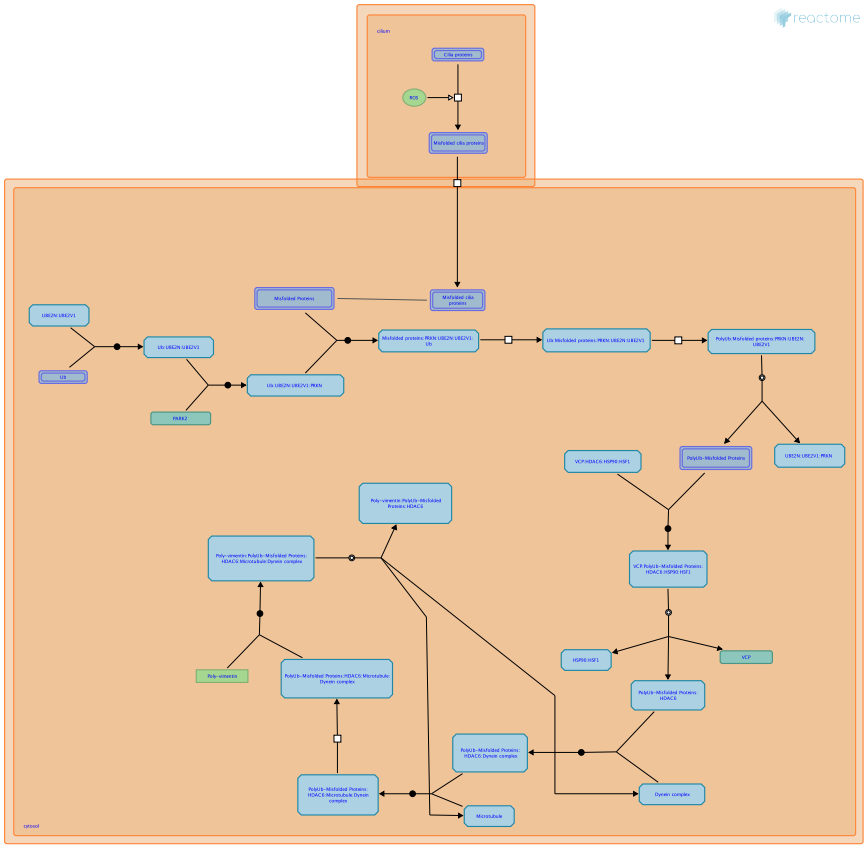
Aggrephagy



Metzakopian, E., Varusai, TM.

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03/09/2021

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. ↗

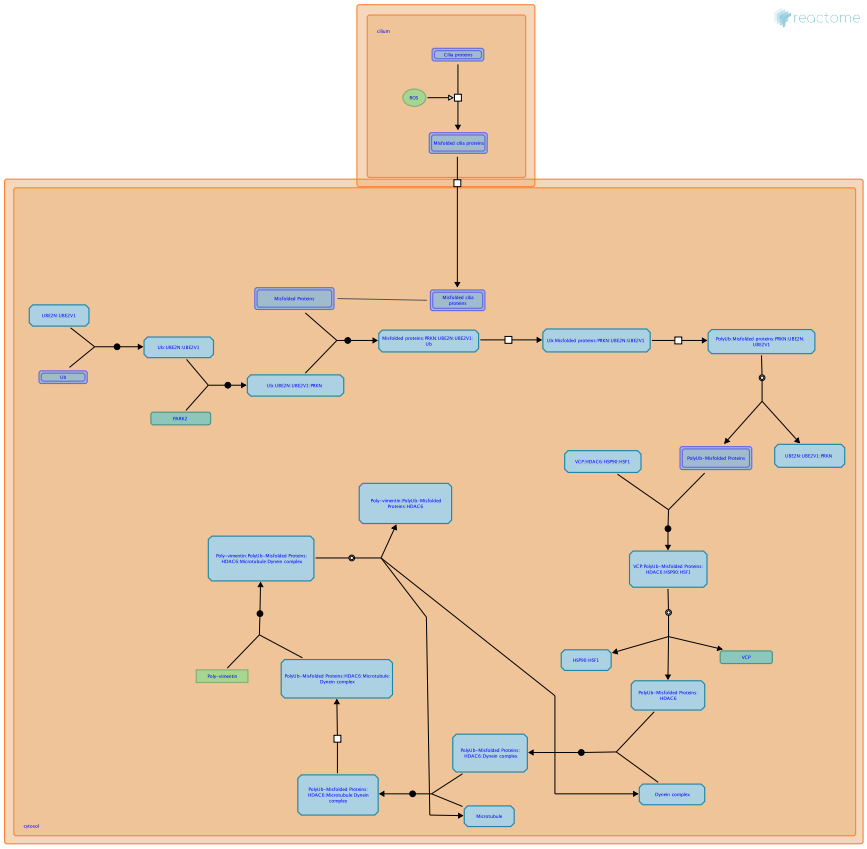
Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655. ↗

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. ↗

Aggrephagy ↗

Stable identifier: R-HSA-9646399

Compartments: cytosol



When the capacity of the proteosome to degrade misfolded proteins is limited, the alternate route to eliminate denatured proteins is via forming aggresomes - a process known as aggrephagy. Aggresome formation starts with ubiquitination of misfolded proteins following transport to the microtubule-organizing center (MTOC) with the help of dynein motor proteins. At the MTOC the cargo is encapsulated with intermediate filament proteins to result in the aggresome. Subsequently, this aggresome recruits chaperones that result in its autophagic elimination (Garcia Mata R et al. 2002).

Literature references

Garcia-Mata, R., Gao, YS., Sztul, E. (2002). Hassles with taking out the garbage: aggravating aggresomes. *Traffic, 3*, 388-96. ↗

Editions

2019-05-23	Authored	Varusai, TM.
2019-05-24	Reviewed	Metzakopian, E.
2019-11-08	Edited	Varusai, TM.

ROS positively regulates misfolding of cilia proteins ↗

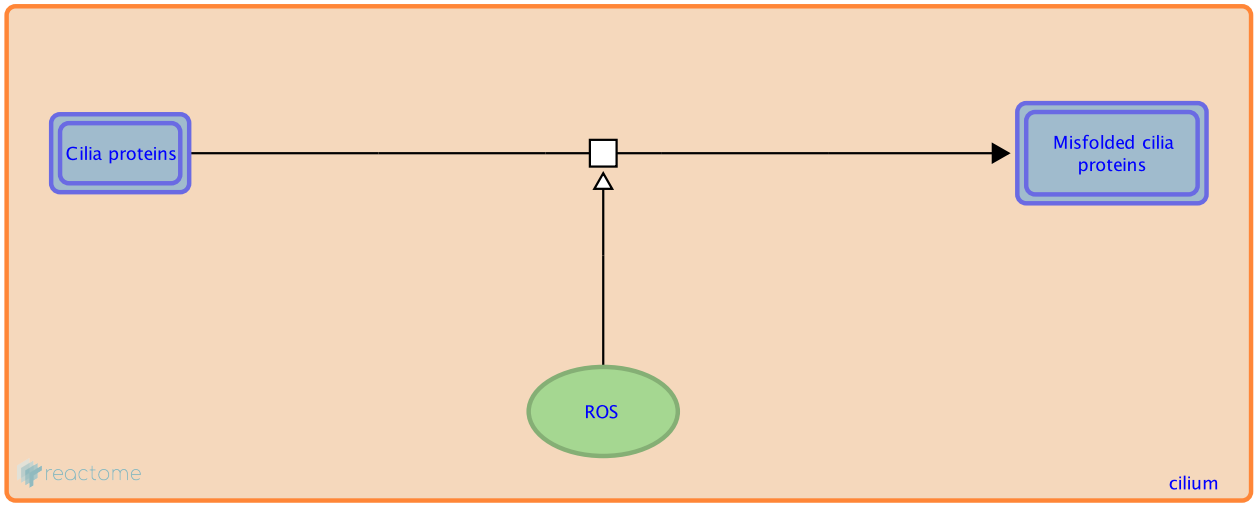
Location: Aggrephagy

Stable identifier: R-HSA-9639698

Type: transition

Compartments: cilium

Inferred from: ROS positively regulates misfolding of cilia proteins (Mus musculus)



Accumulation of excessive reactive oxygen species (ROS) within cells results in oxidative stress. This stress can trigger proteins misfolding and make them dysfunctional. Cilia proteins are damaged when subjected to oxidative stress and may be targeted to the autophagy machinery. This results in the shortening of the cilium (Lam HC et al. 2013, Kim JI et al. 2013). Experiments leading to this finding were performed in mice.

Followed by: Misfolded proteins translocate from cilium to cytosol

Literature references

Lam, HC., Cloonan, SM., Bhashyam, AR., Haspel, JA., Singh, A., Sathirapongsasuti, JF. et al. (2013). Histone deacetylase 6-mediated selective autophagy regulates COPD-associated cilia dysfunction. *J. Clin. Invest., 123*, 5212-30. ↗

Kim, JI., Kim, J., Jang, HS., Noh, MR., Lipschutz, JH., Park, KM. (2013). Reduction of oxidative stress during recovery accelerates normalization of primary cilia length that is altered after ischemic injury in murine kidneys. *Am. J. Physiol. Renal Physiol., 304*, F1283-94. ↗

Editions

2019-03-18	Authored	Varusai, TM.
2019-05-24	Reviewed	Metzakopian, E.
2019-11-08	Edited	Varusai, TM.

Misfolded proteins translocate from cilium to cytosol ↗

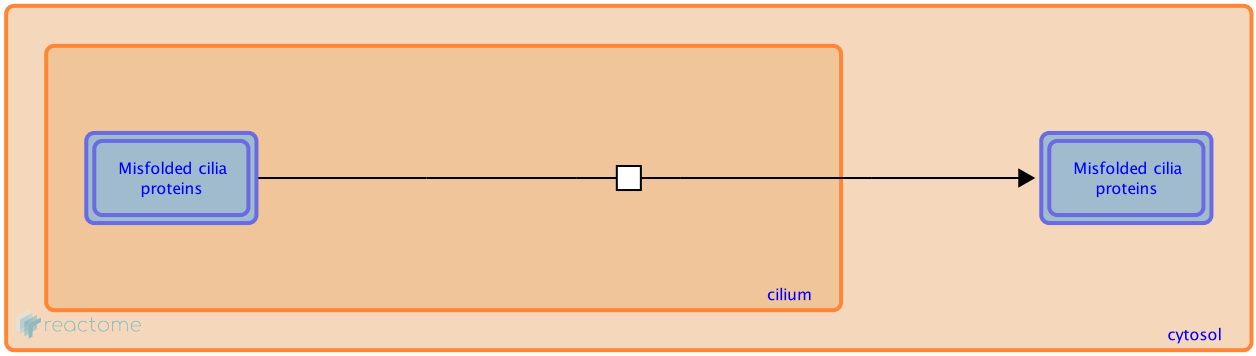
Location: Aggrephagy

Stable identifier: R-HSA-9640114

Type: transition

Compartments: cilium, cytosol

Inferred from: Misfolded proteins translocate from cilium to cytosol (Mus musculus)



Cellular stress factors damage several cilia proteins and result in their misfolding. These misfolded proteins are translocated into the cytosol of the cell where they are ubiquitinated and eliminated (Lam HC et al. 2013). Confirmatory experiments were performed in mice.

Preceded by: ROS positively regulates misfolding of cilia proteins

Followed by: Misfolded proteins bind PRKN:UBE2N:UBE2V1:Ub

Literature references

Lam, HC., Cloonan, SM., Bhashyam, AR., Haspel, JA., Singh, A., Sathirapongsasuti, JF. et al. (2013). Histone deacetylase 6-mediated selective autophagy regulates COPD-associated cilia dysfunction. *J. Clin. Invest., 123*, 5212-30. ↗

Editions

2019-03-19	Authored	Varusai, TM.
2019-05-24	Reviewed	Metzakopian, E.
2019-11-08	Edited	Varusai, TM.

E2 enzyme UBE2N:UBE2V1 binds ubiquitin ↗

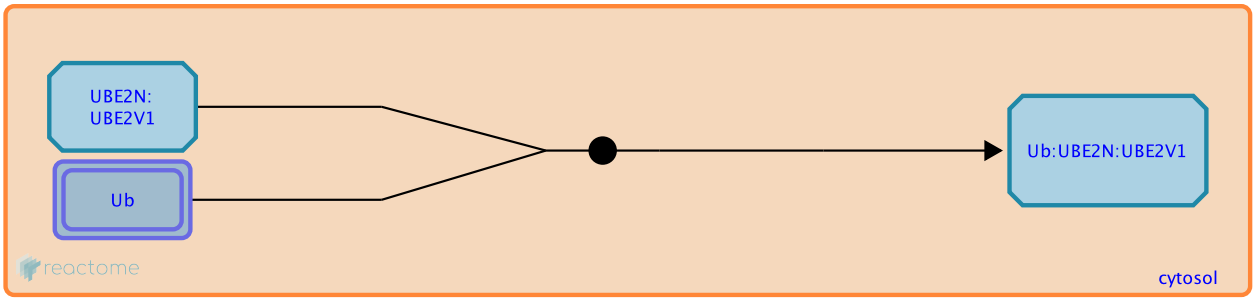
Location: Aggrephagy

Stable identifier: R-HSA-9640480

Type: binding

Compartments: cytosol

Inferred from: E2 enzyme MMS2:UBC13 binds ubiquitin (Saccharomyces cerevisiae)



Ubiquitination is the covalent attachment of ubiquitin molecules to substrate proteins with three enzymatic steps - E1 ubiquitin activation, E2 ubiquitin conjugation and E3 ubiquitin protein ligase. UBE2V1 and UBE2N are E2 ubiquitin-conjugating enzymes that form a complex and bind ubiquitin molecules at K63. This leads to the additional binding of ubiquitin entities and formation of a polyubiquitin chain (Hofmann RM et al. 1999). Experiments confirming this finding were performed in yeast cells.

Followed by: Parkin binds Ub:UBE2N:UBE2V1

Literature references

Hofmann, RM., Pickart, CM. (1999). Noncanonical MMS2-encoded ubiquitin-conjugating enzyme functions in assembly of novel polyubiquitin chains for DNA repair. *Cell, 96,* 645-53. ↗

Editions

2019-05-24	Reviewed	Metzakopian, E.
2019-06-14	Authored	Varusai, TM.
2019-11-08	Edited	Varusai, TM.

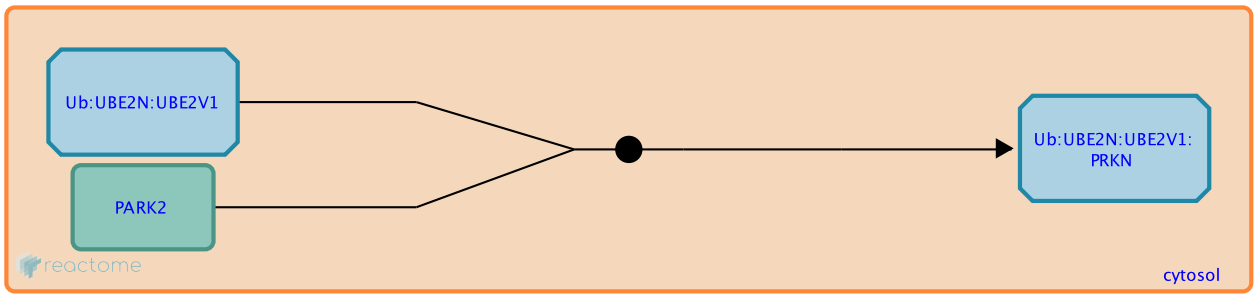
Parkin binds Ub:UBE2N:UBE2V1 ↗

Location: Aggrephagy

Stable identifier: R-HSA-9641089

Type: binding

Compartments: cytosol



Ubiquitination is the covalent attachment of ubiquitin molecules to substrate proteins with three enzymatic steps - E1 ubiquitin activation, E2 ubiquitin conjugation and E3 ubiquitin protein ligase. UBE2V1 and UBE2N are E2 ubiquitin-conjugating enzymes that form a complex and bind ubiquitin molecules at K63. Consequently, the E3 ligase PRKN (Parkin) binds this complex and facilitates the addition of more ubiquitin molecules. (Olzmann JA et al. 2007).

Preceded by: E2 enzyme UBE2N:UBE2V1 binds ubiquitin

Followed by: Misfolded proteins bind PRKN:UBE2N:UBE2V1:Ub

Literature references

Olzmann, JA., Li, L., Chudaev, MV., Chen, J., Perez, FA., Palmiter, RD. et al. (2007). Parkin-mediated K63-linked polyubiquitination targets misfolded DJ-1 to aggresomes via binding to HDAC6. *J. Cell Biol., 178*, 1025-38. ↗

Editions

2019-04-02	Authored	Varusai, TM.
2019-05-24	Reviewed	Metzakopian, E.
2019-11-08	Edited	Varusai, TM.

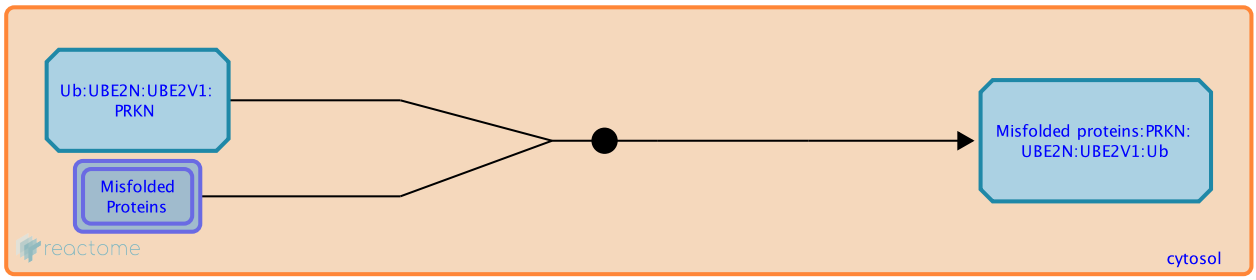
Misfolded proteins bind PRKN:UBE2N:UBE2V1:Ub ↗

Location: Aggrephagy

Stable identifier: R-HSA-9641096

Type: binding

Compartments: cytosol



Stress factors damage and misfold cilia proteins, which are then translocated to the cytosol. Here, they are ubiquitinated via the UBE2N:UBE2V1:Parkin complex. The E3 ligase Parkin recruits the misfolded proteins to the E2 ubiquitin conjugation complex. This results in the polyubiquitination of misfolded proteins targeting them to degradation (Olzmann JA et al. 2007).

Preceded by: Misfolded proteins translocate from cilium to cytosol, Parkin binds Ub:UBE2N:UBE2V1

Followed by: Parkin transfers Ub to misfolded proteins

Literature references

Olzmann, JA., Li, L., Chudaev, MV., Chen, J., Perez, FA., Palmiter, RD. et al. (2007). Parkin-mediated K63-linked polyubiquitination targets misfolded DJ-1 to aggresomes via binding to HDAC6. *J. Cell Biol., 178*, 1025-38. ↗

Editions

2019-04-02	Authored	Varusai, TM.
2019-05-24	Reviewed	Metzakopian, E.
2019-11-08	Edited	Varusai, TM.

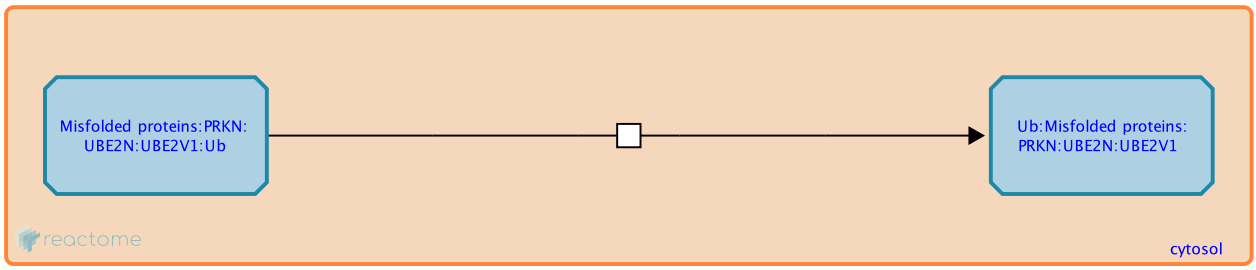
Parkin transfers Ub to misfolded proteins ↗

Location: Aggrephagy

Stable identifier: R-HSA-9641111

Type: transition

Compartments: cytosol



Misfolded proteins in the cytosol are tagged with ubiquitin molecules via the E2 UBE2N/UBE2V1 conjugation complex and E3 ligase Parkin. Misfolded proteins bind Parkin and subsequently Parkin transfers ubiquitin from E2 complex to the proteins (Olzmann JA et al. 2007).

Preceded by: Misfolded proteins bind PRKN:UBE2N:UBE2V1:Ub

Followed by: Ub:misfolded proteins polymerize to PolyUb:misfolded proteins

Literature references

Olzmann, JA., Li, L., Chudaev, MV., Chen, J., Perez, FA., Palmiter, RD. et al. (2007). Parkin-mediated K63-linked polyubiquitination targets misfolded DJ-1 to aggresomes via binding to HDAC6. *J. Cell Biol., 178*, 1025-38. ↗

Editions

2019-04-04	Authored	Varusai, TM.
2019-05-24	Reviewed	Metzakopian, E.
2019-11-08	Edited	Varusai, TM.

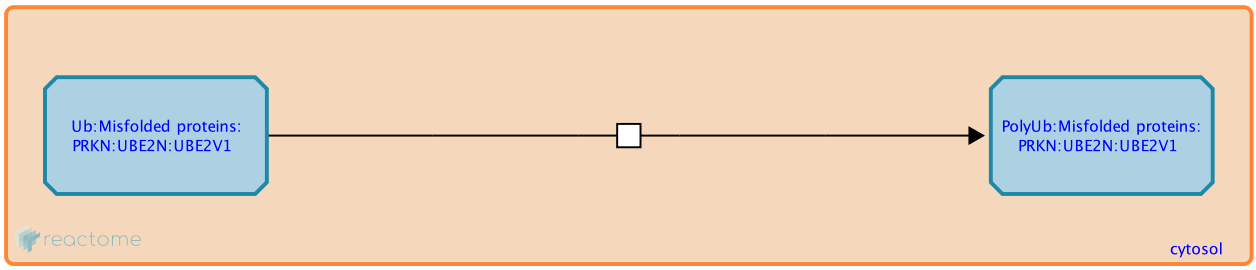
Ub:misfolded proteins polymerize to PolyUb:misfolded proteins ↗

Location: Aggrephagy

Stable identifier: R-HSA-9641127

Type: transition

Compartments: cytosol



Misfolded proteins in the cytosol are targeted to degradation via ubiquitination. The E2 UBE2N/UBE2V1 and E3 ligase ubiquitination system recruits and transfers ubiquitin molecules to misfolded proteins. The E3 ligase Parkin tags the proteins with multiple K63-linked ubiquitin molecules (Olzmann JA et al. 2007).

Preceded by: Parkin transfers Ub to misfolded proteins

Followed by: PolyUb:misfolded proteins dissociate from PRKN:UBE2N:UBE2V1

Literature references

Olzmann, JA., Li, L., Chudaev, MV., Chen, J., Perez, FA., Palmiter, RD. et al. (2007). Parkin-mediated K63-linked polyubiquitination targets misfolded DJ-1 to aggresomes via binding to HDAC6. *J. Cell Biol., 178*, 1025-38. ↗

Editions

2019-04-04	Authored	Varusai, TM.
2019-05-24	Reviewed	Metzakopian, E.
2019-11-08	Edited	Varusai, TM.

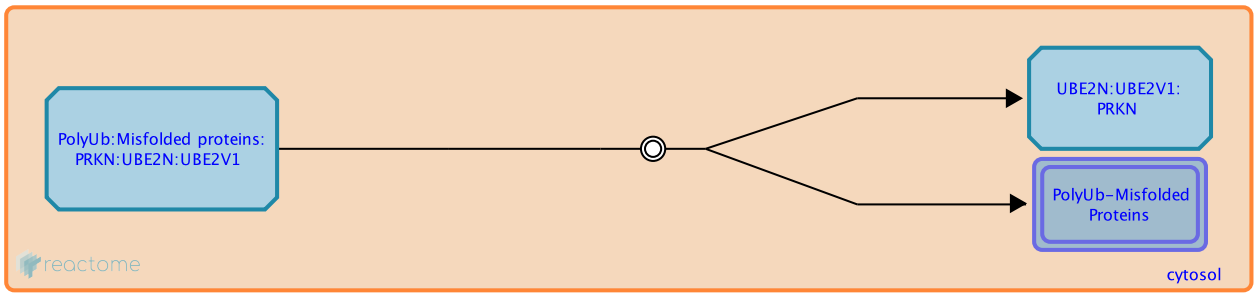
PolyUb:misfolded proteins dissociate from PRKN:UBE2N:UBE2V1 ↗

Location: Aggrephagy

Stable identifier: R-HSA-9641109

Type: dissociation

Compartments: cytosol



Misfolded proteins from cellular stress are destined for degradation via ubiquitination. The E2 ubiquitin conjugating enzymes UBE2N/UBE2V1 and E3 ligase enzyme Parkin recruit and tag multiple K63-linked ubiquitin molecules to the misfolded proteins. Subsequently, the polyubiquitinated proteins dissociate from the E2/E3 system and are driven to degradation (Olzmann JA et al. 2007).

Preceded by: Ub:misfolded proteins polymerize to PolyUb:misfolded proteins

Followed by: PolyUb-misfolded proteins bind VCP:HDAC6:HSP90:HSF1

Literature references

Olzmann, JA., Li, L., Chudaev, MV., Chen, J., Perez, FA., Palmiter, RD. et al. (2007). Parkin-mediated K63-linked polyubiquitination targets misfolded DJ-1 to aggresomes via binding to HDAC6. *J. Cell Biol., 178*, 1025-38. ↗

Editions

2019-04-04	Authored	Varusai, TM.
2019-05-24	Reviewed	Metzakopian, E.
2019-11-08	Edited	Varusai, TM.

PolyUb-misfolded proteins bind VCP:HDAC6:HSP90:HSF1 ↗

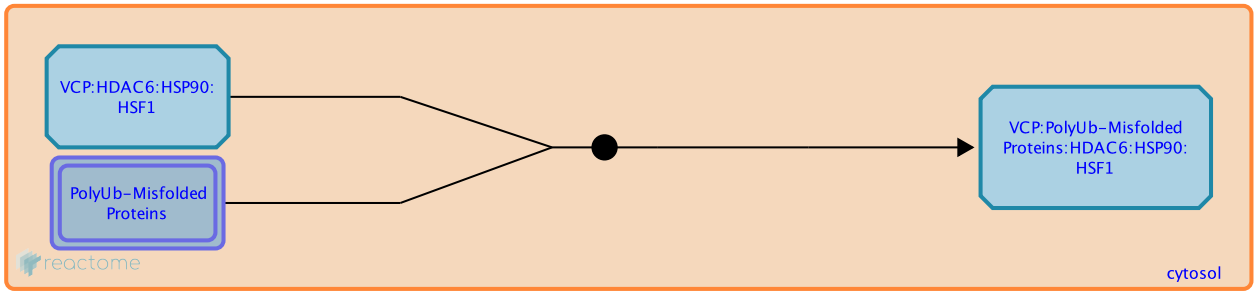
Location: Aggrephagy

Stable identifier: R-HSA-9646347

Type: binding

Compartments: cytosol

Inferred from: Ubiquitin binds Vcp:Hdac6:Hsp90:Hsf1 (Mus musculus)



When the proteasome machinery is deregulated, misfolded proteins are eliminated by forming aggresomes. To this end, poly-ubiquitinated misfolded proteins bind to a complex comprising of Transitional endoplasmic reticulum ATPase (VCP), Histone deacetylase 6 (HDAC6), Heat shock protein HSP 90 (HSP90) and Heat shock factor protein 1 (HSF1). HDAC6 in the complex interacts with the ubiquitin molecules in the misfolded proteins. Following this binding event, this complex starts dissociating (Boyault C et al. 2007).

Preceded by: PolyUb:misfolded proteins dissociate from PRKN:UBE2N:UBE2V1

Followed by: PolyUb-Misfolded Proteins:HDAC6 dissociate from complex

Literature references

Boyault, C., Zhang, Y., Fritah, S., Caron, C., Gilquin, B., Kwon, SH. et al. (2007). HDAC6 controls major cell response pathways to cytotoxic accumulation of protein aggregates. *Genes Dev., 21*, 2172-81. ↗

Editions

2019-05-07	Authored	Varusai, TM.
2019-05-24	Reviewed	Metzakopian, E.
2019-11-08	Edited	Varusai, TM.

PolyUb-Misfolded Proteins:HDAC6 dissociate from complex ↗

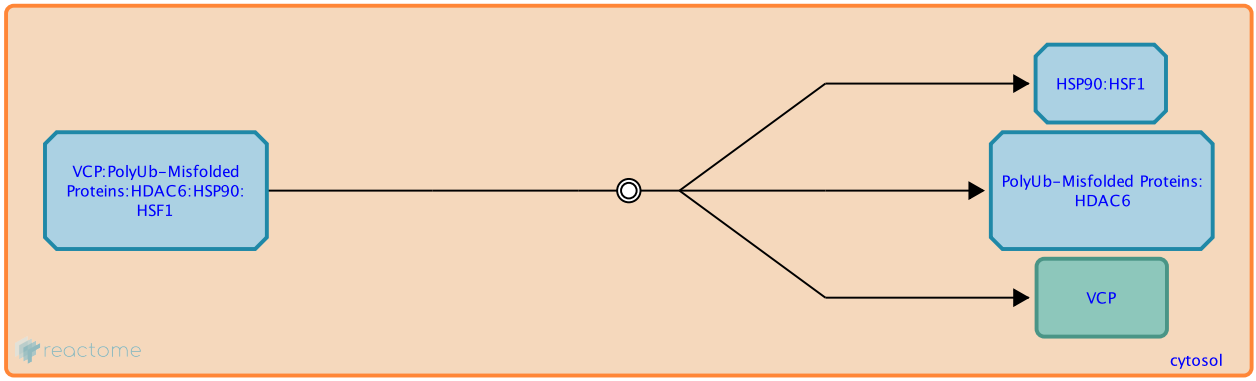
Location: Aggrephagy

Stable identifier: R-HSA-9646354

Type: dissociation

Compartments: cytosol

Inferred from: PolyUb-Misfolded Proteins:Hdac6 dissociate from complex (Mus musculus)



Histone deacetylase 6 (HDAC6) appears to be a master regulator of the cell protective response to cytotoxic protein aggregate formation (Boyault et al. 2007).

Preceded by: PolyUb-misfolded proteins bind VCP:HDAC6:HSP90:HSF1

Followed by: PolyUb-Misfolded Proteins:HDAC6 bind dynein motor

Literature references

Boyault, C., Zhang, Y., Fritah, S., Caron, C., Gilquin, B., Kwon, SH. et al. (2007). HDAC6 controls major cell response pathways to cytotoxic accumulation of protein aggregates. *Genes Dev., 21*, 2172-81. ↗

Editions

2019-05-07	Authored	Varusai, TM.
2019-05-24	Reviewed	Metzakopian, E.
2019-11-08	Edited	Varusai, TM.

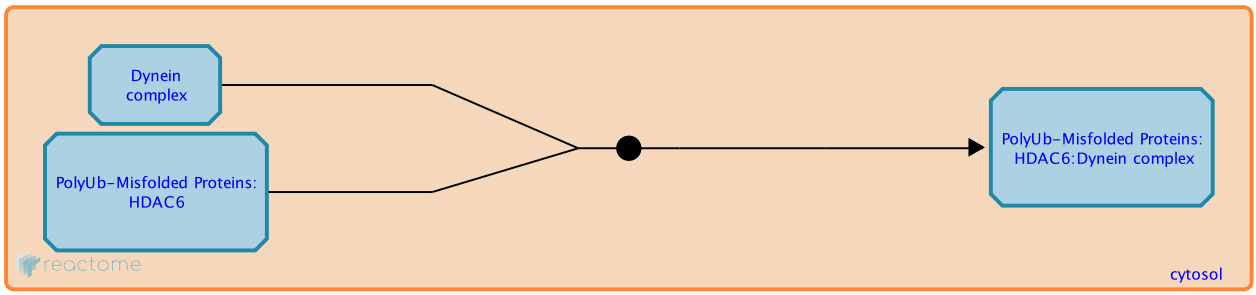
PolyUb-Misfolded Proteins:HDAC6 bind dynein motor ↗

Location: Aggrephagy

Stable identifier: R-HSA-9646348

Type: binding

Compartments: cytosol



Histone deacetylase 6 (HDAC6) plays a key role in the removal of misfolded proteins when the proteosome system is dysregulated. HDAC6 associates with poly-ubiquitinated misfolded proteins and also to the dynein motor system. Subsequently, this complex of HDAC6,misfolded proteins and dynein motor form aggresomes (Kawaguchi Y et al. 2003).

Preceded by: PolyUb-Misfolded Proteins:HDAC6 dissociate from complex, Aggresome dissociates from dynein and microtubule

Followed by: Misfolded proteins:HDAC6:Dynein motor binds microtubule

Literature references

Kawaguchi, Y., Kovacs, JJ., McLaurin, A., Vance, JM., Ito, A., Yao, TP. (2003). The deacetylase HDAC6 regulates aggresome formation and cell viability in response to misfolded protein stress. *Cell, 115*, 727-38. ↗

Editions

2019-05-07	Authored	Varusai, TM.
2019-05-24	Reviewed	Metzakopian, E.
2019-11-08	Edited	Varusai, TM.

Misfolded proteins:HDAC6:Dynein motor binds microtubule ↗

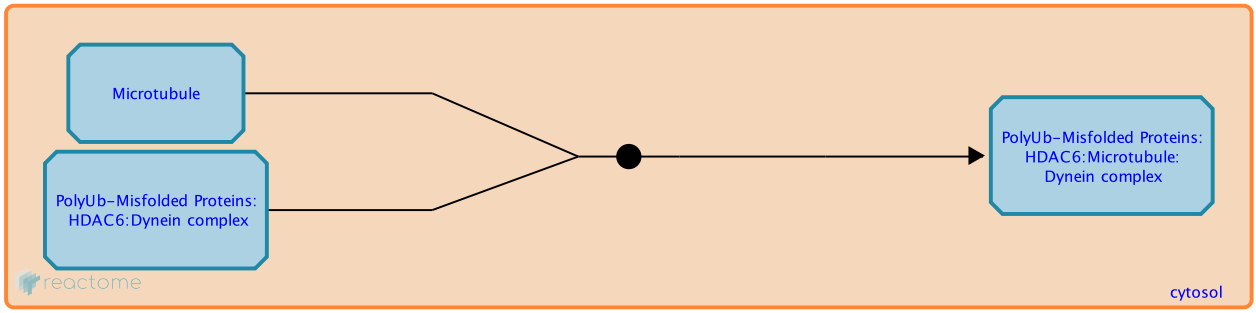
Location: Aggrephagy

Stable identifier: R-HSA-9646390

Type: binding

Compartments: cytosol

Inferred from: Hdac6 binds microtubule (Mus musculus)



Histone deacetylase 6 (HDAC6) binds misfolded proteins destined to form aggresomes and subsequently delivers this to dynein motor proteins. HDAC6 can also bind to microtubules thereby anchoring the misfolded proteins and the dynein motor to the microtubule (Hubbert C et al. 2002). Following this, the dynein motors traverse the microtubule to reach the microtubule-organizing center (MTOC).

Preceded by: PolyUb-Misfolded Proteins:HDAC6 bind dynein motor, Aggresome dissociates from dynein and microtubule

Followed by: Dynein motors transport misfolded proteins

Literature references

Hubbert, C., Guardiola, A., Shao, R., Kawaguchi, Y., Ito, A., Nixon, A. et al. (2002). HDAC6 is a microtubule-associated deacetylase. *Nature, 417*, 455-8. ↗

Editions

2019-05-23	Authored	Varusai, TM.
2019-05-24	Reviewed	Metzakopian, E.
2019-11-08	Edited	Varusai, TM.

Dynein motors transport misfolded proteins ↗

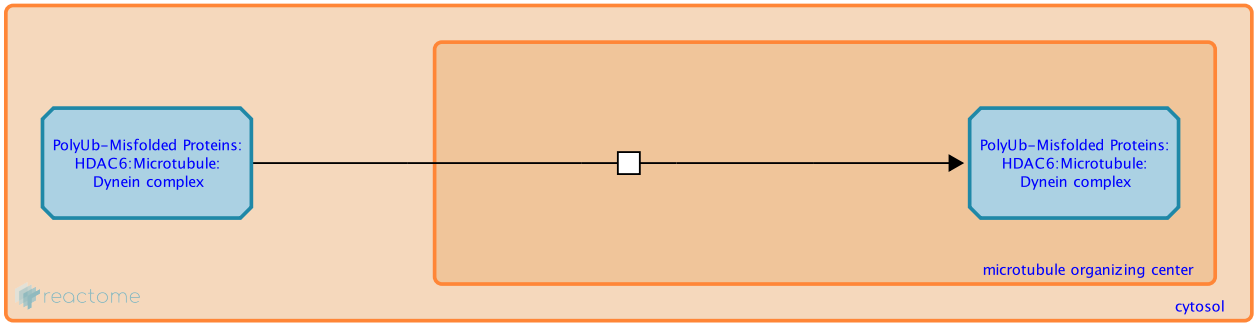
Location: Aggrephagy

Stable identifier: R-HSA-9646383

Type: transition

Compartments: microtubule organizing center, cytosol

Inferred from: Dynein motors transport misfolded proteins (Cercopithecus aethiops)



Misfolded proteins are transported from the microtubule to the microtubule-organizing center (MTOC) in a dynein-mediated mechanism. Dynein motors carry the cargo along the microtubules from the plus end to the minus end (Garcia Mata R et al. 1999). Confirmatory experiments were performed in grivet cell lines.

Preceded by: Misfolded proteins:HDAC6:Dynein motor binds microtubule

Followed by: PolyUb-Misfolded proteins bind vimentin to form aggresome

Literature references

García-Mata, R., Bebök, Z., Sorscher, EJ., Sztul, ES. (1999). Characterization and dynamics of aggresome formation by a cytosolic GFP-chimera. *J. Cell Biol., 146*, 1239-54. ↗

Editions

2019-05-23	Authored	Varusai, TM.
2019-05-24	Reviewed	Metzakopian, E.
2019-11-08	Edited	Varusai, TM.

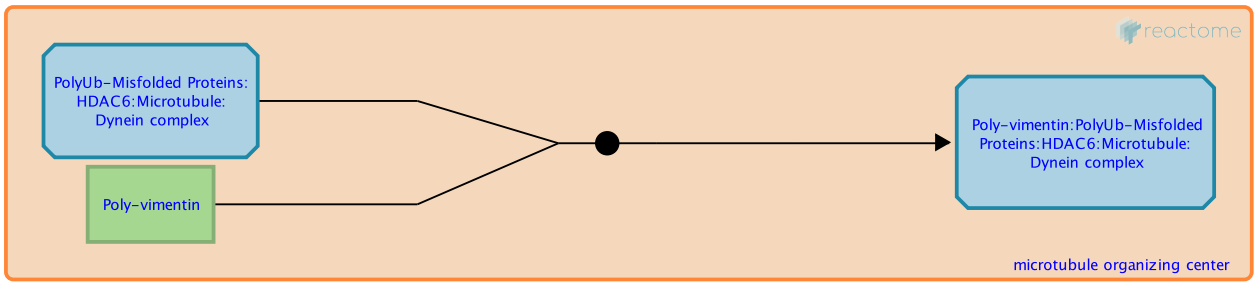
PolyUb-Misfolded proteins bind vimentin to form aggresome ↗

Location: Aggrephagy

Stable identifier: R-HSA-9646679

Type: binding

Compartments: microtubule organizing center



Dynein motor complex drives the multi-ubiquitinated misfolded proteins along the microtubule towards the microtubule organizing center. Here, intermediate filament proteins such as vimentin (VIM) are re-distributed to ensheath misfolded proteins to form the aggresome (Johnston JA et al. 1998). Subsequently, the aggresome is removed with the help of autophagy machinery.

Preceded by: Dynein motors transport misfolded proteins

Followed by: Aggresome dissociates from dynein and microtubule

Literature references

Johnston, JA., Ward, CL., Kopito, RR. (1998). Aggresomes: a cellular response to misfolded proteins. *J. Cell Biol., 143,* 1883-98. ↗

Editions

2019-05-23	Authored	Varusai, TM.
2019-05-24	Reviewed	Metzakopian, E.
2019-11-08	Edited	Varusai, TM.

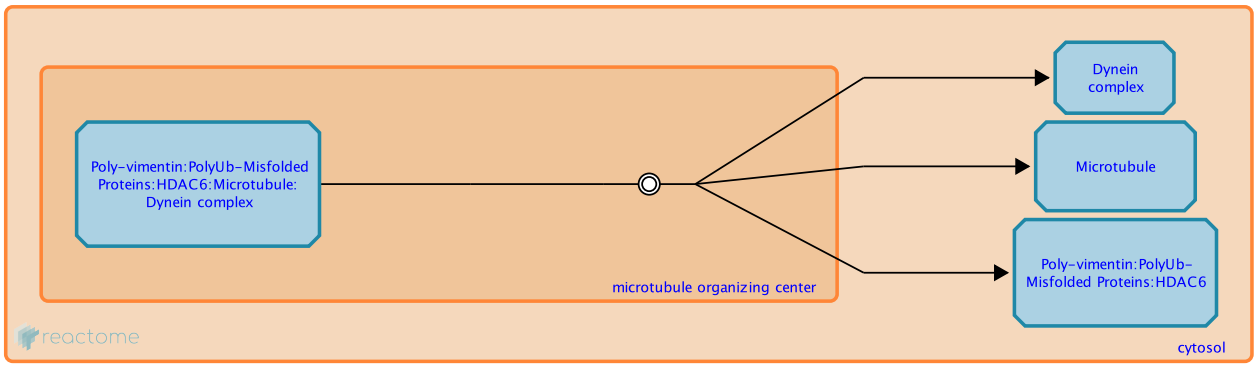
Aggresome dissociates from dynein and microtubule ↗

Location: Aggrephagy

Stable identifier: R-HSA-9646685

Type: dissociation

Compartments: microtubule organizing center



Misfolded proteins are transformed into aggresomes at the microtubule organizing center. Dynein motor proteins facilitate the transport of misfolded proteins along the microtubule. Subsequently, the system disassembles to release the aggresome. The aggresome then recruits chaperone to be degraded by the autophagy machinery (Garcia Mata R et al. 1999).

Preceded by: PolyUb-Misfolded proteins bind vimentin to form aggresome

Followed by: PolyUb-Misfolded Proteins:HDAC6 bind dynein motor, Misfolded proteins:HDAC6:Dynein motor binds microtubule

Literature references

García-Mata, R., Bebök, Z., Sorscher, EJ., Sztul, ES. (1999). Characterization and dynamics of aggresome formation by a cytosolic GFP-chimera. *J. Cell Biol., 146*, 1239-54. ↗

Editions

2019-05-23	Authored	Varusai, TM.
2019-05-24	Reviewed	Metzakopian, E.
2019-11-08	Edited	Varusai, TM.

Table of Contents