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Why is autophagy important in human diseases?

Kaipeng Jing[1,3] and Kyu Lim[1,2,3,4]

[1]Department of Biochemistry
College of Medicine
[2]Cancer Research Institute and
[3]Infection Signaling Network Research Center
Chungnam National University
Daejeon 301-747, Korea
[4]Corresponding author: Tel, 82-42-580-8223;
Fax, 82-42-580-8121; E-mail, kyulim@cnu.ac.kr
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Abbreviations: ATG, autophagy-related; LC3, microtubule-associated protein 1 light chain 3; UPS, ubiquitin-proteasome system

Abstract

The process of macroautophagy (referred to hereafter as autophagy), is generally characterized by the prominent formation of autophagic vesicles in the cytoplasm. In the past decades, studies of autophagy have been vastly expanded. As an essential process to maintain cellular homeostasis and functions, autophagy is responsible for the lysosome-mediated degradation of damaged proteins and organelles, and thus misregulation of autophagy can result in a variety of pathological conditions in human beings. Although our understanding of regulatory pathways that control autophagy is still limited, an increasing number of studies have shed light on the importance of autophagy in a wide range of physiological processes and human diseases. The goal of the reviews in the current issue is to provide a general overview of current knowledge on autophagy. The machinery and regulation of autophagy were outlined with special attention to its role in diabetes, neurodegenerative disorders, infectious diseases and cancer.

Keywords: autophagy; disease; physiology

What is autophagy?

Macroautophagy (referred to hereafter as autophagy) is a genetically regulated and dynamic process associated with the formation of autophagosome, a double-membrane cytoplasmic vesicle that engulfs cellular components. The autophagosome formation starts at phagophore (also known as isolation membrane or sequestering membrane) and requires the conjugation of microtubule-associated protein 1 light chain 3 (LC3), which regulates the phagophore expansion and completion of the sequestering vesicle (Xie *et al*., 2008). The completed autophagosome then fuse with lysosome, becoming autolysosome. Sequestered components are degraded by lysosomal hydrolases and released into the cytosol by lysosomal efflux permeases. This lysosome-mediated degradation system plays a regulatory role in mammalian cell biology by clearing damaged organelles and recycling autophagy-derived nutrients (Figure 1).

General functions of autophagy

The process of protein degradation and organelle turnover is required for the survival of cells, and the disruption of this process can result in the abnormal cell growth or cell death, leading to various disease states (Klionsky and Emr, 2000). In eukaryotic cells, this process is mainly regulated by two major systems named the ubiquitin-proteasome system (UPS) and autophagy, which work cooperatively to control intracellular protein degradation and organelle turnover (Klionsky and Emr, 2000; Rubinsztein, 2006). Whereas the UPS specializes in short-lived protein degradation, autophagy mainly functions to degrade long-lived proteins and damaged organelles (Rubinsztein, 2006; Nedelsky *et al*., 2008). Although autophagy is considered to be a nonselective degradation process of engulfment of cytoplasm traditionally, increasing evidence indicates the existence of selective autophagy which specifically degrades mitochondria (mitophagy), endoplasmic reticulum (reticulophagy), microorganisms (xenophagy) and aggregated proteins (aggrephagy), etc. (Johansen and Lamark, 2011).

Depending on the different cellular contexts and stimuli, the outcome of autophagy can promote either

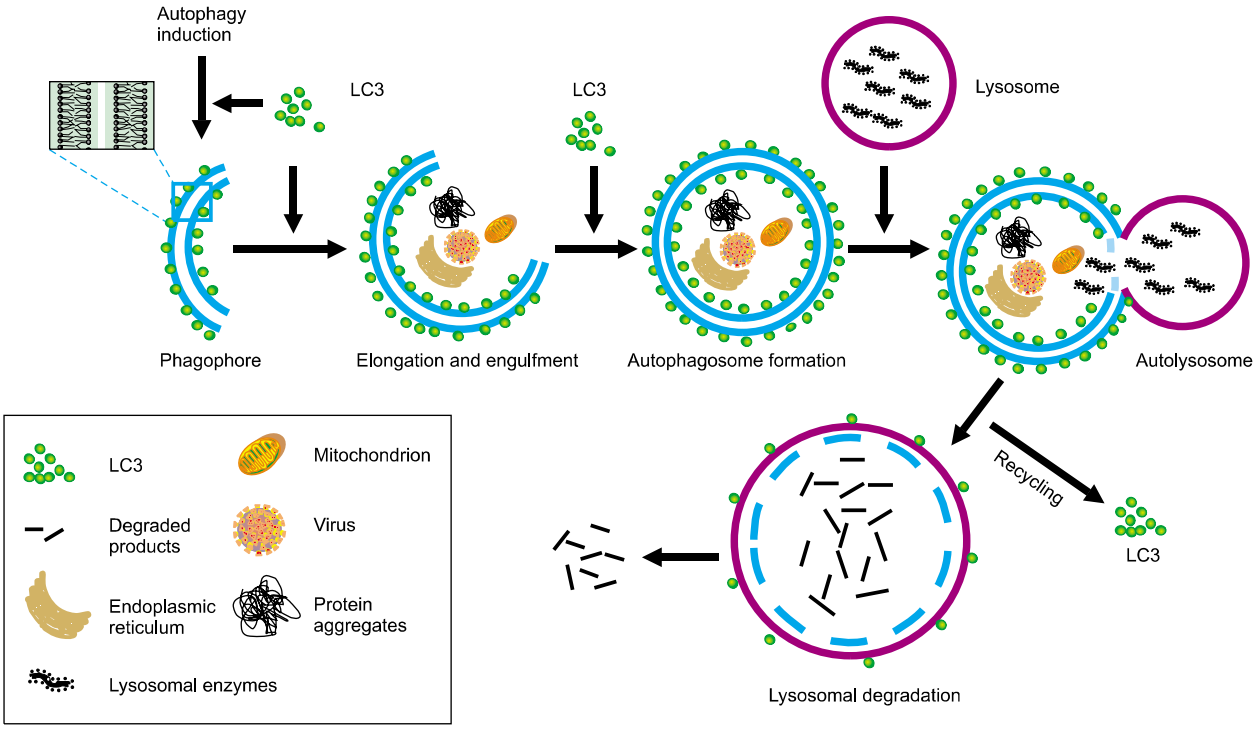

Figure 1. Schematic diagram of autophagic progression. Autophagy induction signal leads to form a sequestering membrane called phagophore. Following a sequence of ubiquitination-like reactions, LC3 conjugates to the sequestering membrane and controls the elongation of phagophore. As the phagophore expands, cytoplasmic constituents, including organelles such as mitochondria and endoplasmic reticulum, aggregated proteins and foreign organisms (bacteria and virus) are enwrapped. At the end of elongation, sequestering membrane closes and results in the formation of a double-membrane vesicle, autophagosome. Once the autophagosome is formed, it is delivered to fuse with lysosome to form autolysosome for degradation. Lysosomal hydrolases degrades the cargo together with the inner membrane of autophagosome, and LC3 from the outer membraneas well as the autophagy-derived nutrients are recycled.This autophagic process can act as a mechanism to keep homeostatic balance and support cell survival. However, it can also cause cell death directly or indirectly.

cell survival or cell death. However, the mechanisms underlying the dual role for autophagy in deciding the destiny of cells remain unclear. On one hand, since autophagy provides cells with nutrients and eliminates damaged organelles, it is primarily believed to function as a protective mechanism for cell survival, particularly under unfavorable conditions. Indeed, cytotoxic drugs often trigger autophagy activation, and then autophagy inhibition has been reported to potentiate apoptotic cell death induced by several anticancer drugs (Amaravadi *et al*., 2007; Song *et al*., 2008). Nevertheless, autophagy impairment can also block or delay the development of cell death (Berry and Baehrecke, 2007; Yuk *et al*., 2010; Jing *et al*., 2011), and in some instances, autophagy itself is capable of inducing cell death (Shao *et al*., 2004; Yousefi *et al*., 2006). This role of autophagy in enhancing cell death may be related to the degradation of essential factors for cell survival (Yu *et al*., 2006) or its effect on energy maintenance considering that ATP is required during programmed cell death, such as apoptosis (Qu *et al*., 2007).

The impacts of autophagy on human physiology and diseases

Nearly all eukaryotic cells undergo autophagy at a basal level under normal physiological conditions, and cells deficient in autophagy show diffuse abnormal protein accumulation and mitochondria disorganization (Hara *et al*., 2006; Ebato *et al*., 2008), suggesting that cells use autophagy to maintain cellular homeostasis by eliminating damaged organelles and protein aggregates, which resist degradation *via* UPS in normal growing conditions. In addition to the effect on cellular homeostasis maintenance, autophagy also regulates rapid cellular changes essential for mammalian development and differentiation. For instance, it has been demonstrated that autophagy is required in mitochondrial elimination during erythrocyte and adipocyte maturation (Mortensen *et al*., 2010; Goldman *et al*., 2011). Furthermore, autophagy is not only responsible for the clearance of abnormal proteins and organelles, but also participates in the removing of infectious agents, including bacteria and viruses from host cells. Recent data from stud-

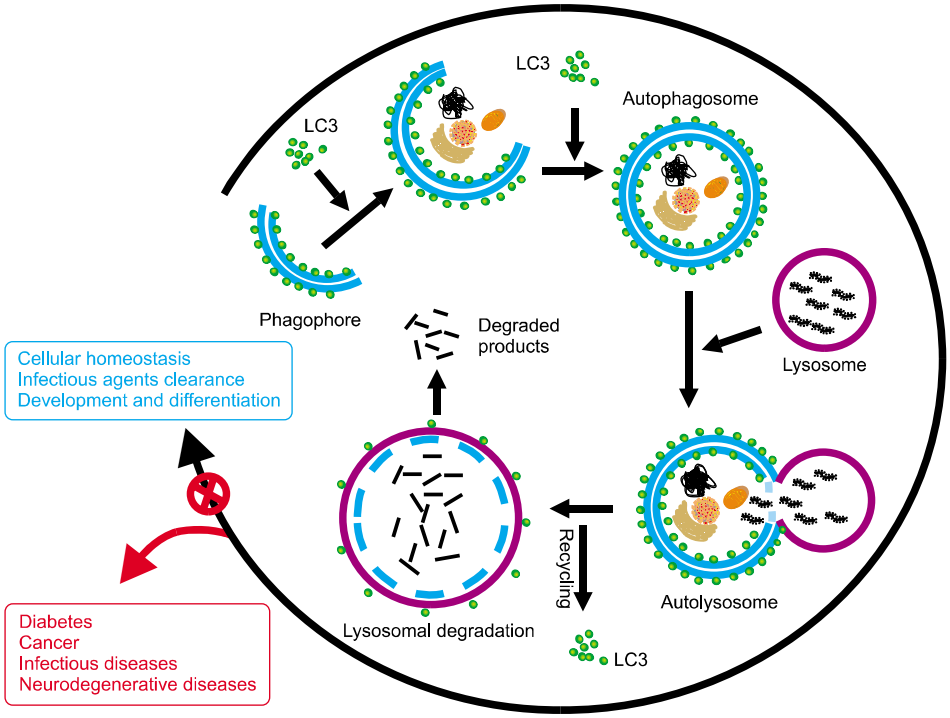

Figure 2. Dysregulated autophagy is involved in several human diseases. Autophagy contributes to maintain cellular homeostasis and is critical in a wide range of normal human physiological processes. Accordingly, a growing number of diseases are linked to the misregulation of autophagic process. ⓧ, dysregulation of autophagy.

ies of cell models show that autophagy upregulation might be valuable for eliminating *Mycobacterium tuberculosis* (Gutierrez *et al*., 2004), *Streptococcus* (Nakagawa *et al*., 2004), mycobacteria (Singh *et al*., 2006; Shin *et al*., 2010) and herpes simplex virus (Talloczy *et al*., 2006). This function of autophagy appears to be accounted for by both innate and adaptive immune responses (Levine and Deretic, 2007).

Because of the importance of autophagy in mammalian physiology, it is therefore reasonable to assume that autophagy impairment could contribute to human diseases. However, although autophagy was first described morphologically in mammalian cells in 1960s (Deter *et al*., 1967), until the discovery of a group of autophagy-related (ATG) genes in 1990s (Tsukada and Ohsumi, 1993), the role of autophagy in various human disease states was unclear, and only in the past decade has the connection between autophagy and human disease become the subject of intense study. To date, autophagy has been linked to a growing list of diseases, and it appears that more autophagy-associated diseases will be discovered in the future. Although the exact mechanisms underlying the autophagy-associated diseases at the molecular level remain not fully understood, the recent advances in autophagy research present a potential target for manipulation of autophagy in human diseases (Figure 2).

The following reviews aim at outlining our current understanding of mechanisms involved in autophagy activation, and its important roles in human physiology and diseases, including diabetes mellitus, neurodegenerative disorders, infectious diseases and cancer.

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