List of Relevant Cellular Housekeeping Proteins and Genes:

Diagram, schematic

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Focus more on proteostasis network and autophagy/mitophagy?

**Protein Quality Control: Proteostasis**

Unfolded protein response

inositol-requiring enzyme 1 (IRE1), PKR-like endoplasmic reticulum kinase (PERK), and activating transcription factor 6 (ATF6) 🡪 trigger signaling cascades with functional objectives of expanding ER refolding capacity and promoting translational attenuation

IRE1 protein, ERN1 gene 🡪 <https://www.ncbi.nlm.nih.gov/gene/2081>

PERK protein, EIF2AK3 gene 🡪 <https://www.ncbi.nlm.nih.gov/gene/9451>

ATF6 protein, ATF6 gene 🡪 <https://www.ncbi.nlm.nih.gov/gene/22926>

The transcription factors X-box binding protein 1 (XBP-1), ATF6 p50, and ATF4 bind to nuclear ER stress–responsive elements (ERSEs) to upregulate chaperones including glucose-regulated protein 78/binding immunoglobulin protein (GRP78/BiP). Translation attenuation is promoted via phosphorylation of elongation initiation factor 2-α (eIF2α).

XBP-1 protein, XBP1 gene 🡪 <https://www.ncbi.nlm.nih.gov/gene/7494>

ATF4 protein, ATF4 gene 🡪 <https://www.ncbi.nlm.nih.gov/gene/468>

EIF2a protein, EIF2S1 gene 🡪 <https://www.ncbi.nlm.nih.gov/gene/1965>

GRP78/BiP protein, HSPA5 gene 🡪 <https://www.ncbi.nlm.nih.gov/gene/3309>

Autophagy

Diagram

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The autophagic pathway responds to input from environmental cues. Nutrient signals modulate a signaling pathway dependent on the mammalian (mechanistic) target of rapamycin (mTOR). Class I phosphatidylinositol-3-kinase (PI3K)–Akt activates mTOR in response to insulin and other growth-factor signaling, acting as a negative regulator of autophagy. Akt may also negatively regulate autophagy by phosphorylating Beclin 1. AMP-activated protein kinase (AMPK), which is regulated by AMP levels, negatively regulates mTOR and also directly phosphorylates UNC-51–like kinase 1 (ULK1), thereby acting as a positive regulator of autophagy in response to energy depletion. The mTOR protein resides in mTOR signaling complex 1 (mTORC1, which contains the regulatory-associated protein of mTOR [Raptor], G protein beta subunit–like protein [GβL], and proline-rich Akt/PKB substrate 40 kDa [PRAS40]), which in turn regulates the mTOR substrate complex, consisting of the mammalian uncoordinated-51–like protein kinase ULK1, ATG13, ATG101, and FIP200. Under conditions of nutrient repletion, mTORC1 inhibits ULK1 activity, thereby inhibiting the activation of autophagy. Autophagy is also regulated by the Beclin 1–interacting complex, consisting of Beclin 1, class III phosphatidylinositol-3-kinase (PIK3C3, or VPS34), and ATG14L. Stimulation of this complex generates phosphatidylinositol-3-phosphate (PI3P), which promotes autophagosomal membrane nucleation. Several interacting factors may participate in this regulation, including UVRAG and BIF1, which substitute for ATG14L, autophagy/beclin-1 regulator 1 (AMBRA1), and the putative negative regulator Rubicon. Autophagosomal elongation requires two ubiquitin-like conjugation systems. The ubiquitin-like protein ATG12 is conjugated to ATG5 by ATG7 (E1-like) and ATG10 (E2-like) enzymes. The resulting ATG5–ATG12 forms a complex with ATG16L1, which participates in elongation of the autophagic membrane. A second conjugation system requires the ubiquitin-like protein microtubule–associated protein 1 light chain 3 (LC3, ATG8). LC3 and its homologues are modified with the cellular lipid phosphatidylethanolamine (PE). The precursor form of LC3 is cleaved by the protease ATG4B to generate the LC3-I form, with an exposed lipid conjugation site at the C-terminal glycine residue. Conjugation of PE with LC3-I occurs from the sequential action of ATG7 (E1-like) and ATG3 (E2-like) activities. In mammals, the conversion of LC3-I (free form) to LC3-II (PE-conjugated form) is a key regulatory step in autophagosome formation.

Table

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ULK1 gene 🡪 <https://www.ncbi.nlm.nih.gov/gene/8408>

ATG3 gene 🡪 <https://www.ncbi.nlm.nih.gov/gene/64422>

ATG4B gene 🡪 <https://www.ncbi.nlm.nih.gov/gene/23192>

ATG5 gene 🡪 <https://www.ncbi.nlm.nih.gov/gene/9474>

BECN1 gene 🡪 <https://www.ncbi.nlm.nih.gov/gene/8678>

ATG7 gene 🡪 <https://www.ncbi.nlm.nih.gov/gene/10533>

MAP1LC3B gene 🡪 <https://www.ncbi.nlm.nih.gov/gene/81631>

ATG9A gene 🡪 <https://www.ncbi.nlm.nih.gov/gene/79065>

ATG10 gene 🡪 <https://www.ncbi.nlm.nih.gov/gene/83734>

ATG12 gene 🡪 <https://www.ncbi.nlm.nih.gov/gene/9140>

ATG14 gene 🡪 <https://www.ncbi.nlm.nih.gov/gene/22863>

ATG16L1 gene 🡪 <https://www.ncbi.nlm.nih.gov/gene/55054>

The autophagosome-lysosome system targets cytosolic protein aggregates (macroautophagy) and dysfunctional organelles, such as mitochondria (mitophagy), for degradation. Ubiquitin-binding receptors, such as p62/SQSTM1, recognize K-48–linked polyubiquitinated protein aggregates or K-63–linked polyubiquitin-tagged mitochondrial outer membrane proteins (initiated by PINK1 recruitment of the E3 ligase parkin). LC3 binding envelopes ubiquitinated cargo and leads to elongation of isolation membranes (phagophores) and maturation into autophagosomes. Fusion with LAMP1+ lysosomes results in an acidified and functional autophagolysosome (autolysosome) that degrades the internalized content.

p62/SQSTM1 protein, SQSTM1 gene 🡪 <https://www.ncbi.nlm.nih.gov/gene/8878>

LC3 protein, MAP1LC3A gene 🡪 <https://www.ncbi.nlm.nih.gov/gene/84557>

LAMP1 protein, LAMP1 gene 🡪 <https://www.ncbi.nlm.nih.gov/gene/3916>

**Organellular Quality Control: Mitophagy**

Degradation of mitochondria requires the coordination of cytosolic factors and signals assembled at the outer mitochondrial membrane to identify and target dysfunctional mitochondria to the autophagosome. Key steps in the process include stabilization of PTEN-induced putative kinase 1 (PINK1) in the outer mitochondrial membrane in response to lowered transmembrane potential; recruitment of the E3 ligase parkin, resulting in K-63–linked polyubiquitination of a variety of mitochondrial protein substrates (e.g., mitofusins [MFN1, MFN2]); and sequestration of ubiquitin-decorated mitochondria in the same autophagic machinery commissioned for protein removal.

VPS13D gene?

PINK1 protein, PINK1 gene 🡪 <https://www.ncbi.nlm.nih.gov/gene/65018>

E3 ligase parkin protein, PRKN gene 🡪 <https://www.ncbi.nlm.nih.gov/gene/5071>

**Citations:**

Choi, Augustine M K et al. “Autophagy in human health and disease.” *The New England journal of medicine* vol. 368,7 (2013): 651-62. doi:10.1056/NEJMra1205406

Katzen, Jeremy, and Michael F Beers. “Contributions of alveolar epithelial cell quality control to pulmonary fibrosis.” *The Journal of clinical investigation* vol. 130,10 (2020): 5088-5099. doi:10.1172/JCI139519