

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Abbreviations: LKB1, liver kinase B1; AMPK, AMP-activated protein kinase; mTOR, mammalian target of rapamycin; ULK1/2, unc-51-like kinase1/2; FIP200, focal adhesion kinase family-interacting protein of 200 kDa; PI, phosphatidylinositol; LC3, microtuble-associated protein 1 light chain 3; LAMP, lysosome-associated membrane protein; FKBP12, FK506-binding protein 12; ROS, reactive oxygen species; MPT, mitochondrial permeability transition; SOD, superoxide anion dismutase; PINK1, PTEN-inducible putative kinase protein1; BNIP3, BCL2/adenovirus E1B nineteen kDa protein-interacting protein 3; Nix, NIP3-like protein X; NPC, Niemann–Pick type C; p62/SQSTM1, p62/sequestosome1; NBR1, neighbor of Brca1 gene; Nrf2, nuclear factor-erythroid 2-related factor 2; Keap1, Kelch-like ECH associated protein1; PML/RARA, promyelocytic leukemia protein/retinoic acid receptor α; CYP2E1, cytochrome P450 2E1; TFEB, transcription factor EB.

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1. Introduction

Autophagy is a lysosomal pathway to degrade cytoplasmic components. Autophagy is activated during starvation to recycle cytplasmic materials. Also, autophagy is activated during stress conditions to eliminate dysfunctional proteins/organelles. Autophagy had already been observed in the 1960s under electron microscopy, although the elucidation of its molecular mechanism started only in the 1990s. Using the method of yeast genetics, at least 14 genes were identified as involved in the execution of autophagy (Tsukada and Ohsumi, 1993). Although these genes were at first referred to as Apg (autophagy-defective) genes (Tsukada and Ohsumi, 1993), they were later renamed Atg (autophagy-related) genes (Klionsky et al., 2003) together with the genes discovered in the analysis of other pathways (Oda et al., 1996). Almost all Atg genes are conserved from yeast to humans, demonstrating that the process of autophagy is highly conserved among eukaryotes. Autophagy has attracted much attention since it plays essential roles in cellular protection processes against pathogenesis in multiple diseases (Mizushima et al., 2008). In yeast, autophagy has been shown to be an essential cellular process for survival during starvation periods. Since nutrient deficiency is a component of various pathological states such as ischemia, it is natural that one might expect autophagy also to play an important role in protection against pathogenesis in mammals. Indeed, the involvement of autophagy in the defense against ischemic heart damage has repeatedly been reported (Gustafsson and Gottlieb, 2009). On the other hand, intracellular autophagic vacuolization has been observed in multiple tissues/organs during the pathogenesis of diseases and drug intoxication. Therefore, autophagy has been suspected to represent another cell-suicide mechanism other than apoptosis. However, in many cases, autophagic vacuolization represents abrogation, not completion, of the autophagy process (Kroemer and Levine, 2008; Shen et al., 2012); impairments in autophagy flux aggravate cellular injuries that ultimately lead to organ damage. Moreover, although autophagy has been considered to be a bulk protein degradation system in cells, recent research progress indicates that autophagy also plays a pivotal role in cargo-specific degradation machineries. These autophagy-targeted cargos include dysfunctional organelles as well as protein aggregates. Hereditary neuronal disorders such as Parkinson's disease, Alzheimer disease, and Huntington's disease have been shown to be associated with defects in the process of cargo-specific autophagy. Genetically modified animals suffering from tissue-specific deficiencies in autophagy frequently show phenotypes resembling these hereditary disorders, suggesting the involvement of unfulfilled autophagy in the pathogenesis of these diseases. Drugs that mimic the pathogenesis of these disorders have been shown to cause perturbations in autophagy, indicating that autophagy impairment needs to be taken into account in the field of toxicology research.

2. Core machinery of autophagy

2.1. Typical process of autophagy during starvation

Three types of autophagy, macroautophagy, microautophagy, and chaperone-mediated autophagy, have been reported (Fig. 1). Macroautophagy is considered to be the central process for cell cannibalism observed during nutrient starvation, and we hereafter refer to macroautophagy as autophagy for simplification. As autophagy is typically observed during starvation, energy-sensing serine/threonine kinases, LKB1 (liver kinase B1), AMPK (AMP-activated protein kinase), and mTOR (mammalian target of rapamycin), are involved in the initiation of autophagy. The LKB1-AMPK axis is activated when a decrease in the intracellular ATP/ADP ratio is sensed (Alexander and Walker, 2011), while mTOR is activated under nutrient-rich conditions (Jewell et al., 2013). AMPK and mTOR phosphorylate the same target protein, ULK1/2 (unc-51-like kinase1/2, mammalian orthologue for Atg1), at distinct serine/threonine residues (Alers et al., 2012). The phosphorylation of ULK1/2 by AMPK results in its activation while, on the other hand, mTOR phosphorylates and inactivates ULK1/2 under nutrient-rich conditions (Alers et al., 2012). FIP200 (focal adhesion kinase family-interacting protein of 200 kDa, a putative mammalian orthologue of Atg17) is a substrate of ULK1/2, and forms a stable complex along with Atg13, another ULK1/2 substrate. Although this complex seems to be formed even under nutrient-rich conditions, ULK1/2-Atg13-FIP200 is a prerequisite for the formation of the phagophore (Hosokawa et al., 2009) at the so-called PAS (phagophore assembly site, also referred to as the pre-autophagosomal structure). Dynamic membrane rearrangement during autophagy is initiated by the formation of the phagophore, in which beclin-1 (a mammalian homologue of yeast Atg6) forms a complex with Vps34 (class III phosphatidylinositol-3 kinase) and generates phosphatidylinositol-3-phosphate (PI3P) (Kihara et al., 2001; Rubinsztein et al., 2012; Suzuki and Ohsumi, 2010). The ER–mitochondria contact site seems to be at least one of the places where autophagosomal membranes arise (Hamasaki et al., 2013). Two ubiquitin-like conjugation systems are essential for autophagosome formation (Ohsumi, 2001; Ohsumi and Mizushima, 2004). In one, a ubiquitin-like protein, Atg12, is activated through E1-like Atg7 and E2-like Atg10, and is thereby conjugated to Atg5. This Atg12-Atg5 conjugate associates with Atg16L, and then the Atg5-Atg12-Atg16L complex formed attaches to the phagophore (Fujita et al., 2008). Second, another ubiquitin-like protein, LC3 (microtuble-associated protein 1 light chain 3), a mammalian homologue of yeast Atg8, is C-terminally proteolyzed by a cysteine protease, Atg4, to yield form I of LC3 (LC3-I). Phosphatidylethanol amine (PE) is then added at the C-terminus of LC3-I to produce form II of LC3 (LC3-II), which is then anchored to the phagohore membrane (Ichimura et al., 2000; Kabeya et al., 2000). Compared with the Atg12-Atg5 conjugation system, the formation of LC3-II is mediated through the same E1-like Atg7 and other

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