Autophagy: Mechanisms and Function

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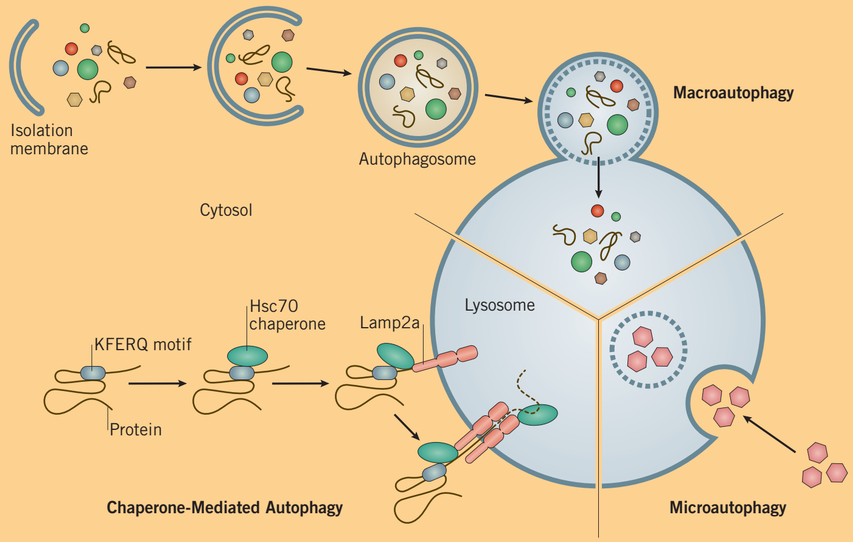
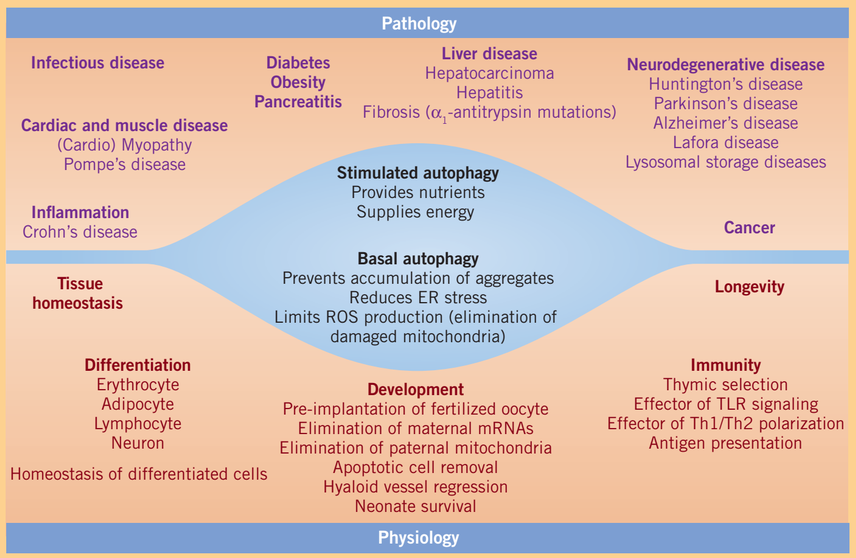
Autophagy is a cellular process used by cells for degradation and recycling. The word autophagy means 'self-eating', and refers to the digestion that occurs inside lysosomes. Once digestion has occurred, the degradation products are translocated to the cytoplasm and used to maintain cellular homeostasis. Autophagy is conserved from yeast to humans and is regulated by the Atg proteins. It is a cellular response to starvation and stress, and its dysregulation has been implicated in many pathological situations, from infection to cancer and neurodegeneration.



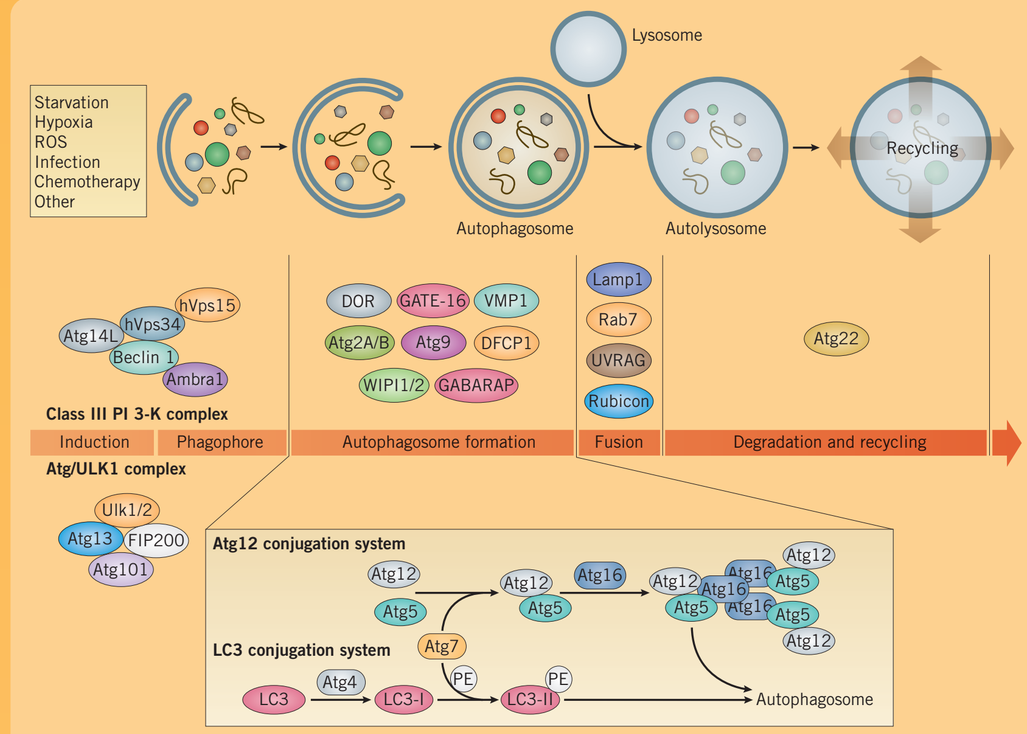
Types of Autophagy

Three main types of autophagy have been described in mammalian cells: macroautophagy, microautophagy and chaperone-mediated autophagy (CMA). All of these pathways converge in lysosomes to ensure intracellular degradation. Macroautophagy facilitates the recycling of cellular components, including organelles, through the formation of an autophagosome. During microautophagy, proteins translocate directly into the lysosomes. Chaperone-mediated autophagy enables the degradation of proteins which harbor a protein sequence that is recognized by chaperones (e.g. Hsc70). Recognition of the lysosomal membrane protein Lamp2A by Hsc70 facilitates the unfolding and translocation of this protein inside the lysosomal lumen, where degradation then occurs.



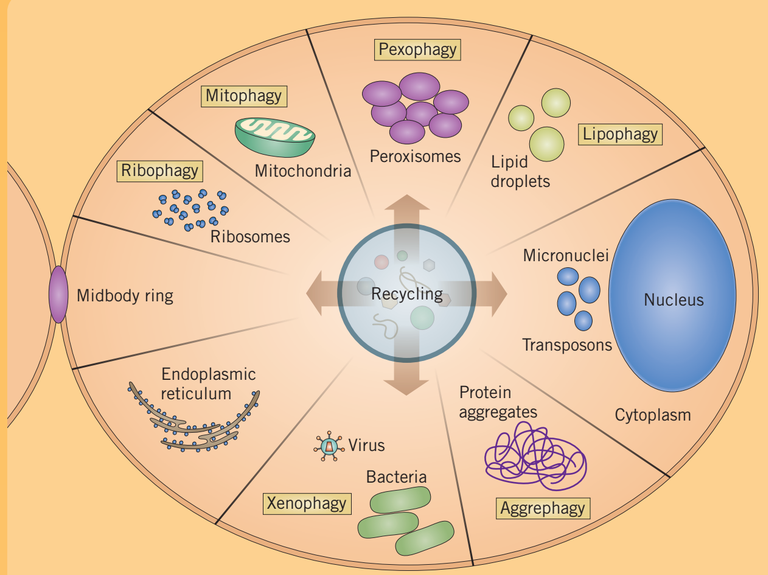
Physiology and Pathology

Autophagy has many essential functions in cells and tissues. Basal autophagy is essential to prevent the accumulation of damaged proteins and organelles; reduce ER stress; and limit the production of reactive oxygen species (ROS). On the other hand, induced autophagy is important for the provison of nutrients and building blocks during periods of starvation. Autophagy is essential during the development and differentiation of many cell types and in maintaining tissue homeostasis. Moreover, autophagy plays an essential role during immunity, participating in thymic selection and antigen presentation. Autophagy is also important in maintaining cellular homeostasis during aging. Given these essential physiological roles, it is unsurprising that dysregulation of autophagy has profound implications, and is implicated in the pathology of many diseases. Defects in autophagy have been associated with numerous neurodegenerative diseases, including proteinopathies and lysosomal storage diseases, and have also been reported in liver and muscle diseases. Other pathological situations such as diabetes and obesity, as well as inflammatory pathologies such as Crohn's disease, have also been correlated with defective autophagy.



The Molecular Machinery Implicated in Macroautophagy

During the first stages of autophagy in mammals, two macromolecular complexes are formed: the Class III PI 3-K complex and the Atg1/ULK1 complex. Other regulators – including Atg2A/B, WIPI 1/2, DFCP1 and VMP1 – cooperate during autophagosome formation, together with two conjugation reactions catalyzed by Atg7. First, Atg5 and Atg12 are conjugated and bind to Atg16. Second, LC3 is cleaved by the protease Atg4 and binds to the lipid phosphatidylethanolamine (PE), which facilitates its anchoring at the autophagosomal membrane. Once formed, the autophagosome then fuses with lysosomes or endosomes, a process that involves several lysosomal proteins such as Lamp1 and Rab7. After degradation by the action of lysosomal hydrolases, the final products – including amino acids, lipids and nucleotides – translocate to the cytoplasm via permeases, such as Atg22 (in yeast), present in the lysosomal membrane. They are then recycled for new anabolic reactions to sustain cell homeostasis.



Selective Autophagy

Subcellular structures are specifically targeted for lysosomal degradation by autophagy. Depending on the cargo, the processes are named differently: mitophagy for the specific elimination of mitochondria; ribophagy for ribosomes; and lipophagy for the degradation of lipid droplets. Pexophagy degrades peroxisomes and aggrephagy degrades intracellular protein aggregates and misfolded proteins such as those observed in many neurodegenerative conditions. Xenophagy denotes the degradation of intracellular pathogens such as viruses and intracellular bacteria. Other cellular components – such as the endoplasmic reticulum (ER), micronuclei, glycogen and transposons – can also be specifically targeted by autophagosomes for degradation.

Products available from Tocris

Autophagy Activators	
A23187, free acid	Causes ER stress; induces autophagy in mammalian cells
Amiodarone	Causes mitochondrial fragmentation and cell death; stimulates autophagy
Brefeldin A	Causes ER stress; induces autophagy in mammalian cells
Carbamazepine	Reduces inositol levels; induces autophagy
Dexamethasone	Anti-inflammatory glucocorticoid; also induces autophagy in ALL cell lines
Dorsomorphin	Induces autophagy via an AMPK inhibition-independent mechanism
EB 1089	Vitamin D receptor (VDR) agonist; induces autophagy in MCF-7 cells
GF 109203X	Protein kinase C inhibitor
L-690,330	Inositol monophosphatase inhibitor; induces autophagy independently of mTOR inhibition
NF 449	Highly selective $P2X_1$ antagonist
Niclosamide	STAT3 inhibitor; also inhibits mTORC1 signaling. Stimulates autophagy *in vitro*
Nimodipine	Ca^{2+} channel blocker (L-type)
Nitrendipine	Ca^{2+} channel blocker (L-type)
PI 103	Inhibitor of PI 3-kinase, mTOR and DNA-PK
Pifithrin-α hydrobromide	p53 inhibitor; aryl hydrocarbon receptor agonist
Rapamycin	mTOR inhibitor; immunosuppressant
Rottlerin	Reported PKCδ inhibitor; stimulates autophagy
SMER 28	Positive regulator of autophagy
Temozolomide	DNA-methylating antitumor agent; also induces autophagy
Thapsigargin	Causes ER stress; induces autophagy in mammalian cells
Torin 1	Potent and selective mTOR inhibitor
Tunicamycin	Causes ER stress; induces autophagy in mammalian cells
Valproic acid, sodium salt	Reduces inositol levels; induces autophagy
Verapamil	Ca^{2+} channel blocker (L-type)
Autophagy Inhibitors	
Bafilomycin A1	Vacuolar H^+-ATPase inhibitor; also inhibits autophagy
(±)-Bay K 8644	L-type Ca^{2+} channel agonist; inhibits autophagy
Chloroquine	Inhibits apoptosis and autophagy
Concanamycin A	Vacuolar H^+-ATPase inhibitor
DBeQ	Selective p97 inhibitor; blocks autophagosome maturation
E 64d	Cathepsin inhibitor; interferes with lysosomal digestion
LY294002	Selective PI 3-kinase inhibitor; inhibits autophagic sequestration
3-Methyladenine	Class III PI 3-kinase inhibitor; also inhibits autophagy
Nocodazole	Microtubule inhibitor; inhibits autophagosome-lysosome fusion
Pepstatin A	Protease inhibitor; interferes with lysosomal digestion
Taxol	Promotes assembly and inhibits disassembly of microtubules
Vinblastine	Disrupts microtubules; inhibits autophagosome maturation
Wortmannin	Potent, irreversible inhibitor of PI 3-kinase; inhibits PLK1

Further Reading

Kroemer *et al* (2010) Autophagy and the integrated stress response. *Mol.Cell* **40** 280.
Yang and Klionsky (2010) Eaten alive: a history of macroautophagy. *Nat.Cell Biol.* **12** 814.
Mathew and White (2011) Autophagy in tumorigenesis and energy metabolism: friend by day, foe by night. *Curr.Opin.Genet.Dev.* **21** 113.
Mizushima *et al* (2011) The role of atg proteins in autophagosome formation. *Annu.Rev.Cell Dev.Biol.* **27** 107.

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