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Autophagy in the Pathogenesis of Disease

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Autophagy is a lysosomal degradation pathway that is essential for survival, differentiation, development, and homeostasis. Autophagy principally serves an adaptive role to protect organisms against diverse pathologies, including infections, cancer, neurodegeneration, aging, and heart disease. However, in certain experimental disease settings, the self-cannibalistic or, paradoxically, even the prosurvival functions of autophagy may be deleterious. This Review summarizes recent advances in understanding the physiological functions of autophagy and its possible roles in the causation and prevention of human diseases.

Introduction

Fasting has been an integral part of health and healing practices throughout the recorded history of mankind. This ancient tradition may be partially rooted in a cellular process we are now beginning to understand in modern scientific terms. One of the most evolutionarily conserved cellular responses to organismal fasting is the activation of the lysosomal degradation pathway of autophagy, a process in which the cell self-digests its own components. This self-digestion not only provides nutrients to maintain vital cellular functions during fasting but also can rid the cell of superfluous or damaged organelles, misfolded proteins, and invading microorganisms. Interestingly, self-digestion by autophagy—a process that is potently triggered by fasting—is now emerging as a central biological pathway that functions to promote health and longevity.

The Autophagic Pathway

Autophagy (from the Greek, "auto" oneself, "phagy" to eat) refers to any cellular degradative pathway that involves the delivery of cytoplasmic cargo to the lysosome. At least three forms have been identified—chaperone-mediated autophagy, microautophagy, and macroautophagy—that differ with respect to their physiological functions and the mode of cargo delivery to the lysosome. This Review will focus on macroautophagy (herein referred to as autophagy), the major regulated catabolic mechanism that eukaryotic cells use to degrade long-lived proteins and organelles. This form of autophagy involves the delivery of cytoplasmic cargo sequestered inside double-membrane vesicles to the lysosome (Figure 1). Initial steps include the formation (vesicle nucleation) and expansion (vesicle elongation) of an isolation membrane, which is also called a phagophore. The edges of the phagophore then fuse (vesicle completion) to form the autophagosome, a double-membraned vesicle that sequesters the cytoplasmic material. This is followed by fusion of the autophagosome with a lysosome to form an autolysosome where the captured material, together with the inner membrane, is degraded (Figure 1).

Autophagy occurs at low basal levels in virtually all cells to perform homeostatic functions such as protein and organelle turnover. It is rapidly upregulated when cells need to generate intracellular nutrients and energy, for example, during starvation, growth factor withdrawal, or high bioenergetic demands. Autophagy is also upregulated when cells are preparing to undergo structural remodeling such as during developmental transitions or to rid themselves of damaging cytoplasmic components, for example, during oxidative stress, infection, or protein aggregate accumulation. Nutritional status, hormonal factors, and other cues like temperature, oxygen concentrations, and cell density are important in the control of autophagy. The molecular cascade that regulates and executes autophagy has been the subject of recent, comprehensive reviews (Klionsky, 2007; Maiuri et al., 2007a; Mizushima and Klionsky, 2007; Rubinsztein et al., 2007).

One of the key regulators of autophagy is the target of rapamycin, TOR kinase, which is the major inhibitory signal that shuts off autophagy in the presence of growth factors and abundant nutrients. The class I PI3K/Akt signaling molecules link receptor tyrosine kinases to TOR activation and thereby repress autophagy in response to insulin-like and other growth factor signals (Lum et al., 2005). Some of the other regulatory molecules that control autophagy include 5′-AMP-activated protein kinase (AMPK), which responds to low energy; the eukaryotic initiation factor 2α (eIF2α), which responds to nutrient starvation, double-stranded RNA, and endoplasmic reticulum (ER) stress; BH3-only proteins that contain a Bcl-2 homology-3 (BH3) domain and disrupt Bcl-2/Bcl-X_L inhibition of the Beclin 1/class III PI3K complex; the tumor suppressor protein, p53; death-associated protein kinases (DAPk); the ER-membrane-associated protein, Ire-1; the stress-activated kinase, c-Jun-N-terminal kinase; the inositol-trisphosphate (IP_3) receptor (IP_3R); GTPases; Erk1/2; ceramide; and calcium (Criollo et al., 2007; Maiuri et al., 2007a; Meijer and Codogno, 2006; Rubinsztein et al., 2007).

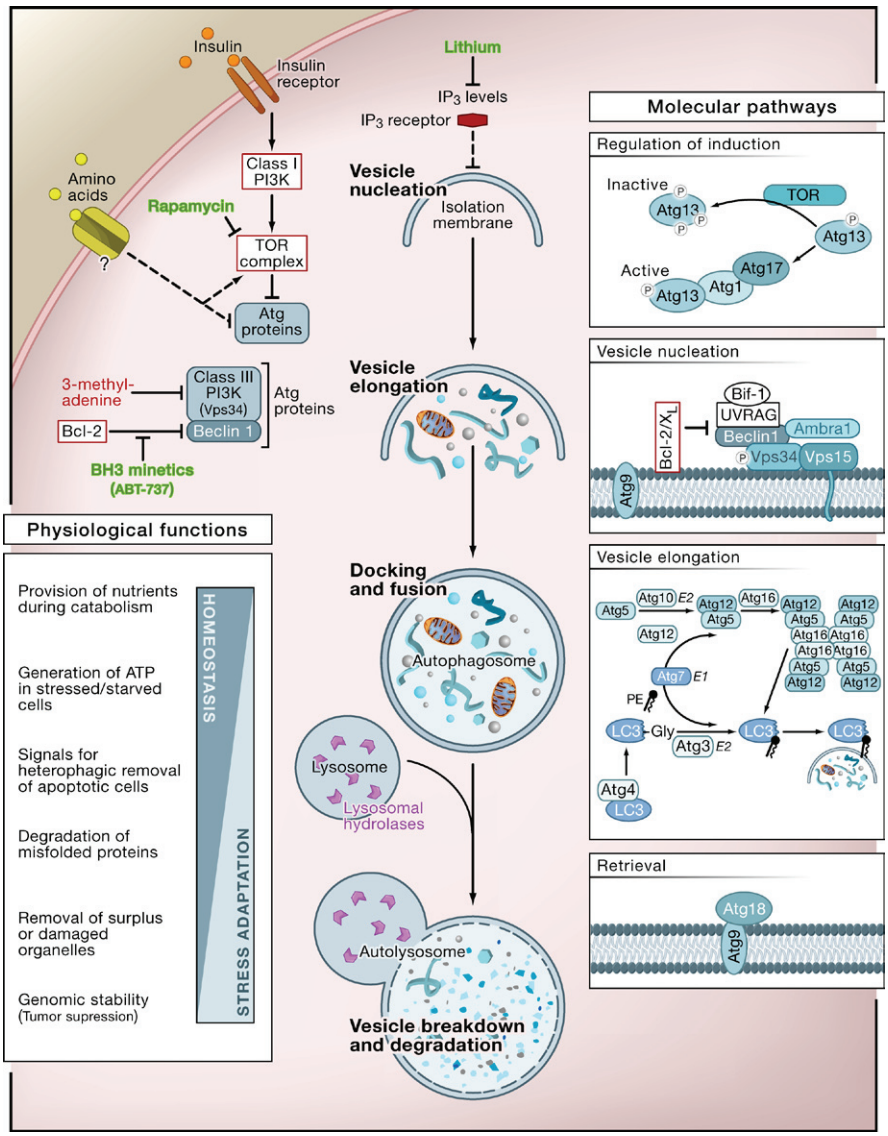

Figure 1. The Cellular, Molecular, and Physiological Aspects of Autophagy

The cellular events during autophagy follow distinct stages: vesicle nucleation (formation of the isolation membrane/phagophore), vesicle elongation and completion (growth and closure), fusion of the double-membraned autophagosome with the lysosome to form an autolysosome, and lysis of the autophagosome inner membrane and breakdown of its contents inside the autolysosome. This process occurs at a basal level and is regulated by numerous different signaling pathways (see text for references). Shown here are only the regulatory pathways that have been targeted pharmacologically for experimental or clinical purposes. Inhibitors and activators of autophagy are shown in red and green, respectively. At the molecular level, Atg proteins form different complexes that function in distinct stages of autophagy. Shown here are the complexes that have been identified in mammalian cells, with the exception of Atg13 and Atg17 that have only been identified in yeast. The autophagy pathway has numerous proposed physiological functions; shown here are functions revealed by in vivo studies of mice that cannot undergo autophagy (see Table 1).

Downstream of TOR kinase, there are more than 20 genes in yeast (known as the *ATG* genes) that encode proteins (many of which are evolutionarily conserved) that are essential for the execution of autophagy (Mizushima and Klionsky, 2007) (Figure 1). These include a protein serine/threonine kinase complex that responds to upstream signals such as TOR kinase (Atg1, Atg13, Atg17), a lipid kinase signaling complex that mediates vesicle nucleation (Atg6, Atg14, Vps34, and Vps15), two ubiquitin-like conjugation pathways that mediate vesicle expansion (the Atg8 and Atg12 systems), a recycling pathway that mediates the disassembly of Atg proteins from mature autophagosomes (Atg2, Atg9, Atg18), and vacuolar permeases that permit the efflux of amino acids from the degradative compartment (Atg22). In mammals, proteins that act more generally in lysosomal function are required for proper fusion with autophagosomes—such as the lysosomal transmembrane proteins, LAMP-2 and CLN3—and for the degradation of autophagosomal contents, such as the lysosomal cysteine proteases, cathepsins B, D, and L (Table 1).

The identification of signals that regulate autophagy and genes that execute autophagy has facilitated detection and manipulation of the autophagy pathway. Phosphatidylethanolamine (PE) conjugation of yeast Atg8 or mammalian LC3 during autophagy results in a nonsoluble form of Atg8 (Atg8-PE) or LC3 (LC3-II) that stably associates with the autophagosomal membrane (Figure 1). Consequently, autophagy can be detected biochemically (by assessing the generation of Atg8-PE or LC3-II) or microscopically (by observing the localization pattern of fluorescently tagged Atg8 or LC3) (Mizushima and Klionsky, 2007). These approaches must be coupled with ancillary measures to discriminate between two physiologically distinct scenarios—increased autophagic flux without impairment in autophagic turnover (i.e., an increased "on-rate") versus impaired clearance of autophagosomes (i.e., a "decreased off-rate"), which results in a functional defect in autophagic catabolism (Figure 2).

Autophagy can be pharmacologically induced by inhibiting negative regulators such as TOR with rapamycin (Rubinsztein et al., 2007); the antiapoptotic proteins Bcl-2 and Bcl-X_L that bind to the mammalian ortholog of yeast Atg6, Beclin 1, with ABT-737 (Maiuri et al., 2007b); IP_3R with xestospongin B, an IP_3R antagonist; or lithium, a molecule that lowers IP_3 levels (Criollo et al., 2007). Autophagy can be pharmacologically inhibited by targeting the class III PI3K involved in autophagosome formation with 3-methyladenine or by targeting the fusion of autophagosomes with lysosomes, using inhibitors of the lysosomal proton pump such as bafilomycin A1 or lysosomotropic alkalines such as chloroquine and 3-hydroxychloro-