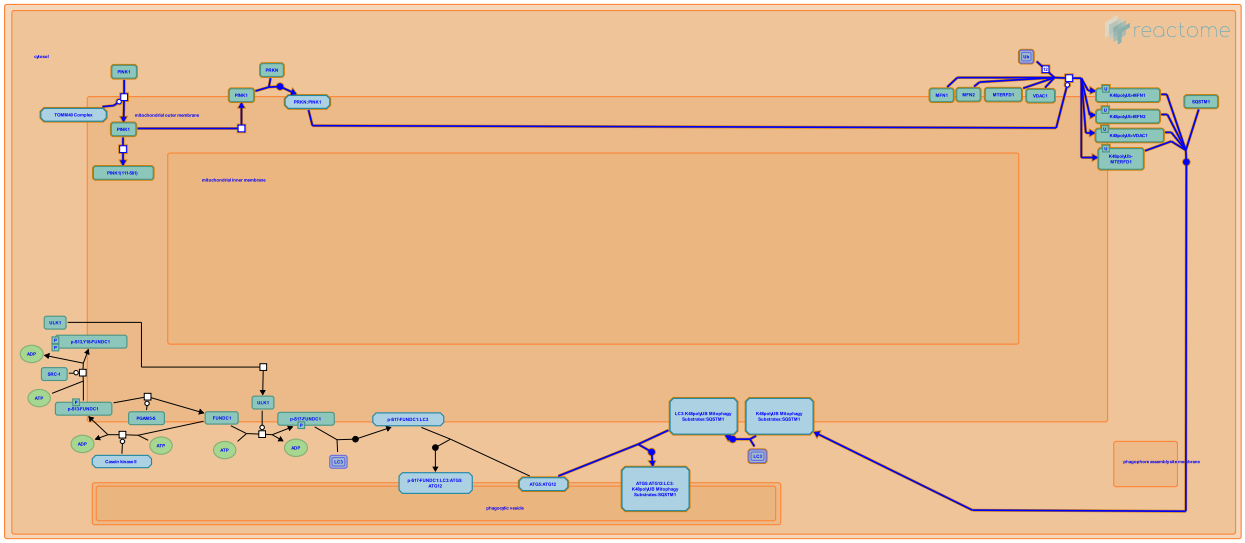
PINK1-PRKN Mediated Mitophagy



Chauss, D., Gillespie, ME., Kantorow, M., Varusai, TM.

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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.

27/04/2024

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. ↗

Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

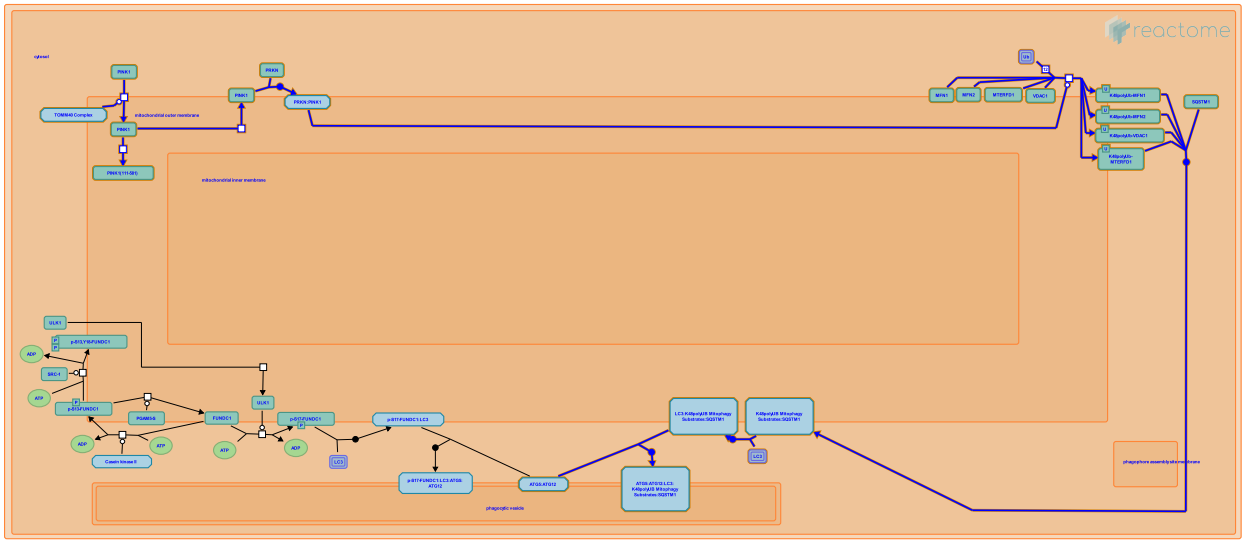
Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655. ↗

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. ↗

PINK1-PRKN Mediated 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.

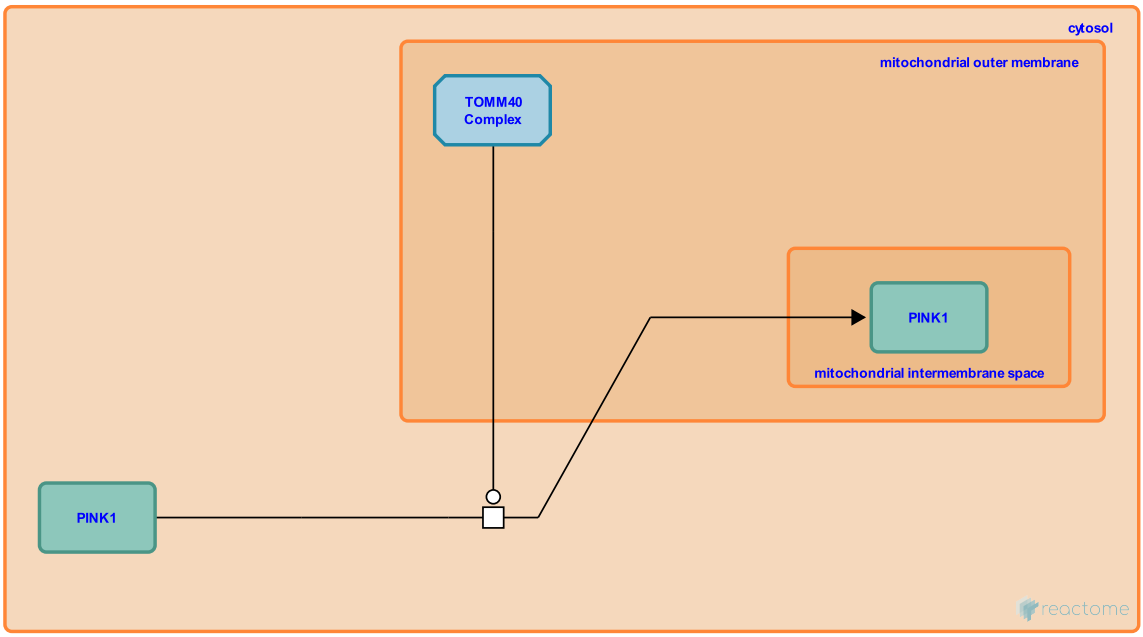
Pink1 is recruited from the cytoplasm to the mitochondria ↗

Location: PINK1-PRKN Mediated Mitophagy

Stable identifier: R-HSA-5205661

Type: transition

Compartments: cytosol



PINK1 is constitutively synthesized and imported into all mitochondria. In healthy mitochondria PINK1 is cleaved by voltage-sensitive proteolysis.

Followed by: Pink1 is cleaved on healthy mitochondria, Uncleaved Pink1 accumulates in damaged mitochondria

Literature references

Tanaka, A., Jin, SM., Cookson, MR., Narendra, DP., Suen, DF., Shen, J. et al. (2010). PINK1 is selectively stabilized on impaired mitochondria to activate Parkin. *PLoS Biol., 8*, e1000298. ↗

Editions

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

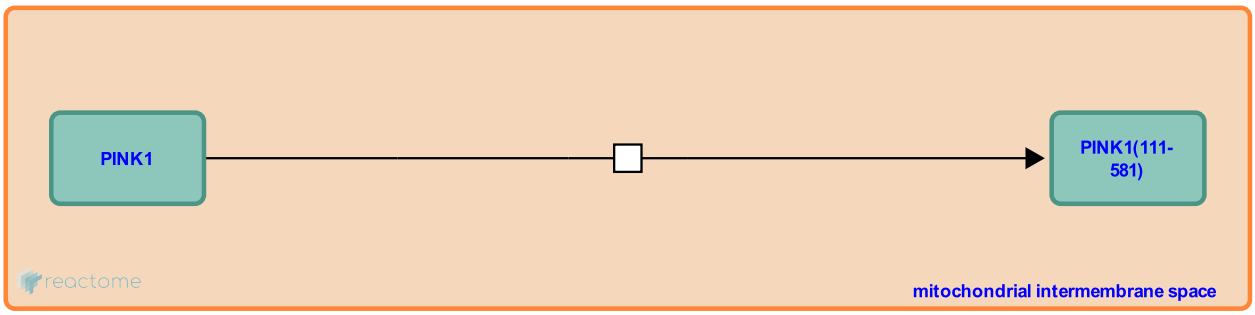
Pink1 is cleaved on healthy mitochondria ↗

Location: PINK1-PRKN Mediated Mitophagy

Stable identifier: R-HSA-5205681

Type: transition

Compartments: mitochondrial intermembrane space



Full-length PINK1 (63 kDa), which is in the inner mitochondrial space, is proteolytically cleaved into a 52-kDa cytosolic fragment (111 - 581) that is released back into the cytoplasm by an unknown mechanism and degraded by the proteasome. Cleavage of PINK1 into an unstable cytosolic form maintains low levels of PINK1 on healthy mitochondria in order to suppress the PINK1/Parkin pathway in the absence of mitochondrial damage. At present, not all of the proteases mediating the cleavage of PINK1 in mammalian cells have been identified.

Preceded by: Pink1 is recruited from the cytoplasm to the mitochondria

Literature references

Tanaka, A., Jin, SM., Cookson, MR., Narendra, DP., Suen, DF., Shen, J. et al. (2010). PINK1 is selectively stabilized on impaired mitochondria to activate Parkin. *PLoS Biol., 8*, e1000298. ↗

Kane, LA., Jin, SM., Wang, C., Narendra, DP., Lazarou, M., Youle, RJ. (2010). Mitochondrial membrane potential regulates PINK1 import and proteolytic destabilization by PARL. *J. Cell Biol., 191*, 933-42. ↗

Narendra, DP., Youle, RJ. (2011). Targeting mitochondrial dysfunction: role for PINK1 and Parkin in mitochondrial quality control. *Antioxid. Redox Signal., 14*, 1929-38. ↗

Editions

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

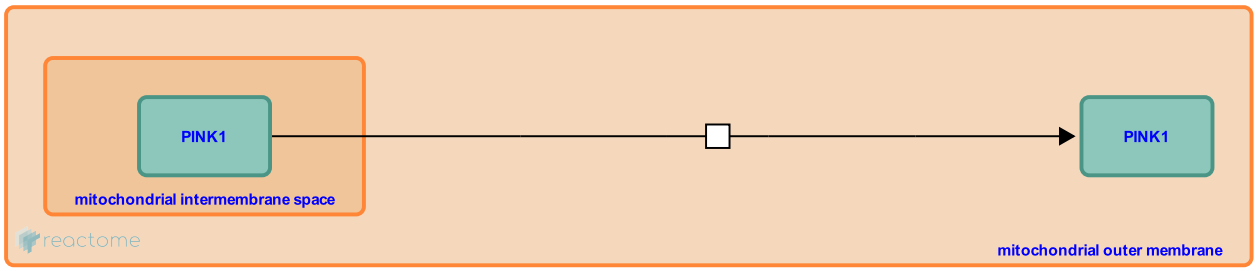
Uncleaved Pink1 accumulates in damaged mitochondria ↗

Location: PINK1-PRKN Mediated Mitophagy

Stable identifier: R-HSA-5205672

Type: transition

Compartments: mitochondrial outer membrane



On damaged mitochondria that have lost their membrane potential, however, PINK1 cleavage is inhibited, leading to high PINK1 protein accumulation on the inner leaf of the mitochondrial outer membrane (MOM) of dysfunctional mitochondria. Full-length mitochondrial PINK1 is the active form in the PINK1/Parkin pathway.

Preceded by: Pink1 is recruited from the cytoplasm to the mitochondria

Followed by: Pink1 recruits Parkin to the outer mitochondrial membrane.

Literature references

Tanaka, A., Jin, SM., Cookson, MR., Narendra, DP., Suen, DF., Shen, J. et al. (2010). PINK1 is selectively stabilized on impaired mitochondria to activate Parkin. *PLoS Biol., 8*, e1000298. ↗

Kane, LA., Jin, SM., Wang, C., Narendra, DP., Lazarou, M., Youle, RJ. (2010). Mitochondrial membrane potential regulates PINK1 import and proteolytic destabilization by PARL. *J. Cell Biol., 191*, 933-42. ↗

Narendra, DP., Youle, RJ. (2011). Targeting mitochondrial dysfunction: role for PINK1 and Parkin in mitochondrial quality control. *Antioxid. Redox Signal., 14*, 1929-38. ↗

Editions

2013-11-21	Authored	Gillespie, ME.
2014-10-31	Edited	Gillespie, ME.
2015-09-01	Reviewed	Kantorow, M., Chauss, D.
2019-03-05	Revised	Varusai, TM.

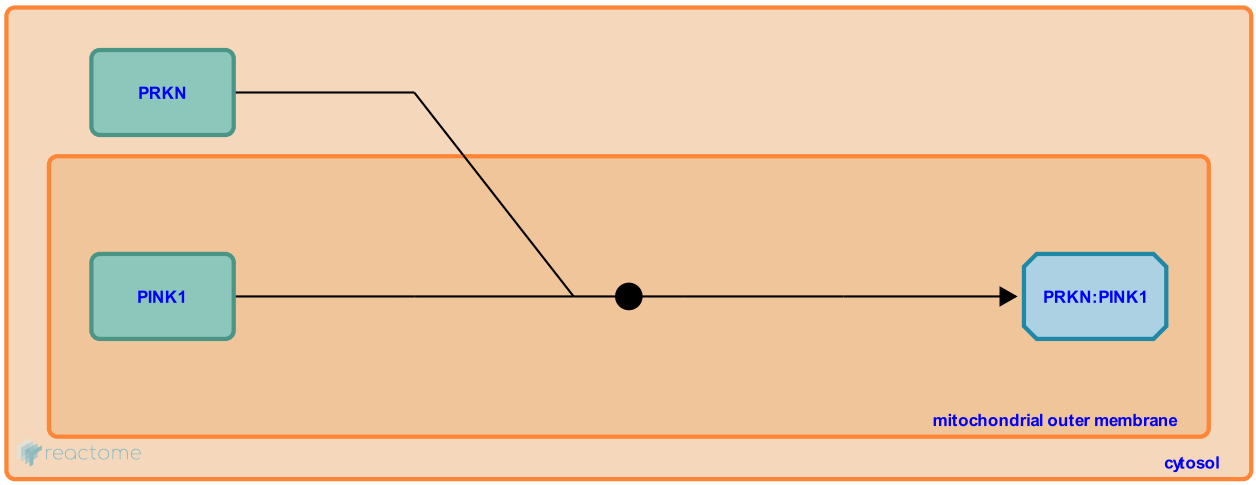
Pink1 recruits Parkin to the outer mitochondrial membrane. ↗

Location: PINK1-PRKN Mediated Mitophagy

Stable identifier: R-HSA-5205652

Type: binding

Compartments: mitochondrial outer membrane



Parkin promotes the ubiquitination of outer mitochondrial membrane imbedded proteins including the mitofusin mitochondrial assembly regulatory factor (MARF), mitofusin 1, mitofusin 2 and voltage dependent anion selective channel protein 1 (vDAC1).

Preceded by: Uncleaved Pink1 accumulates in damaged mitochondria

Followed by: Parkin promotes the ubiquitination of mitochondrial substrates

Literature references

Tanaka, A., Jin, SM., Cookson, MR., Narendra, DP., Suen, DF., Shen, J. et al. (2010). PINK1 is selectively stabilized on impaired mitochondria to activate Parkin. *PLoS Biol., 8*, e1000298. ↗

Editions

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

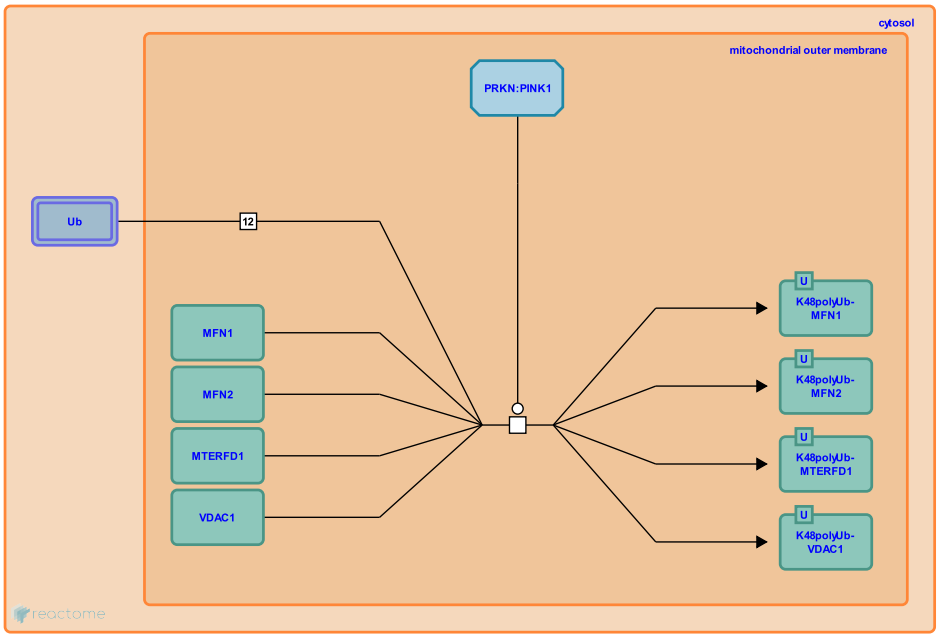
Parkin promotes the ubiquitination of mitochondrial substrates ↗

Location: PINK1-PRKN Mediated Mitophagy

Stable identifier: R-HSA-5205682

Type: transition

Compartments: mitochondrial outer membrane



Parkin promotes the ubiquitination of the mitofusin mitochondrial assembly regulatory factor (MARF), mitofusin 1, mitofusin 2 and voltage-dependent anion-selective channel protein 1 (vDAC1), all of which are embedded in the MOM.

Preceded by: Pink1 recruits Parkin to the outer mitochondrial membrane.

Followed by: p62 binds ubiquitinated mitochondrial substrates

Literature references

Kanthasamy, AG., Anantharam, V., Sun, F., Kanthasamy, A. (2009). Mitochondrial accumulation of polyubiquitinated proteins and differential regulation of apoptosis by polyubiquitination sites Lys-48 and -63. *J. Cell. Mol. Med., 13*, 1632-43. ↗

Editions

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

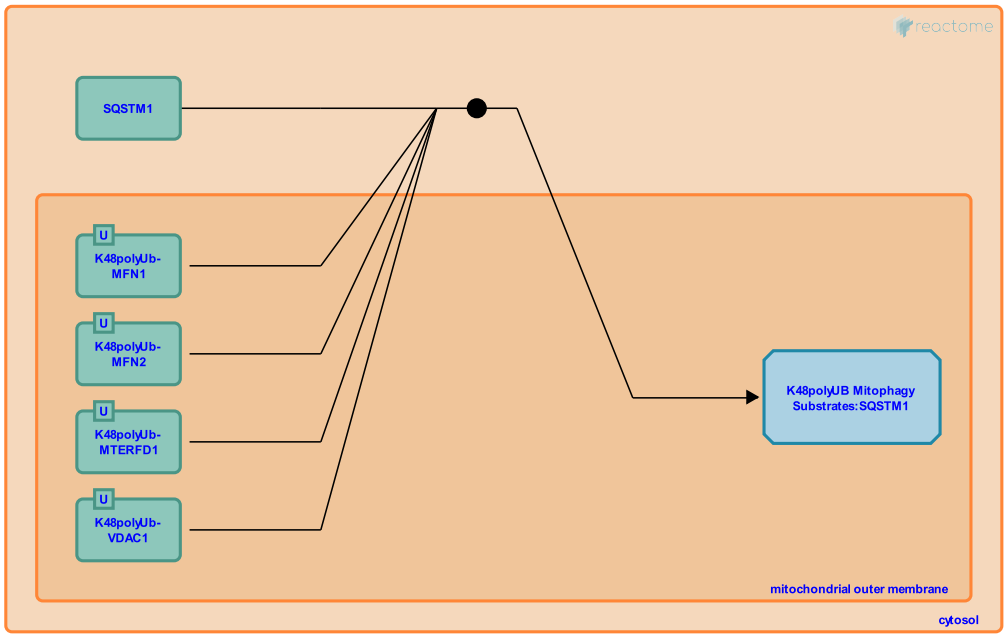
p62 binds ubiquitinated mitochondrial substrates ↗

Location: PINK1-PRKN Mediated Mitophagy

Stable identifier: R-HSA-5205673

Type: binding

Compartments: cytosol



After the ubiquitination events, p62 is recruited to mitochondria, binding the Parkin-ubiquitinated substrates.

Preceded by: Parkin promotes the ubiquitination of mitochondrial substrates

Followed by: p62 links damaged mitochondria to LC3

Literature references

Tanida, I. (2011). Autophagosome formation and molecular mechanism of autophagy. *Antioxid. Redox Signal., 14*, 2201-14. ↗

Editions

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

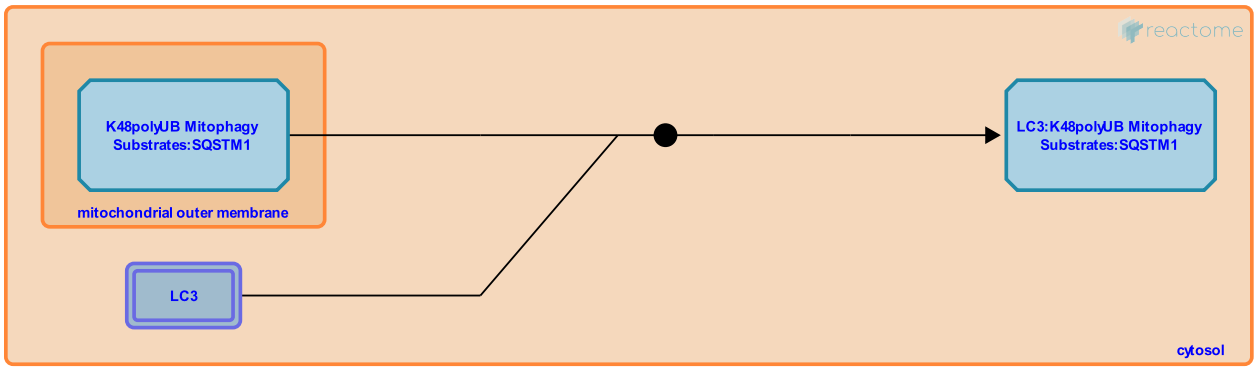
p62 links damaged mitochondria to LC3 ↗

Location: PINK1-PRKN Mediated Mitophagy

Stable identifier: R-HSA-5205649

Type: binding

Compartments: cytosol



p62 links to the microtubule-associated protein Autophagy marker Light Chain 3 (LC3). This initiates the recruitment of the autophagy machinery to the damaged mitochondrion, targeting it for autophagic degradation.

Preceded by: p62 binds ubiquitinated mitochondrial substrates

Followed by: LC3 binds the autophagosome membrane Atg5-Atg12 complex

Literature references

Tanida, I. (2011). Autophagosome formation and molecular mechanism of autophagy. *Antioxid. Redox Signal., 14*, 2201-14. ↗

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2019-03-05	Revised	Varusai, TM.

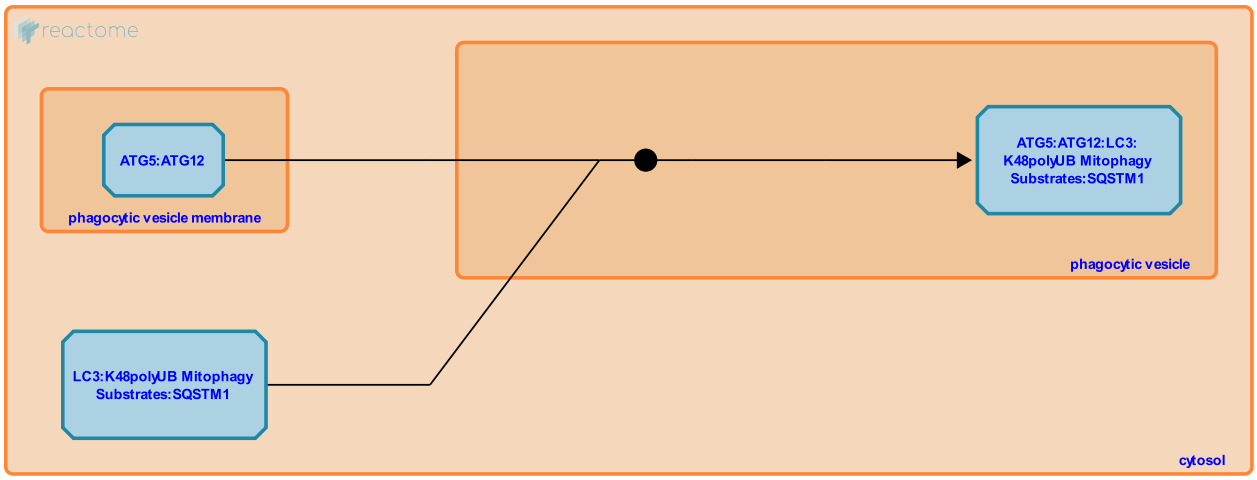
LC3 binds the autophagosome membrane Atg5-Atg12 complex ↗

Location: PINK1-PRKN Mediated Mitophagy

Stable identifier: R-HSA-5205663

Type: binding

Compartments: phagocytic vesicle



The mitochondrion is engulfed after elongation of the isolation membrane. Once the autophagosome is formed, its outer membrane fuses with lysosomes to form the autolysosome. The lysosomal hydrolases (cathepsins and lipases) ultimately degrade the damaged mitochondrion and its associated proteins.

Preceded by: p62 links damaged mitochondria to LC3

Literature references

Tanida, I. (2011). Autophagosome formation and molecular mechanism of autophagy. *Antioxid. Redox Signal., 14,* 2201-14. ↗

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