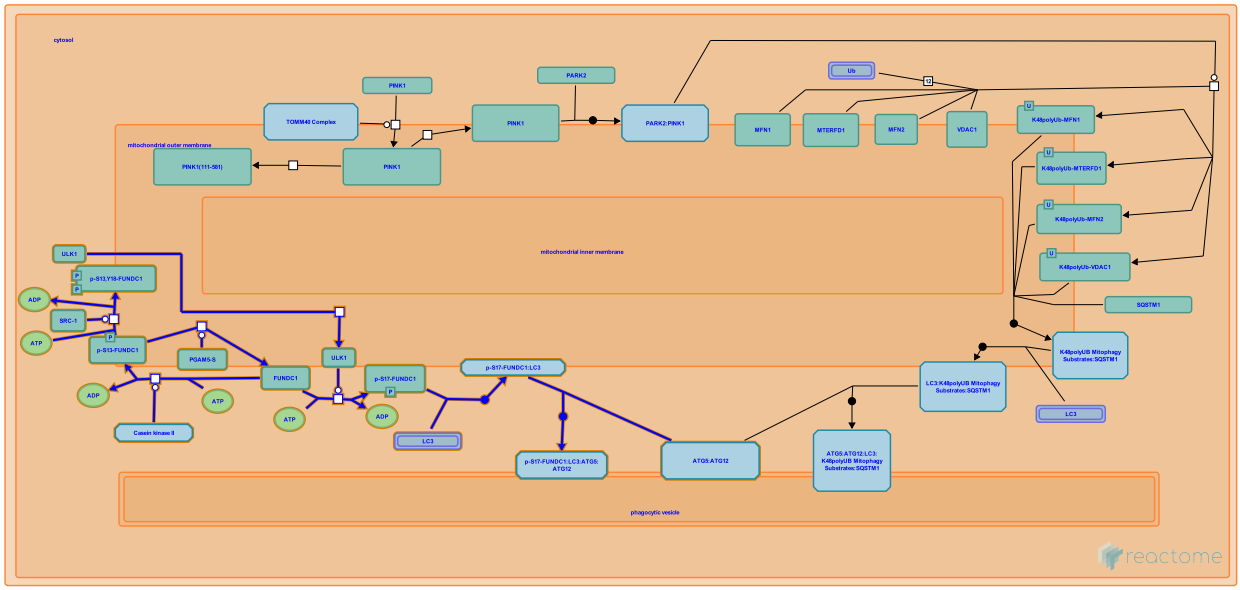
Receptor Mediated Mitophagy



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19/04/2021

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. ↗

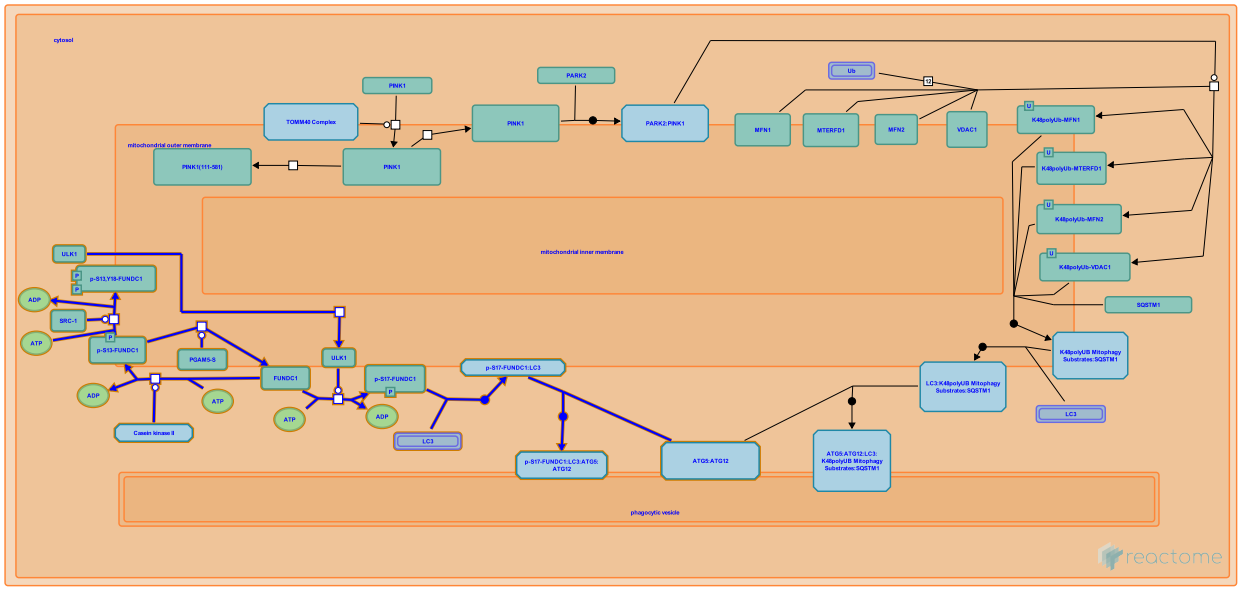
Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655. ↗

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. ↗

Receptor Mediated 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.

Literature references

Wei, H., Liu, L., Chen, Q. (2015). Selective removal of mitochondria via mitophagy: distinct pathways for different mitochondrial stresses. *Biochim. Biophys. Acta, 1853*, 2784-90. ↗

Feng, D., Liu, L., Zhu, Y., Chen, Q. (2013). Molecular signaling toward mitophagy and its physiological significance. *Exp. Cell Res., 319*, 1697-705. ↗

Sandoval, H., Thiagarajan, P., Dasgupta, SK., Schumacher, A., Prchal, JT., Chen, M. et al. (2008). Essential role for Nix in autophagic maturation of erythroid cells. *Nature, 454*, 232-5.

Liu, L., Feng, D., Chen, G., Chen, M., Zheng, Q., Song, P. et al. (2012). Mitochondrial outer-membrane protein FUNDC1 mediates hypoxia-induced mitophagy in mammalian cells. *Nat. Cell Biol., 14*, 177-85.

Wu, W., Tian, W., Hu, Z., Chen, G., Huang, L., Li, W. et al. (2014). ULK1 translocates to mitochondria and phosphorylates FUNDC1 to regulate mitophagy. *EMBO Rep., 15*, 566-75.

Editions

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

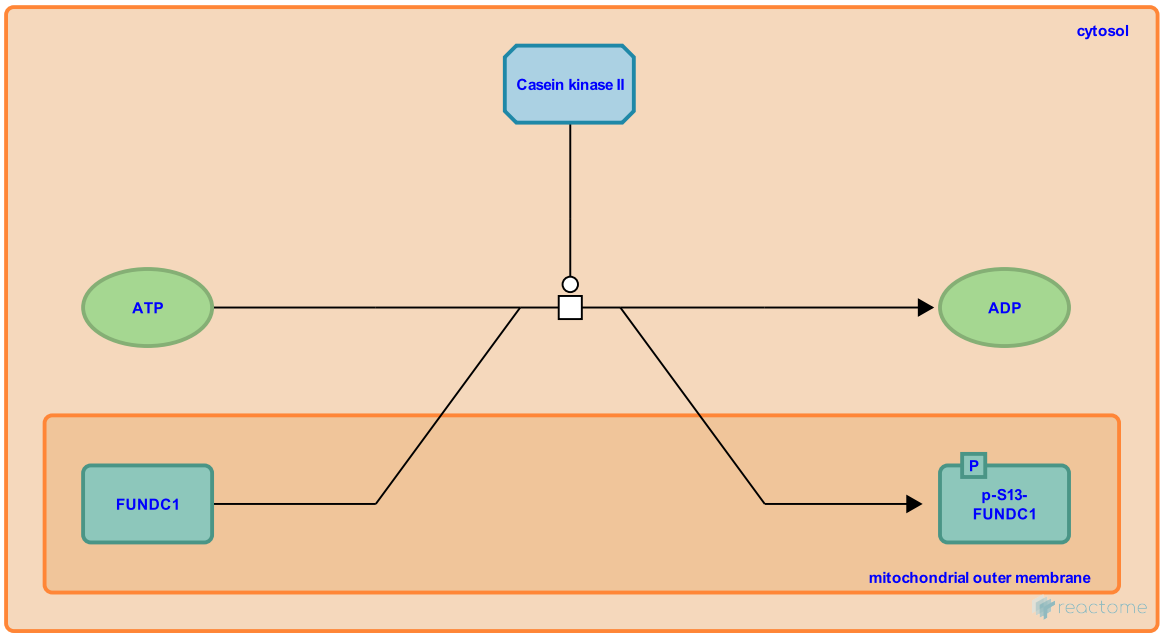
FUNDC1 is phosphorylated by CK2 ↗

Location: Receptor Mediated Mitophagy

Stable identifier: R-HSA-8948039

Type: transition

Compartments: cytosol



FUNDC1-mediated mitophagy is inhibited by its phosphorylation at the Serine 13 positions in the LIR motif by CK2kinase under normoxia conditions. These phosphorylation events insure that FUNDC1 cannot bind LC3.

Preceded by: p-S13-FUNDC1 is dephosphorylated by PGAM5

Followed by: p-S13, FUNDC1 is phosphorylated by CK2 at Tyr18, p-S13-FUNDC1 is dephosphorylated by PGAM5

Literature references

Chen, G., Han, Z., Feng, D., Chen, Y., Chen, L., Wu, H. et al. (2014). A regulatory signaling loop comprising the PGAM5 phosphatase and CK2 controls receptor-mediated mitophagy. *Mol. Cell, 54*, 362-77. ↗

Editions

2016-11-11	Authored	Gillespie, ME.
2017-01-26	Reviewed	Feng, D.
2017-02-28	Edited	Gillespie, ME.
2019-03-05	Revised	Varusai, TM.

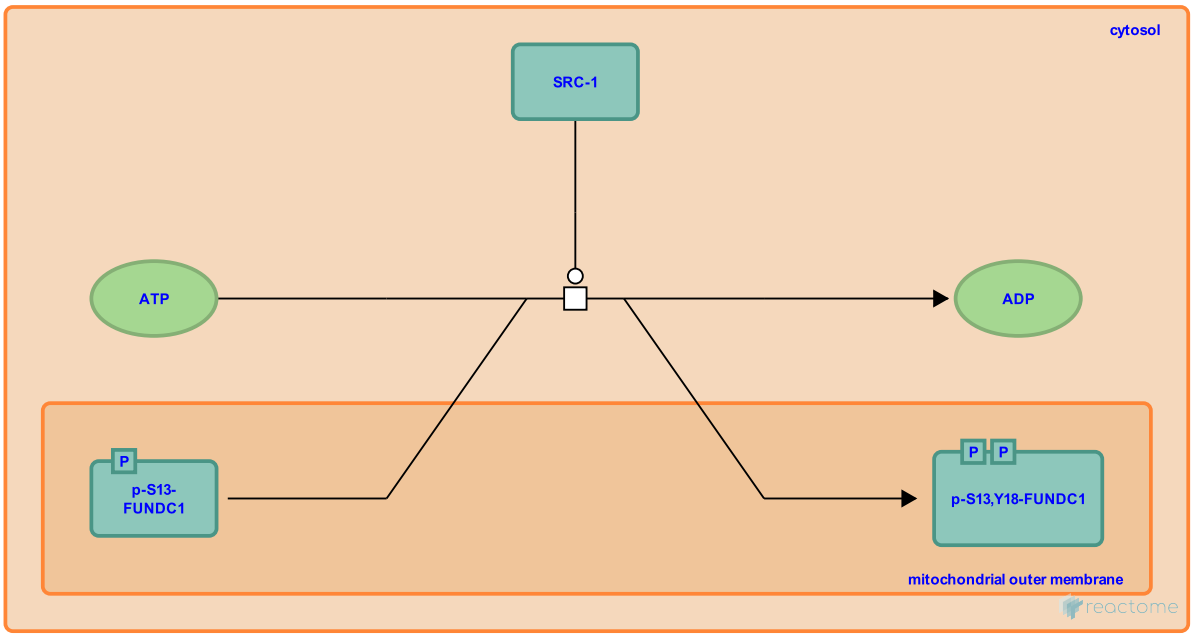
p-S13, FUNDC1 is phosphorylated by CK2 at Tyr18 ↗

Location: Receptor Mediated Mitophagy

Stable identifier: R-HSA-8948143

Type: transition

Compartments: cytosol



FUNDC1-mediated mitophagy is inhibited by its phosphorylation at the Tyr 18 position in the LIR motif by Src kinase under normoxia conditions. These phosphorylation events insure that FUNDC1 cannot bind LC3.

Preceded by: FUNDC1 is phosphorylated by CK2

Literature references

Chen, G., Han, Z., Feng, D., Chen, Y., Chen, L., Wu, H. et al. (2014). A regulatory signaling loop comprising the PGAM5 phosphatase and CK2 controls receptor-mediated mitophagy. *Mol. Cell, 54*, 362-77. ↗

Editions

2016-11-02	Authored	Gillespie, ME.
2017-01-26	Reviewed	Feng, D.
2017-02-28	Edited	Gillespie, ME.
2019-03-05	Revised	Varusai, TM.

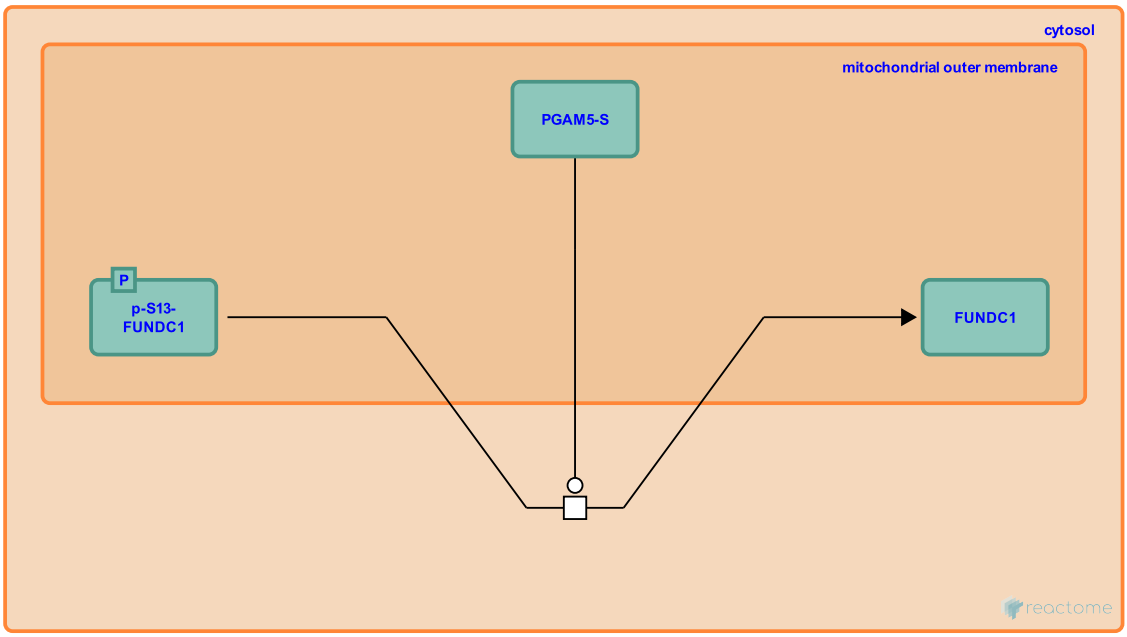
p-S13-FUNDC1 is dephosphorylated by PGAM5

Location: Receptor Mediated Mitophagy

Stable identifier: R-HSA-8948139

Type: transition

Compartments: cytosol



Mitochondria are selectively removed by interactions between LC3 and the FUNDC1 mitophagy receptor which harbors an LC3-interacting region (LIR). When mitochondrial stresses are sensed mitochondrially localized PGAM5 phosphatase interacts with and dephosphorylates FUNDC1 at serine 13 (Ser-13) upon hypoxia.

Preceded by: FUNDC1 is phosphorylated by CK2

Followed by: FUNDC1 is phosphorylated by CK2, FUNDC1 is phosphorylated by ULK1 at Ser17

Literature references

Chen, G., Han, Z., Feng, D., Chen, Y., Chen, L., Wu, H. et al. (2014). A regulatory signaling loop comprising the PGAM5 phosphatase and CK2 controls receptor-mediated mitophagy. *Mol. Cell, 54*, 362-77.

Editions

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2017-01-26	Reviewed	Feng, D.
2017-02-28	Edited	Gillespie, ME.
2019-03-05	Revised	Varusai, TM.

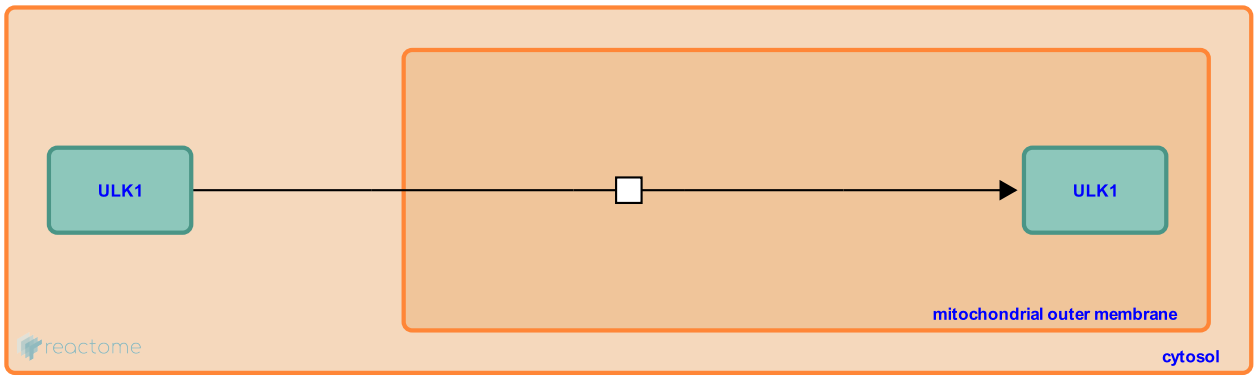
ULK1 Translocates to the mitochondria ↗

Location: Receptor Mediated Mitophagy

Stable identifier: R-HSA-8948136

Type: transition

Compartments: mitochondrial outer membrane



ULK1 is critical for the induction of autophagy, translocating to fragmented mitochondria upon mitophagy induction by either hypoxia or mitochondrial uncouplers. At mitochondria, ULK1 interacts with FUNDC1.

Followed by: FUNDC1 is phosphorylated by ULK1 at Ser17

Literature references

Wu, W., Tian, W., Hu, Z., Chen, G., Huang, L., Li, W. et al. (2014). ULK1 translocates to mitochondria and phosphorylates FUNDC1 to regulate mitophagy. *EMBO Rep., 15*, 566-75. ↗

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2017-01-26	Reviewed	Feng, D.
2017-02-28	Edited	Gillespie, ME.
2019-03-05	Revised	Varusai, TM.

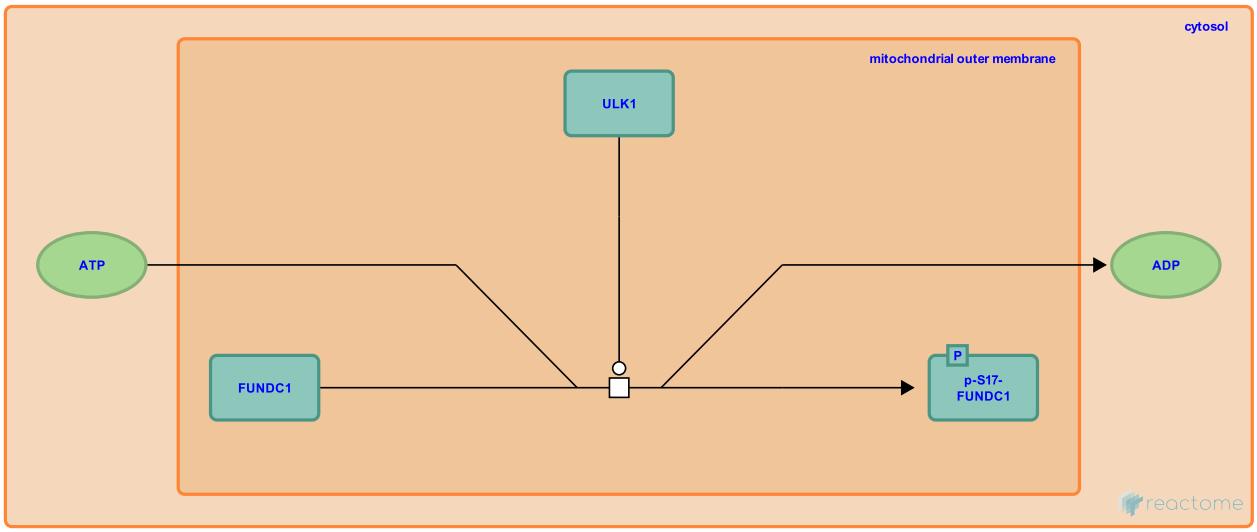
FUNDC1 is phosphorylated by ULK1 at Ser17 ↗

Location: Receptor Mediated Mitophagy

Stable identifier: R-HSA-8948146

Type: transition

Compartments: mitochondrial outer membrane



At mitochondria, ULK1 interacts with FUNDC1, phosphorylating it at serine 17, which enhances FUNDC1 binding to LC3. FUNDC1 regulates ULK1 recruitment to damaged mitochondria; FUNDC1 phosphorylation by ULK1 is crucial for mitophagy.

Preceded by: ULK1 Translocates to the mitochondria, p-S13-FUNDC1 is dephosphorylated by PGAM5

Followed by: Phosphorylated FUNDC1 links damaged mitochondria to LC3

Literature references

Wu, W., Tian, W., Hu, Z., Chen, G., Huang, L., Li, W. et al. (2014). ULK1 translocates to mitochondria and phosphorylates FUNDC1 to regulate mitophagy. *EMBO Rep., 15*, 566-75. ↗

Editions

2016-11-02	Authored	Gillespie, ME.
2017-01-26	Reviewed	Feng, D.
2017-02-28	Edited	Gillespie, ME.
2019-03-05	Revised	Varusai, TM.

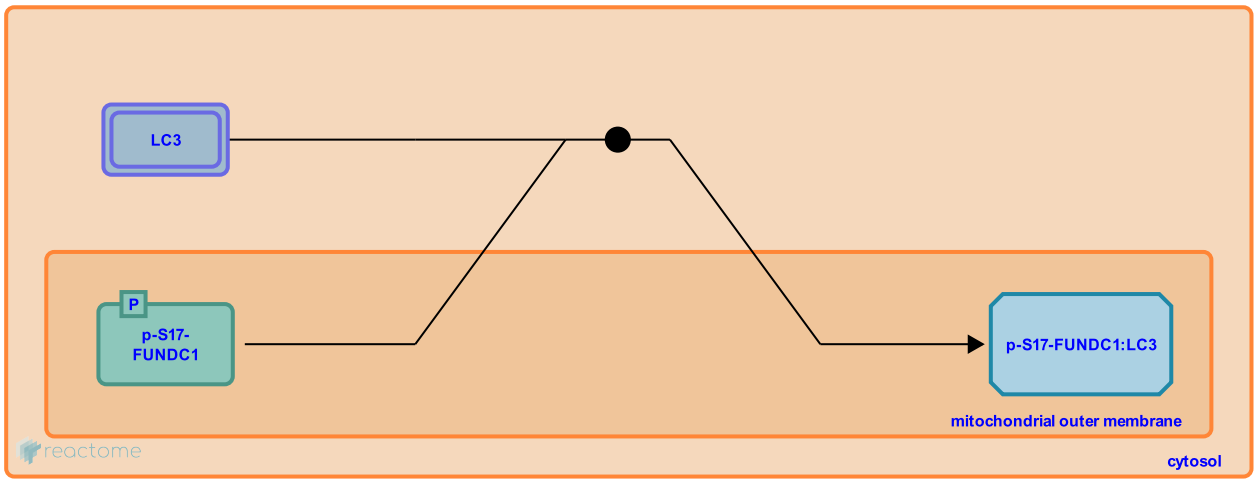
Phosphorylated FUNDC1 links damaged mitochondria to LC3 ↗

Location: Receptor Mediated Mitophagy

Stable identifier: R-HSA-8959573

Type: binding

Compartments: cytosol



s17 Phosphorylated FUNDC1 links to the microtubule-associated protein Autophagy marker Light Chain 3 (LC3). This begins the recruitment of the autophagy machinery to the damaged mitochondria, targeting it for autophagic degradation.

Preceded by: FUNDC1 is phosphorylated by ULK1 at Ser17

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

Literature references

Liu, L., Feng, D., Chen, G., Chen, M., Zheng, Q., Song, P. et al. (2012). Mitochondrial outer-membrane protein FUNDC1 mediates hypoxia-induced mitophagy in mammalian cells. *Nat. Cell Biol., 14*, 177-85. ↗

Editions

2017-01-26	Reviewed	Feng, D.
2017-01-27	Authored	Gillespie, ME.
2017-02-28	Edited	Gillespie, ME.
2019-03-05	Revised	Varusai, TM.

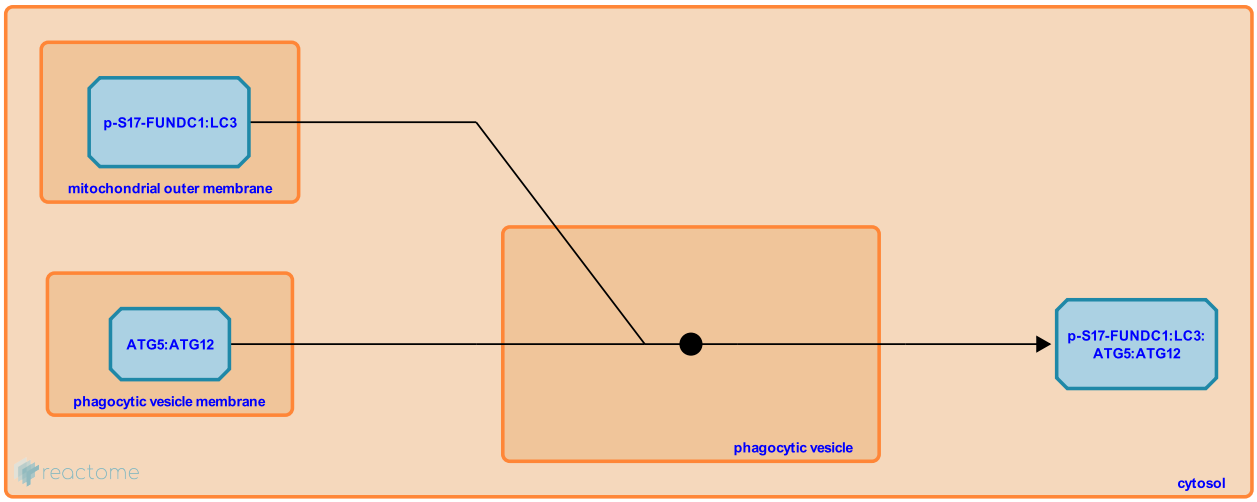
LC3 binds the autophagosome membrane Atg5-Atg12 complex ↗

Location: Receptor Mediated Mitophagy

Stable identifier: R-HSA-8959571

Type: binding

Compartments: phagocytic vesicle



The mitochondria are 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 mitochondria and its associated proteins.

Preceded by: Phosphorylated FUNDC1 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.
2017-01-26	Reviewed	Feng, D.
2019-03-05	Revised	Varusai, TM.

Table of Contents