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Review

Ubiquitin-Dependent And Independent Signals In Selective Autophagy

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Selective autophagy regulates the abundance of specific cellular components via a specialized arsenal of factors, termed autophagy receptors, that target protein complexes, aggregates, and whole organelles into lysosomes. Autophagy receptors bind to LC3/GABARAP proteins on phagophore and autophagosome membranes, and recognize signals on cargoes to deliver them to autophagy. Ubiquitin (Ub), a well-known signal for the degradation of polypeptides in the proteasome, also plays an important role in the recognition of cargoes destined for selective autophagy. In addition, a variety of cargoes are committed to selective autophagy pathways by Ub-independent mechanisms employing protein–protein interaction motifs, Ub-like modifiers, and sugar- or lipid-based signals. In this article we summarize Ub-dependent and independent selective autophagy pathways, and discuss regulatory mechanisms and challenges for future studies.

Trends

Ubiquitin is a universal degradation signal used for protein disposal via proteasome and autophagy.

Selective autophagy pathways are regulated by phosphorylation and ubiquitination.

In contrast to core autophagy machinery, autophagy receptors are divergent and poorly conserved from yeast to humans; however, functional homologs are present.

Autophagy receptors target damaged or foreign cytosolic material by recognizing specific protein, sugar, or lipid moieties.

Autophagy receptors act together with autophagy adaptors in recognizing and processing cargo via selective autophagy.

Mechanisms and Machinery of Selective Autophagy

Macroautophagy (thereafter called autophagy) is a quality control mechanism that delivers intracellular material to the lysosome in mammals and to the vacuole in yeast for degradation [1,2]. Autophagy initiates with the formation of a phagophore at the phagophore assembly site (PAS) in yeast and the omegasome in mammals [1]. The phagophore elongates and seals to generate a mature autophagosome, which can fuse with endosomes and lysosomes to degrade the cellular material it has engulfed (Figure 1). Various organelles, including the endoplasmic reticulum (ER), Golgi, mitochondria, recycling endosomes, and plasma membrane, have been shown to supply membrane to growing autophagic structures [1–3].

More than 30 autophagy-related genes (Atgs) have been documented in yeast, and most of these are conserved in mammals. These factors form several complexes that sequentially control autophagosome formation and development during canonical autophagy [1,3]: (i) ULK (unc-51-like) 1 kinase complex (Atg1 complex in yeast), (ii) the class III phosphatidylinositol 3-kinase [PI(3)KC3] complex composed of VPS34 (the mammalian counterpart of yeast Vps34), p150 (counterpart of yeast Vps15), and beclin-1 (Atg6 in yeast), (iii) the transmembrane protein Atg9 and its trafficking system, and (iv) the Ub-like (UBL) proteins of the LC3 (microtubule-associated protein 1 light chain 3) and GABARAP (γ-aminobutyric acid receptor-associated protein) family in mammals (Atg8 in yeast) and the conserved ATG12 (Atg12 in yeast). The cytosolic form of LC3 (LC3-I) is conjugated to phosphatidylethanolamine (PE) to form an LC3–PE conjugate (LC3-II), which is recruited to autophagosomal membranes. By contrast, ATG12 is conjugated to ATG5 and acts as a catalyst for the LC3 conjugation reaction. In addition, some autophagy factors are represented by several paralogs or isoforms in mammals, suggesting higher complexity and additional functions in and outside autophagy networks [4].

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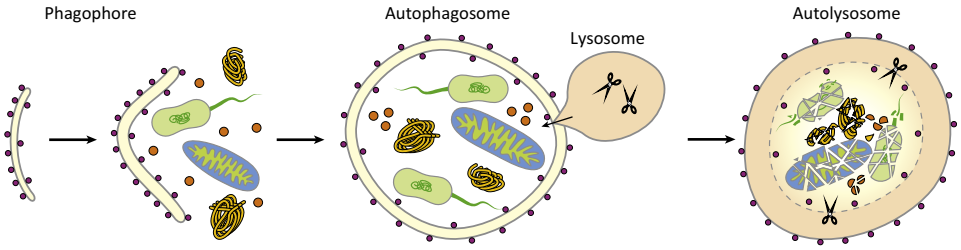

Figure 1. Mechanism of Macroautophagy. Autophagy begins with the formation of the phagophore. The phagophore (also known as isolation membrane) expands by acquiring membrane from intracellular organelles and carriers, sequesters intracellular material (e.g., proteins, protein aggregates, organelles, intracellular pathogens), and finally seals to form the mature autophagosome. The autophagosome fuses with late endosomes and lysosomes to generate the autolysosome that degrades and recycles the enclosed content.

Autophagy has been formerly considered to be a strictly nonselective bulk degradation pathway; however, comprehensive studies have revealed its selective nature. Selectivity of autophagy is controlled by specialized factors, the autophagy receptors (Figure 2), that physically link defined cellular material with the autophagy compartment by interacting simultaneously with cargo and Atg8- or LC3/GABARAP-like proteins on autophagosomes [5,6]. Numerous selective autophagy pathways have been characterized and named according to the type of targeted cellular material: mitochondria (mitophagy), protein aggregates (aggrephagy), pathogens (xenophagy), ribosomes (ribophagy), endoplasmic reticulum (ER-phagy or reticulophagy), nuclear envelope (nucleophagy), liposomes (lipophagy), ferritin (ferritinophagy), lysosomes (lysophagy), and cytosol-to-vacuole targeting (Cvt) pathway [5–14] (Table 1). Other pathways are known to recycle

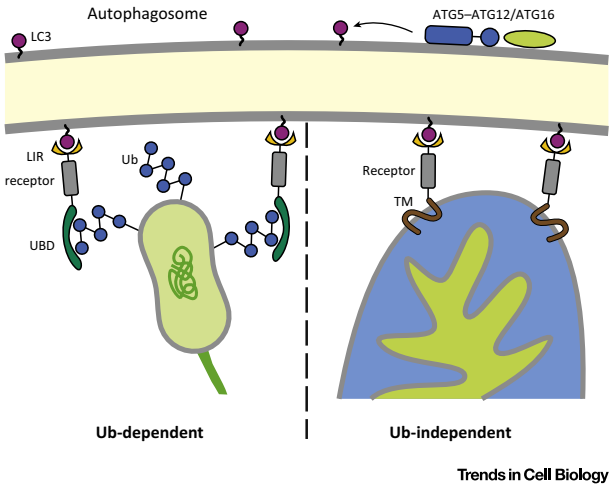

Figure 2. Principles of Ub-Dependent and -Independent Selective Autophagy. ATG8/LC3/GABARAP-like proteins play crucial roles in selective autophagy. LC3-like modifiers are conjugated to phosphatidylethanolamine (PE) in a Ub-like cascade requiring the E3-like activity of the ATG5–ATG12/ATG16 complex. PE-modified LC3-like modifiers are incorporated into the phagophore and mediate selective autophagy by interacting with autophagy receptors that are equipped with LC3-interacting regions (LIR, yellow). In Ub-dependent selective autophagy (left part), autophagy receptors simultaneously recognize Ub chains (Ub, blue) attached to intracellular cargo (e.g., bacteria) via Ub-binding domains (UBD, green), thereby linking targeted material to the autophagosomal membrane. In Ub-independent autophagy (right part), autophagy receptors directly bind to intracellular cargo (e.g., mitochondria), in some cases via transmembrane domains (TM, brown). Autophagy receptors tend to cluster their cargo through specialized oligomerization domains (grey). Abbreviations: ATG, autophagy-related gene; GABARAP, γ-aminobutyric acid receptor-associated protein; LC3, microtubule-associated protein 1 light chain 3; Ub, ubiquitin.