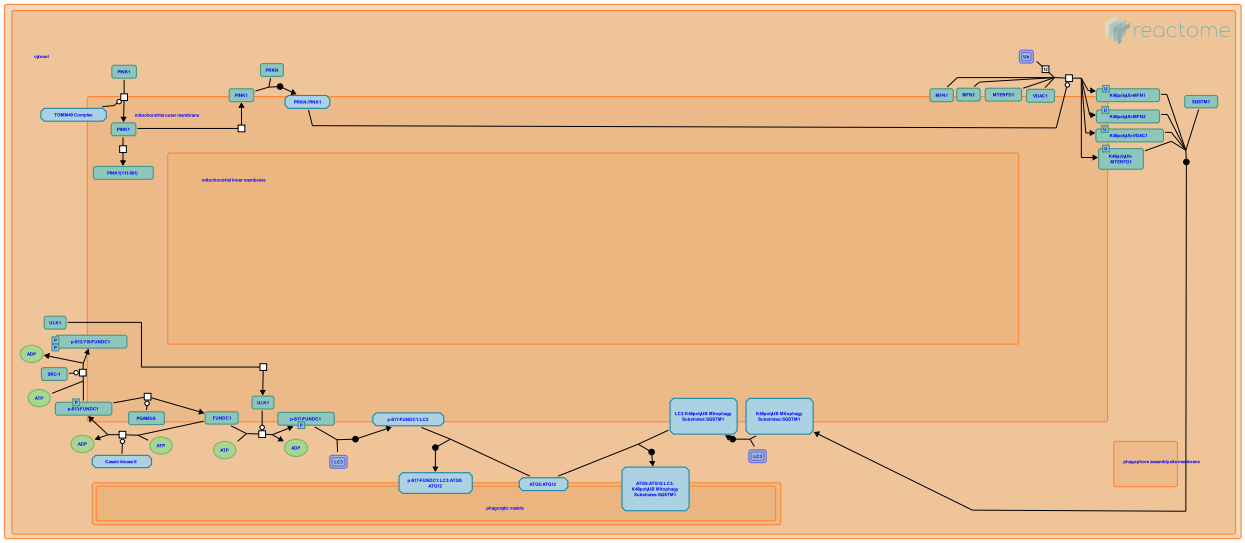
Mitophagy



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This is just an excerpt of a full-length report for this pathway. To access the complete report, please download it at the Reactome Textbook.

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Introduction

Reactome is open-source, open access, manually curated and peer-reviewed pathway database. Pathway annotations are authored by expert biologists, in collaboration with Reactome editorial staff and cross-referenced to many bioinformatics databases. A system of evidence tracking ensures that all assertions are backed up by the primary literature. Reactome is used by clinicians, geneticists, genomics researchers, and molecular biologists to interpret the results of high-throughput experimental studies, by bioinformaticians seeking to develop novel algorithms for mining knowledge from genomic studies, and by systems biologists building predictive models of normal and disease variant pathways.
The development of Reactome is supported by grants from the US National Institutes of Health (P41 HG003751), University of Toronto (CFREF Medicine by Design), European Union (EU STRP, EMI-CD), and the European Molecular Biology Laboratory (EBI Industry program).

Literature references

Fabregat, A., Sidiropoulos, K., Viteri, G., Forner, O., Marin-Garcia, P., Arnau, V. et al. (2017). Reactome pathway analysis: a high-performance in-memory approach. *BMC bioinformatics, 18*, 142. ↗

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Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655. ↗

Fabregat, A., Korninger, F., Viteri, G., Sidiropoulos, K., Marin-Garcia, P., Ping, P. et al. (2018). Reactome graph database: Efficient access to complex pathway data. *PLoS computational biology, 14*, e1005968. ↗

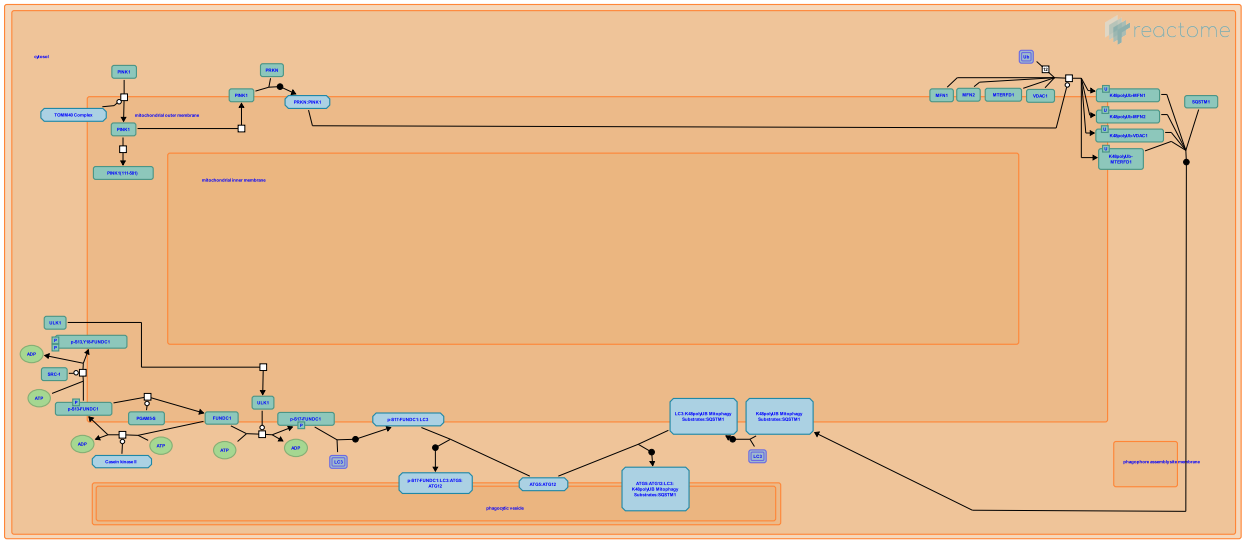
Reactome database release: 88

This document contains 3 pathways (see Table of Contents)

Mitophagy ↗

Stable identifier: R-HSA-5205647

Compartments: cytosol



Mitophagy is a specific form of autophagy where mitochondria are specifically targeted for degradation by autophagolysosomes. In mammals there are a number of known mechanisms of mitophagy. One ensures maternal inheritance of mitochondrial DNA through the elimination of sperm derived mitochondria. A second is elimination of functional mitochondria during erythrocyte maturation and eye lens maturation. It is established that the outer mitochondrial membrane receptor Nix (or Bnip3l) and autophagosome associated protein LC3 are important for mitochondrial degradation in erythrocytes. A third mechanism is driven by the PINK1 and Parkin (PRKN) proteins. PRKN is recruited to the mitochondria when the mitochondrial membrane potential is reduced due to uncoupling, thereby initiating mitophagy.

Literature references

Narendra, DP., Youle, RJ. (2011). Mechanisms of mitophagy. *Nat. Rev. Mol. Cell Biol., 12*, 9-14. ↗

Editions

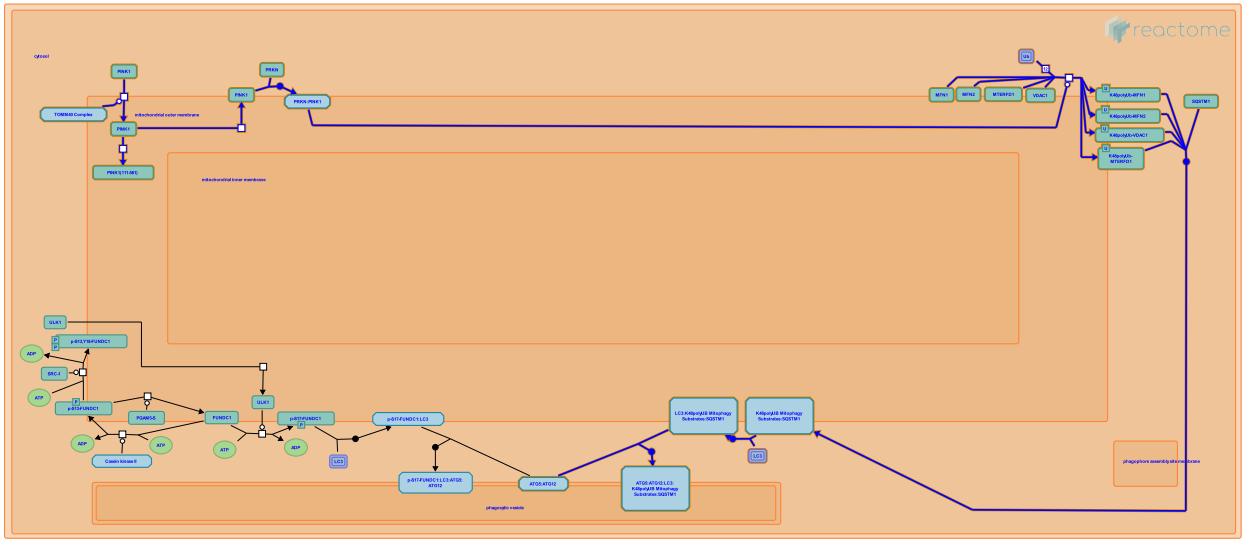
2013-11-21	Authored, Edited	Gillespie, ME.
2019-03-05	Revised	Varusai, TM.

PINK1-PRKN Mediated Mitophagy ↗

Location: Mitophagy

Stable identifier: R-HSA-5205685

Compartments: cytosol



This is the process of selective removal of damaged mitochondria by autophagosomes and subsequent catabolism by lysosomes. In healthy mitochondria, PTEN-induced putative kinase 1 (PINK1) is imported to the inner mitochondrial membrane, presumably through the TOM/TIM complex. The TIM complex associated protease, mitochondrial MPP, cleaves PINK1 mitochondrial targeting sequence (MTS). PINK1 may be cleaved by the inner membrane presenilin-associated rhomboid-like protease (PARL) and ultimately proteolytically degraded. Loss of membrane potential in damaged mitochondria prevents the import of PINK1 which accumulates on the mitochondrial outer membrane (MOM) of the defective mitochondria. Activation of PINK1 at MOM is achieved via dimerization-mediated trans-autophosphorylation of PINK1 at multiple sites including S228 and S402 (Okatsu K et al., 2012, 2013; Aerts L et al., 2015; Rasool S et al., 2018, 2022; Gan ZY et al., 2022). Activated PINK1 phosphorylates S65 of ubiquitin (Ub) on MOM proteins which leads to increased recruitment of the E3 ubiquitin ligase Parkin (PRKN) to damaged mitochondria (Koyano F et al., 2014; Shiba-Fukushima K et al., 2014; Ordureau A et al., 2015). Activated PINK1 also phosphorylates PRKN at S65 in the N-terminal Ub-like domain inducing the E3 ligase activity of PRKN (Kondapalli et al., 2012; Kazlauskaite A et al., 2015; Ordureau A et al., 2015). Activated PRKN promotes the ubiquitination of mitochondrial substrates including mitofusin 1 and 2 (MFN1, 2) and the voltage-dependent anion channel 1 and 3 (VDAC1, 3). The E3 ligase activity of PRKN generates Ub moieties for PINK1-mediated phosphorylation of Ub thus leading to a feedforward loop in the PINK1:PRKN pathway (Ordureau A et al., 2015; Sauve V et al., 2022). Ubiquitin chains on PRKN-ubiquitinated substrates recruit cargo receptors such as SQSTM1 (p62) and OPTN linking the ubiquitinated substrates to the microtubule-associated proteins 1A/1B light chain 3 (LC3, MAP1LC3) (Heo LM et al., 2015; Lazarou M et al., 2015). The recruitment of both MAP1LC3 (LC3) complexes and the autophagy proteins 5 and 12 (Atg5: Atg12) complex to the autophagosome membrane promotes autophagosome formation. The mitochondrion is engulfed after the isolation membrane grows to a sufficient size to engulf the mitochondrion. Once autophagic vesicle formation is complete, vesicle fusion with lysosomes occurs to form autophagolysosomes in which the lysosomal hydrolases (cathepsins and lipases) degrade the intra autophagosomal content. Cathepsin also degrades LC3 on the intra autophagosomal surface of the autophagic vesicle.

Literature references

Narendra, DP., Youle, RJ. (2011). Mechanisms of mitophagy. *Nat. Rev. Mol. Cell Biol., 12*, 9-14. ↗

Editions

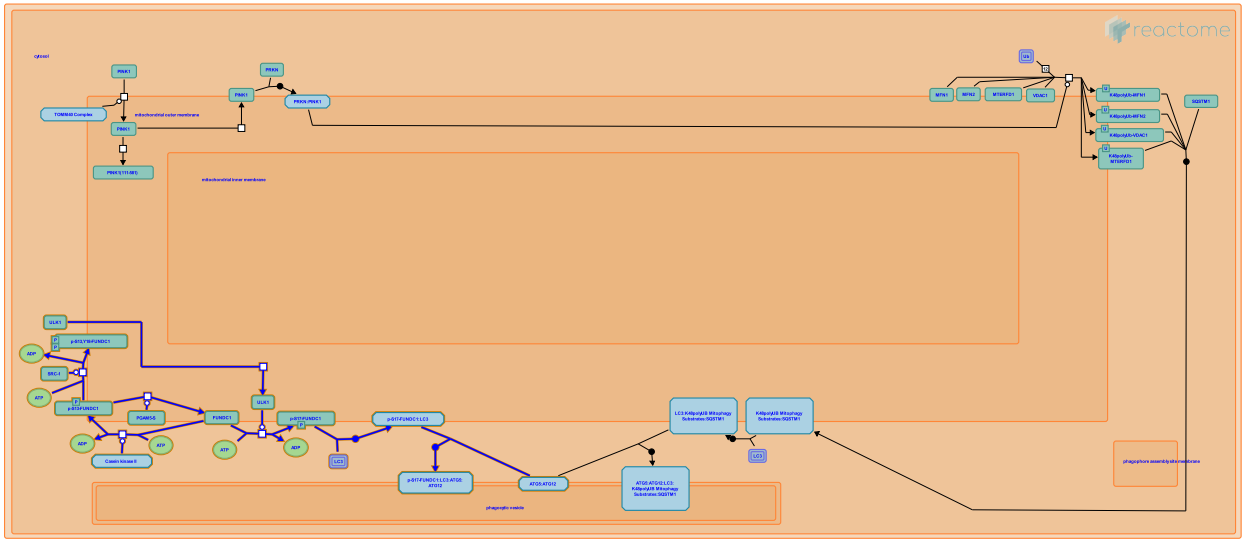
2013-11-21	Authored, Edited	Gillespie, ME.
2015-09-01	Reviewed	Kantorow, M., Chauss, D.
2019-03-05	Revised	Varusai, TM.

Receptor Mediated Mitophagy ↗

Location: Mitophagy

Stable identifier: R-HSA-8934903

Compartments: cytosol



Mitochondrial autophagy in mammalian cells was first observed in glucagon-stimulated hepatocytes. The mechanisms of mitophagy in mammalian cells remain unclear. Oxidative stress and mPTP are involved in the initiation of mitophagy. Receptor mediated mitophagy links both cellular differentiation signals and markers of mitochondrial function to LC3 and Atg32, scaffold proteins important for cargo selection and autophagosome formation. These scaffold proteins recruit other autophagy proteins to form the autophagosomes; destroying and recycling mitochondria.
Mitophagy receptors have to meet at least three criteria: 1) it must be mitochondrially localized, 2) it must interact with LC3/ ATG8 in response to a certain stimulus, and 3) it must have a consensus sequence of W/F/YxxL/I known as the LIR motif. This tetrapeptide sequence is present in several Atg8 or LC3-binding partners that are important for selective autophagy.

FUNDC1-mediated mitophagy is inhibited by its phosphorylation at the Tyr 18 position in the LIR motif by Src kinase under normoxia conditions. Upon hypoxia stimulation, Src is inactivated and FUNDC1 at the Tyr 18 position is dephosphorylated by an unknown phosphatase, resulting in an increase of the interaction between FUNDC1 and LC3-II, leading to the selective incorporation and autophagic removal of the mitochondrion.

The outer mitochondrial membrane protein NIX/BNIP3L is involved in autophagic turnover of mitochondria in reticulocytes, a process essential for red blood cell maturation [43]. The mechanism through which NIX senses signals from red blood cell differentiation is unclear. Phosphorylation of serine residues 17 and 24 flanking the BNIP3 LIR promotes binding to specific LC3 family members LC3B and GATE-16 and increases lysosomal destruction of mitochondria.

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Editions

2013-11-21	Authored, Edited	Gillespie, ME.
2017-01-26	Reviewed	Feng, D.
2019-03-05	Revised	Varusai, TM.

Table of Contents