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Mammalian Macroautophagy at a Glance

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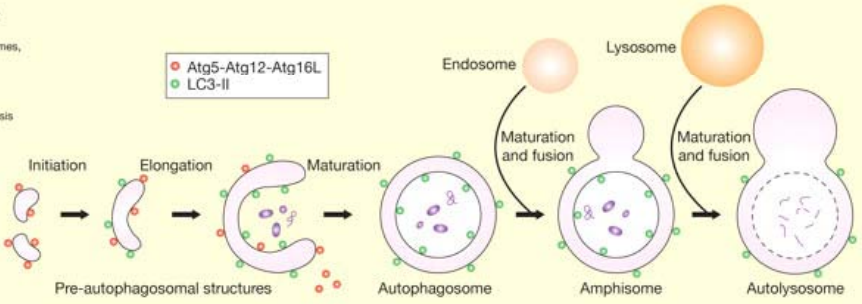
What is autophagy?

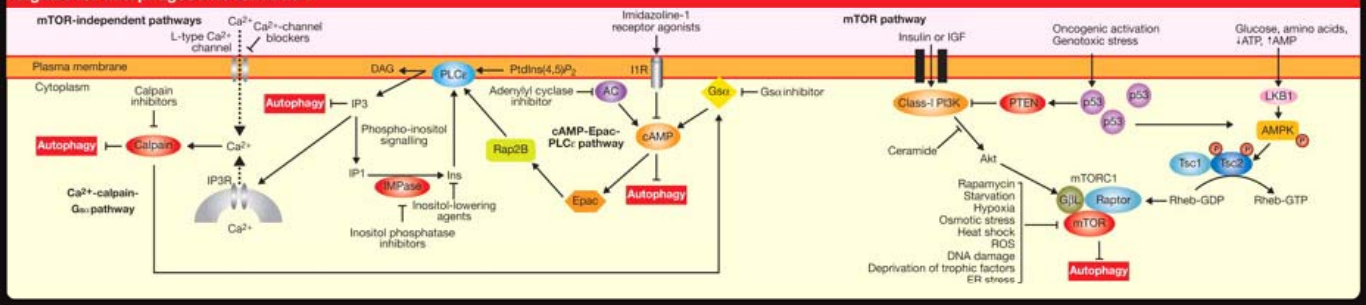
Macroautophagy (here referred to as autophagy) is a bulk intracellular degradation process. Autophagy is initiated when pre-autophagosomal structures of unknown origin elongate and fuse, engulfing portions of the cytosol to form autophagosomes. These initially fuse with endosomes to form hybrid organelles called amphisomes, which ultimately fuse with lysosomes, resulting in degradation of their contents.

Autophagy has several important roles in normal physiology. These include:

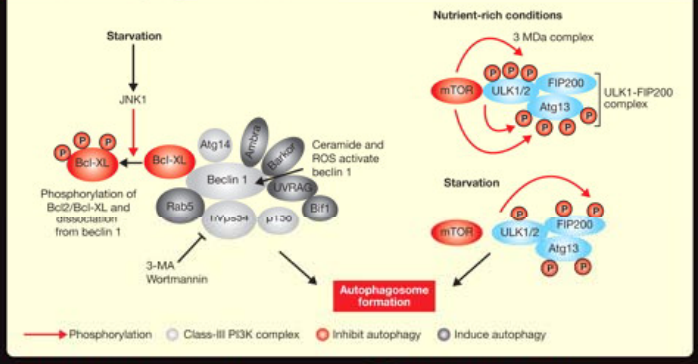
- Efficient clearance of long-lived intracellular proteins to maintain normal cellular homeostasis
- Removal of damaged or dysfunctional mitochondria
- Maintenance of ER quality control
- Nutrient mobilisation upon starvation – autophagic degradation of glycogen in newborn liver is an important survival mechanism, enabling the newborn to adapt to the postnatal environment
- Clearance of dead cells during programmed cell death, such as cavitation during development in the embryoid body
- Embryo development during the one- to four-cell stage



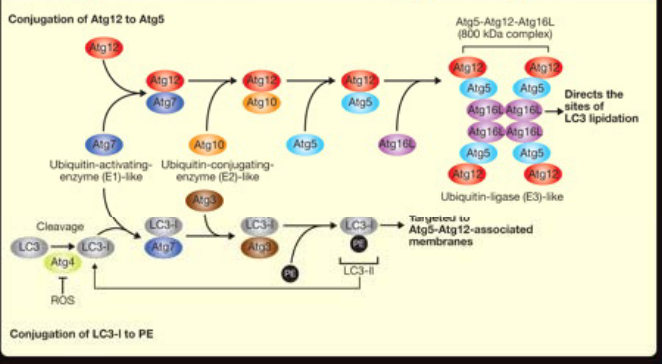
Signals for autophagosome formation



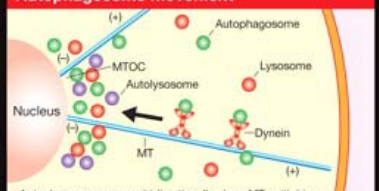
Initiation of autophagosome formation



Two ubiquitin-like modifications involved in autophagosome elongation

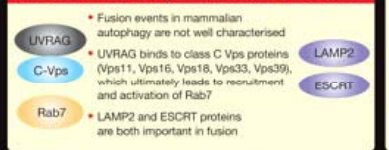


Autophagosome movement



- Autophagosomes move bidirectionally along MTs with bias towards the MTOC, where they fuse with lysosomes
- MT depolymerisation or inhibition of dynein function inhibits fusion

Fusion of autophagosomes with lysosomes



- Fusion events in mammalian autophagy are not well characterised
- UVRAG binds to class C Vps proteins (Vps11, Vps16, Vps18, Vps33, Vps39), which ultimately leads to recruitment and activation of Rab7
- LAMP2 and ESCRT proteins are both important in fusion

Autophagy in pathology

- Autophagy appears to have a key role in several important diseases
- Autophagy can advance disease progression, but can also be protective
- In some cases, disease-causing mutations in autophagy-associated genes have been identified

Gene or protein	Disease
ATG16L, IRGM	Crohn's disease
Beclin 1, UVRAG, gene loci harbouring *ATG7* and *ATG8*	Cancer
LAMP2B	Danon disease
CHMP2B (ESCRT complex)	Frontotemporal dementia Amyotrophic lateral sclerosis

Disease	Positive effects of autophagy	Negative effects of autophagy
Infection	Aids in the clearance of intracellular bacteria, viruses and protozoans, such as *Mycobacterium tuberculosis* and *Streptococcus pyogenes*	Some microorganisms subvert the autophagy pathway to establish a replicative niche
Cancer	Acts as a tumour suppressor by removing damaged proteins and organelles and preventing chromosomal instability	Autophagy can contribute to tumour survival as it allows cells to sustain nutrient deprivation or, by targeting damaged mitochondria for degradation, buffers oxidative stress that can be triggered by cancer therapy
Neurodegeneration	Helps in the clearance of toxic, misfolded aggregate-prone proteins involved in neurodegeneration, such as mutant huntingtin, A53T mutant α-synuclein and mutant ataxins	Enhanced autophagy may contribute to increased production of amyloid-β peptide, creating a favourable environment for its deposition in Alzheimer's disease
Cardiac diseases	Has a housekeeping role in the heart under basal conditions, and there is accumulation of autophagy substrates in cardiac aging and acute ischemia	Upregulated autophagy can result in cardiomyocyte dropout, which can worsen heart failure
Myopathies	Prevents accumulation of toxic proteins that result in physiological dysfunction	Excessive autophagy may contribute to muscle wasting
Liver diseases	Allows removal of non-functional ER that results from accumulation of aggregation-prone α1-antitrypsin Z protein	Excessive autophagy may contribute to liver dysfunction

Abbreviations: 3-MA, 3-methyladenine; AC, adenylyl cyclase; Ambra, activating molecule in beclin-1-regulated autophagy; AMPK, AMP-activated protein kinase; ATG, autophagy-related gene; Barkor, Beclin-1-associated autophagy-related key regulator; Bcl2, B-cell lymphoma 2; DAG, diacylglycerol; ER, endoplasmic reticulum; ESCRT, endosomal sorting complex required for transport; FIP200, focal adhesion kinase (FAK) family-interacting protein of 200 kDa; I1R, imidazoline-1 receptor; IGF, insulin-like growth factor; IMPase, inositol monophosphatase; Ins, inositol; IP1, inositol monophosphate; IP3, inositol (1,4,5)-trisphosphate; IP3R, IP3 receptor; IRGM, immunity-related GTPase family M; JNK1, Jun N-terminal kinase 1; LAMP2, lysosome-associated membrane protein 2; LC3, microtubule-associated protein 1 light chain 3; MT, microtubule; MTOC, microtubule-organising centre; mTOR, mammalian target of rapamycin; mTORC1, mTOR complex 1; PE, phosphatidylethanolamine; PI3K, phosphoinositide 3-kinase; $PtdIns(4,5)P_2$, phosphatidylinositol 4,5-bisphosphate; PLCε, phospholipase Cε; PTEN, phosphatase and tensin homolog; Rheb, Ras homology enriched in brain; ROS, reactive oxygen species; Tsc, tuberous sclerosis complex; ULK, Unc-51 like kinase; UVRAG, ultraviolet-radiation resistance-associated gene.

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