Autophagy is a cytoplasmic, homeostatic process by which cells degrade their interior components, including targets that are too large for other degradative systems, in response to external and internal triggers. Of the different types of autophagy, macroautophagy is the best characterized. The morphological hallmark of this process is the sequestration of a portion of the cytoplasm within double-membrane vesicles called autophagosomes. These fuse with the lysosomes in mammalian cells (or the vacuole in yeast) to allow degradation of the cargo. Autophagy can be nonspecific in terms of its cytoplasmic targets in certain situations, for example in response to starvation. However, depending on the signal, highly specific autophagy can target superfluous or damaged organelles, protein aggregates or invasive microorganisms. When properly regulated, autophagy supports normal cellular and developmental processes, whereas autophagic dysfunction is associated with various human diseases. Our molecular understanding of autophagy has evolved exponentially in recent years and is depicted here for both yeast and mammals. This knowledge holds the promise of allowing us to target this pathway for therapeutic purposes.

Autophagy: molecular mechanisms and disease outcomes

Daniel J. Klionsky and Vojo Djeretic

Autophagy

Role in organelle homeostasis allows portions of the ER, Golgi complex, mitochondria and other plasma membrane, cargo transport

Autophagy

Induction

Autophagy occurs at a basal level but can be further induced during developmental programmes by various types of stimuli, including nutrient limitation, hypoxia and accumulation of damaged organelles, protein aggregates or invasive microorganisms. When properly regulated, autophagy supports normal cellular and developmental processes, whereas autophagic dysfunction is associated with various human diseases. Our molecular understanding of autophagy has evolved exponentially in recent years and is depicted here for both yeast and mammals. This knowledge holds the promise of allowing us to target this pathway for therapeutic purposes.

Autophagy in health and disease

Disease or process

Role of autophagy

Can be harmful during reperfusion

Increased levels may lead to muscle and organ damage

May promote excess inflammatory cytokines

Helps eliminate invasive microorganisms and maintain cellular integrity

Regulates nutrient availability and is controlled by a complex network of positive and negative pathways. Proteins known as GATE16) and GABARAPL3. Atg8 (LC3 in mammals) helps determine autophagosome formation, which is regulated by the conjugation of LC3 to PE. DFCP1 also interacts with BECLIN 1 (BECN1), which in part direct the conjugation of LC3 to PE. During maturation into an autolysosome in mammals the autophagosomal membrane is reincorporated into the Golgi network.

Additional modulating proteins in yeast and mammals

The omegasome (the nucleation site) targets the Pilbara complex to the ER. The generation of autophagosomes has been shown to be dependent on both ATG16L1 and ULK1, which in part direct the conjugation of LC3 to PE. The DFCP1 binds Pilbara and directs the formation of the omegasome, a nucleation site for autophagosome formation that is involved in some types of mammalian autophagy.

Chaperone-mediated autophagy

CMA functions temporarily after the induction of mammalian starvation that are in non-viability state. A closely conserved KFERQ consensus motif are unfolded by the activating factor, KIAA1954, to reach the levels of ubiquitinated autophagic receptors and translocated across the lysosome membrane, through the activation of cathepsin L receptors, and chaperone-mediated autophagy.

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Phagophore formation and maturation

Expansions of the phagophore into an autophagosome require the generation of the Atg16L1-Pilbara (PILBA3) complex, which may allow recruitment of certain Agg components to the phagophore. There are multiple Agg complexes, each of which contains one of the Atg16L1, Atg12-Atg5 and Atg12-Atg16L1 complexes. Retrograde movement of Atg9 across the ER (the phagophore) by the PtdIns3K complex. In yeast, Atg9 transits through the secretory pathway, and is found in the ER and Golgi network, juxtanuclear to mitochondria, in mammalian cells, will be initially targeted to the trans-Golgi network.

Ubiquitin-like conjugation systems

Two ubiquitin-like protein conjugation systems regulate expansion. Autophagy is promoted in the absence of Atg1 and its C-terminal domain, activated by Atg8 (known as GABARAPL3) and conjugated to PE by Atg12. Atg12-Atg5-Atg16L1 may act as an E1 ligase for Atg12 conjugation. Autophagy family members in mammals include GABARAP, GABARAPL1, GABARAPL2 (also known as GATE16) and GABARAPL3. Atg8 (LC3 in mammals) helps determine autophagosome formation, which can be deconstructed from PE by a second Atg1-dependent cleavage.

Endosomal pathways

The innovation you expect.

Each Millennium development candidate is being investigated in a broad clinical trial programme designed to support regulatory approval. In addition, certain product candidates have been evaluated in preclinical studies and nonclinical safety evaluations as part of development. Millennium is committed to making our products available to all who can benefit from them.

Phagophore expansion

Initial microtubule-directed movements of the pre-autophagosomal membrane to form the autophagosome, protein translocation across the ER membrane, cargo transport

Autophagy

Cargo selection

Autophagy can selectively target superfluous or damaged organelles, specific proteins or invasive microorganisms. Some targets come with a built-in tag, such as prApe1 (propeptide Ape1), which is deconjugated from PE by a second Atg4-dependent cleavage. Atg4 is the primary transmembrane domain (the phagophore) by the PtdIns3K complex. In yeast, Atg9 transits through the secretory pathway, and is found in the ER and Golgi network, juxtanuclear to mitochondria, in mammalian cells, will be initially targeted to the trans-Golgi network.

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Supplementary information to poster | Autophagy: molecular mechanisms and disease outcomes.  
Daniel J. Klionsky and Vojo Deretic  
April 2010 (http://www.nature.com/nrm/posters/autophagy)

References for Table on Autophagy in health and disease