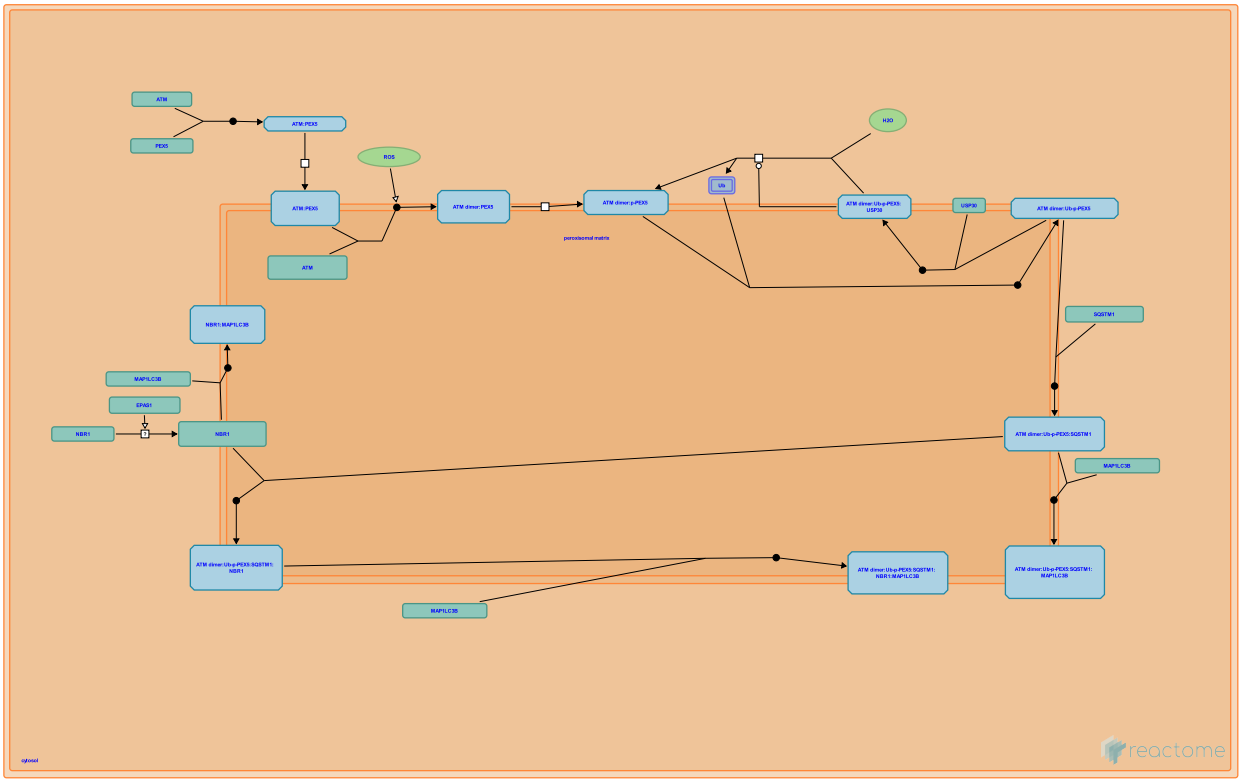
Pexophagy



Metzakopian, E., Varusai, TM.

European Bioinformatics Institute, New York University Langone Medical Center, Ontario Institute for Cancer Research, Oregon Health and Science University.

26/04/2024

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. ↗

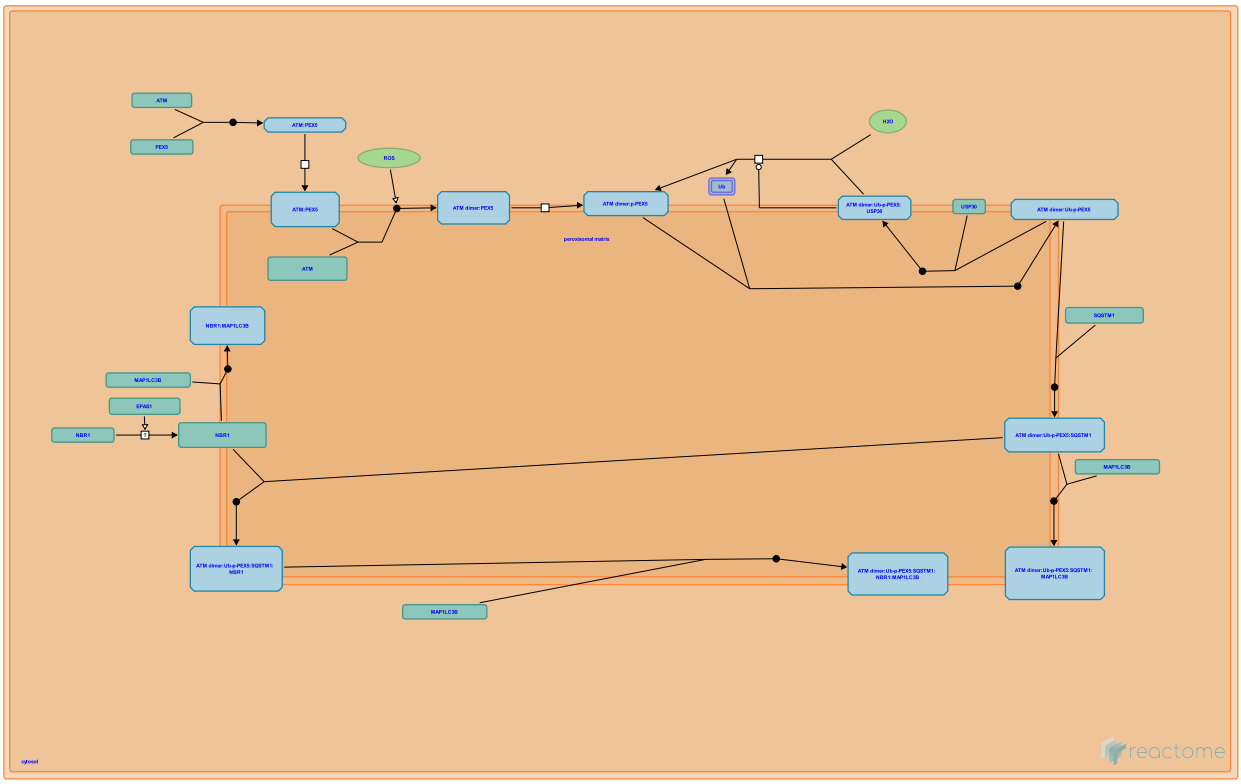
Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655. ↗

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. ↗

Pexophagy ↗

Stable identifier: R-HSA-9664873

Compartments: peroxisomal membrane, cytosol



Peroxisomes are cytosolic organelles involved in the catabolism of branched and long-chain fatty acids and in the reduction of reactive oxygen species (ROS). Peroxisomes homeostasis is critical to maintain ROS levels. Consequently, it is important to eliminate dysfunctional peroxisomes. The degradation of peroxisomes by autophagy is known as pexophagy (Katarzyna ZR et al. 2016). Pexophagy can be triggered by a shift in nutrient conditions.

Literature references

Subramani, S., Zientara-Rytter, K. (2016). Autophagic degradation of peroxisomes in mammals. *Biochem. Soc. Trans., 44*, 431-40. ↗

Editions

2019-10-29	Authored, Edited	Varusai, TM.
2019-10-30	Reviewed	Metzakopian, E.

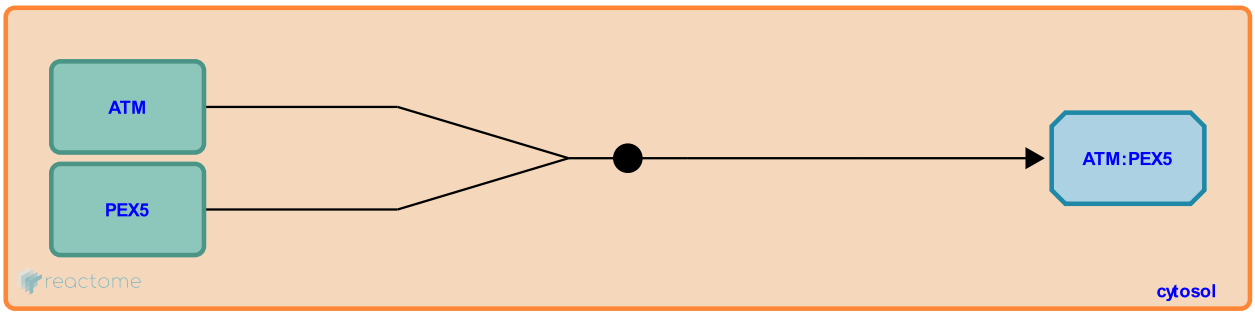
ATM binds PEX5 ↗

Location: Pexophagy

Stable identifier: R-HSA-9664850

Type: binding

Compartments: cytosol



The first step in pexophagy is the initiation by a signal that triggers downstream events to eventually degrade the peroxisome. Ataxia-telangiectasia mutated protein (ATM) is a serine/threonine protein kinase that is involve in DNA damage response. ATM is known to be involved in pexophagy (Katarzyna ZR et al. 2016). ATM binds with Peroxisomal targeting signal 1 receptor (PEX5) with the help of a SRL binding sequence in ATM (Zhang J et al. 2015).

Followed by: ATM:PEX5 translocates from cytosol to peroxisomal membrane

Literature references

Subramani, S., Zientara-Rytter, K. (2016). Autophagic degradation of peroxisomes in mammals. *Biochem. Soc. Trans., 44*, 431-40. ↗

Kim, J., Walker, CL., Pandita, TK., Charaka, VK., Jing, J., Dere, R. et al. (2015). ATM functions at the peroxisome to induce pexophagy in response to ROS. *Nat. Cell Biol., 17*, 1259-69. ↗

Editions

2019-10-29	Authored	Varusai, TM.
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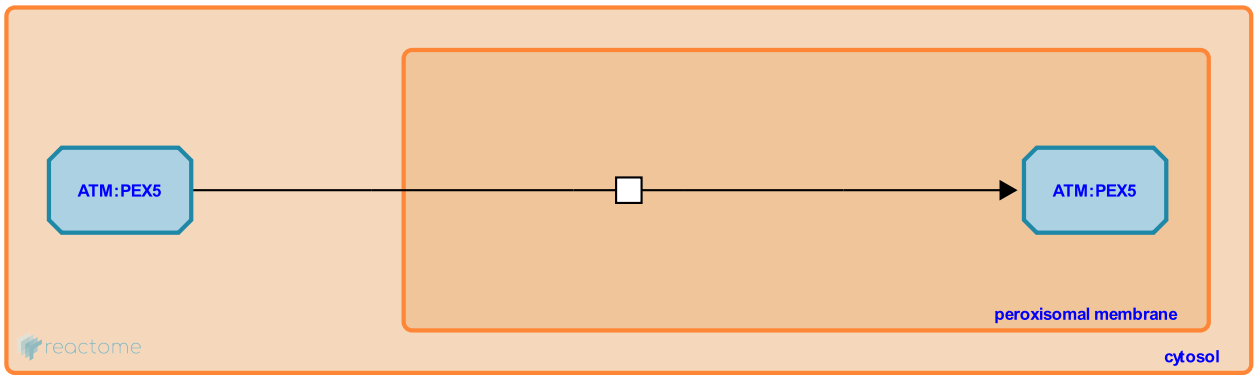
ATM:PEX5 translocates from cytosol to peroxisomal membrane ↗

Location: Pexophagy

Stable identifier: R-HSA-9664883

Type: transition

Compartments: peroxisomal membrane, cytosol



After the binding of Peroxisomal targeting signal 1 receptor (PEX5) and Ataxia telangiectasia mutated protein (ATM), PEX5 recruits the complex to the peroxisomal membrane for the next steps of the degradation process (Zhang J et al. 2015).

Preceded by: ATM binds PEX5

Followed by: ATM:PEX5 binds ATM

Literature references

Kim, J., Walker, CL., Pandita, TK., Charaka, VK., Jing, J., Dere, R. et al. (2015). ATM functions at the peroxisome to induce pexophagy in response to ROS. *Nat. Cell Biol., 17*, 1259-69. ↗

Editions

2019-10-29	Authored	Varusai, TM.
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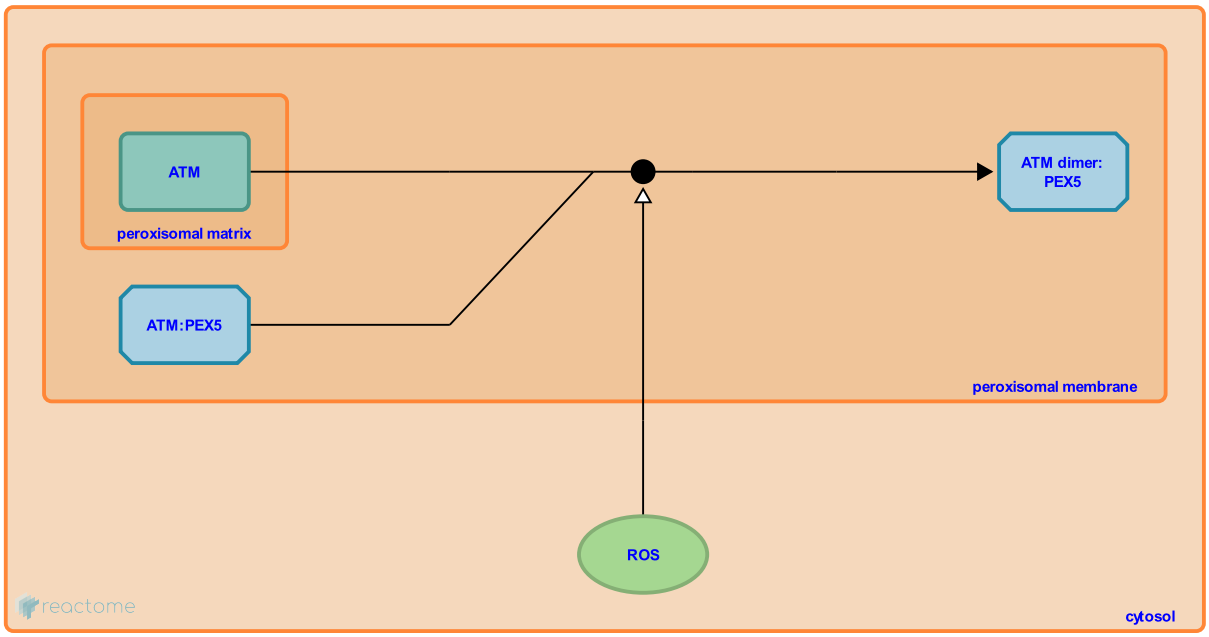
ATM:PEX5 binds ATM ↗

Location: Pexophagy

Stable identifier: R-HSA-9664879

Type: binding

Compartments: peroxisomal membrane



After Peroxisomal targeting signal 1 receptor (PEX5) recruits Ataxia telangiectasia mutated protein (ATM) to the peroxisomal membrane, ATM is activated by the reactive oxygen species (ROS). ROS can oxidize and activate ATM by forming a disulphide cross-linked dimer at the Csy2991 residue (Guo Z et al. 2010).

Preceded by: ATM:PEX5 translocates from cytosol to peroxisomal membrane

Followed by: ATM dimer:PEX5 phosphorylates PEX5

Literature references

Kozlov, S., Person, MD., Lavin, MF., Guo, Z., Paull, TT. (2010). ATM activation by oxidative stress. *Science, 330*, 517-21 . ↗

Editions

2019-10-29	Authored	Varusai, TM.
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2020-01-13	Edited	Varusai, TM.

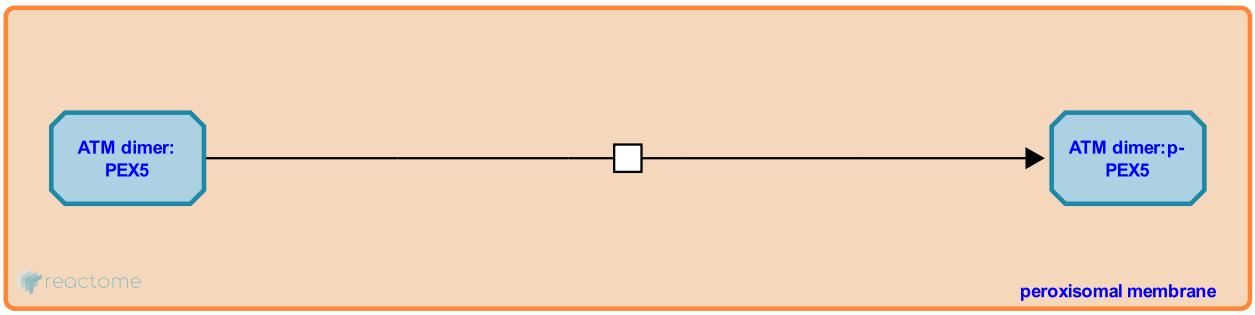
ATM dimer:PEX5 phosphorylates PEX5

Location: Pexophagy

Stable identifier: R-HSA-9664862

Type: transition

Compartments: peroxisomal membrane



When serine/threonine kinase Ataxia telangiectasia mutated protein (ATM) is activated it can phosphorylate Peroxisomal targeting signal 1 receptor protein (PEX5) at Ser141 (Zhang J et al. 2015).

Preceded by: ATM:PEX5 binds ATM

Followed by: ATM dimer:p-PEX5 ubiquitinates to form ATM dimer:Ub-p-PEX5

Literature references

Kim, J., Walker, CL., Pandita, TK., Charaka, VK., Jing, J., Dere, R. et al. (2015). ATM functions at the peroxisome to induce pexophagy in response to ROS. *Nat. Cell Biol., 17*, 1259-69.

Editions

2019-10-29	Authored	Varusai, TM.
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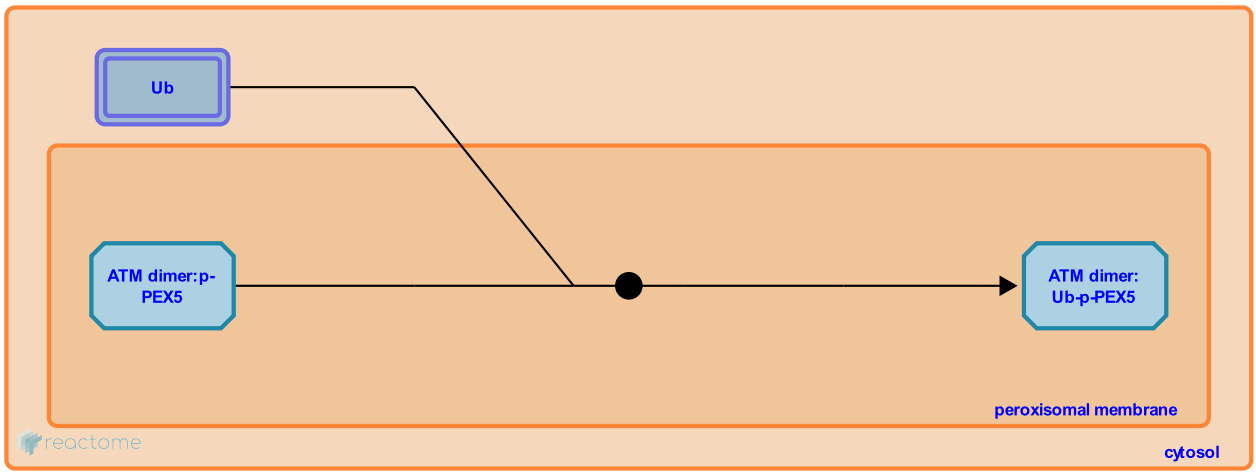
ATM dimer:p-PEX5 ubiquitinates to form ATM dimer:Ub-p-PEX5 ↗

Location: Pexophagy

Stable identifier: R-HSA-9664888

Type: binding

Compartments: peroxisomal membrane



Phosphorylation of Peroxisomal targeting signal 1 receptor protein (PEX5) at Ser141 promotes the ubiquitination of PEX5. The RING peroxins complex composed of: Peroxisome biogenesis factor 2 (PEX2), Peroxisome biogenesis factor 10 (PEX10), and Peroxisome assembly protein 12 (PEX12) form part of a peroxisome localized E3 ligase that ubiquitinates PEX5 at Lys209 (Zhang J et al. 2015). This mono ubiquitination of PEX5 helps to recruit the autophagy machinery to the peroxisome.

Preceded by: ATM dimer:PEX5 phosphorylates PEX5, USP30 deubiquitinates ATM dimer:Ub-p-PEX5

Followed by: SQSTM1 binds ATM dimer:Ub-p-PEX5, USP30 binds ATM dimer:Ub-p-PEX5

Literature references

Kim, J., Walker, CL., Pandita, TK., Charaka, VK., Jing, J., Dere, R. et al. (2015). ATM functions at the peroxisome to induce pexophagy in response to ROS. *Nat. Cell Biol., 17,* 1259-69. ↗

Editions

2019-10-29	Authored	Varusai, TM.
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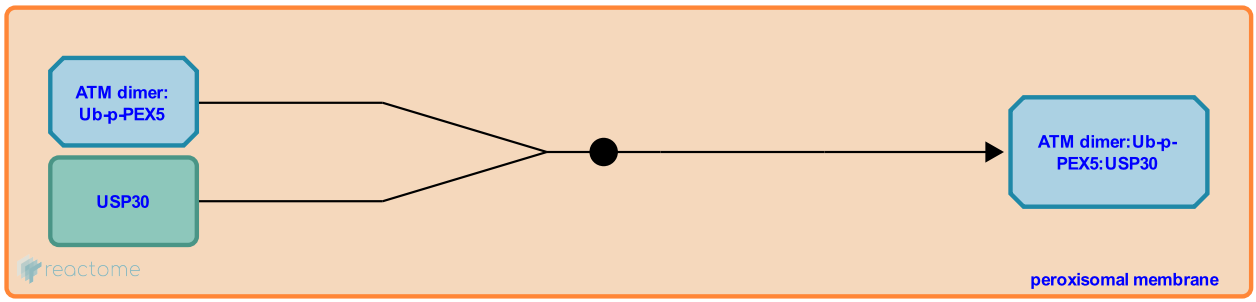
USP30 binds ATM dimer:Ub-p-PEX5 ↗

Location: Pexophagy

Stable identifier: R-HSA-9674131

Type: binding

Compartments: peroxisomal membrane



As a deubiquitinase, Ubiquitin carboxyl-terminal hydrolase 30 (USP30) can reverse the action of E3 ligase on peroxisomal membrane proteins. Studies show that USP30 can localise in the peroxisomal membrane and interact with ubiquitinated PEX5 (Riccio V et al. 2019, Marcassa E et al. 2019).

Preceded by: ATM dimer:p-PEX5 ubiquitinates to form ATM dimer:Ub-p-PEX5

Followed by: USP30 deubiquitinates ATM dimer:Ub-p-PEX5

Literature references

Rusilowicz-Jones, EV., Clague, MJ., Jardine, J., Marcassa, E., Urbé, S., Kallinos, A. (2019). New aspects of USP30 biology in the regulation of pexophagy. *Autophagy, 15*, 1634-1637. ↗

Riccio, V., McQuibban, GA., Kim, PK. (2019). USP30: protector of peroxisomes and mitochondria. *Mol Cell Oncol, 6*, 1600350. ↗

Vissa, M., Strilchuk, AW., Demers, N., Hua, R., Riccio, V., McQuibban, GA. et al. (2019). Deubiquitinating enzyme USP30 maintains basal peroxisome abundance by regulating pexophagy. *J. Cell Biol., 218*, 798-807. ↗

Editions

2019-10-30	Reviewed	Metzakopian, E.
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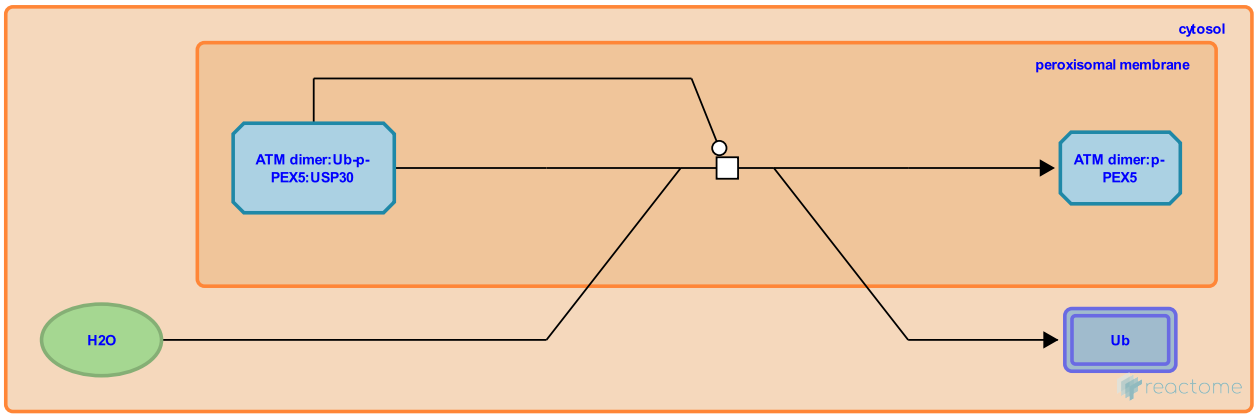
USP30 deubiquitinates ATM dimer:Ub-p-PEX5 ↗

Location: Pexophagy

Stable identifier: R-HSA-9674127

Type: transition

Compartments: peroxisomal membrane



The deubiquitinase, Ubiquitin carboxyl-terminal hydrolase 30 (USP30) counters the action of E3 ligase on peroxisomal membrane proteins. USP30 can remove ubiquitin moieties from PEX5 thereby preventing pexophagy (Riccio V et al. 2019, Marcassa E et al. 2019)

Preceded by: USP30 binds ATM dimer:Ub-p-PEX5

Followed by: ATM dimer:p-PEX5 ubiquitinates to form ATM dimer:Ub-p-PEX5

Literature references

Rusilowicz-Jones, EV., Clague, MJ., Jardine, J., Marcassa, E., Urbé, S., Kallinos, A. (2019). New aspects of USP30 biology in the regulation of pexophagy. *Autophagy, 15*, 1634-1637. ↗

Riccio, V., McQuibban, GA., Kim, PK. (2019). USP30: protector of peroxisomes and mitochondria. *Mol Cell Oncol, 6*, 1600350. ↗

Vissa, M., Strilchuk, AW., Demers, N., Hua, R., Riccio, V., McQuibban, GA. et al. (2019). Deubiquitinating enzyme USP30 maintains basal peroxisome abundance by regulating pexophagy. *J. Cell Biol., 218*, 798-807. ↗

Editions

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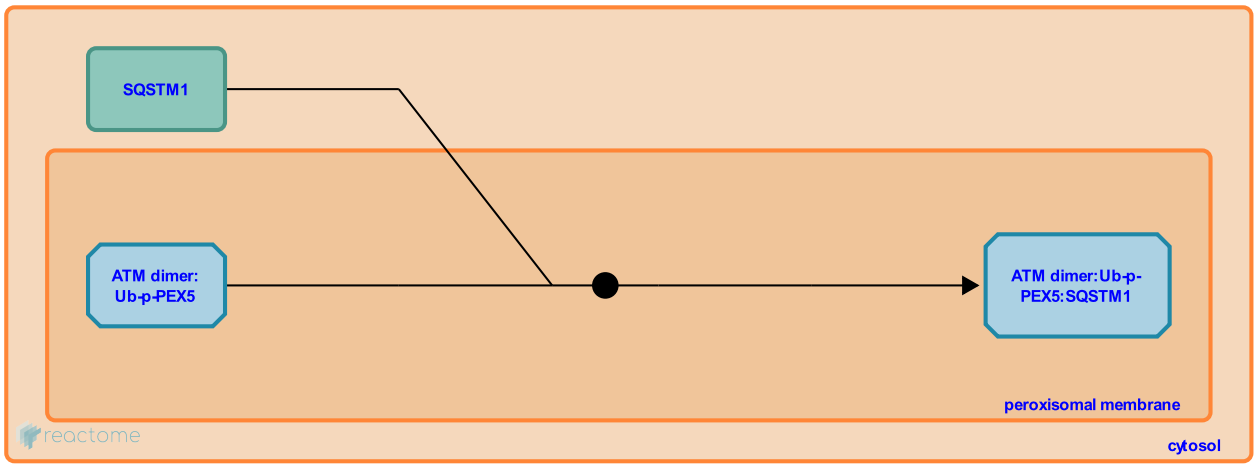
SQSTM1 binds ATM dimer:Ub-p-PEX5 ↗

Location: Pexophagy

Stable identifier: R-HSA-9664892

Type: binding

Compartments: peroxisomal membrane, cytosol



Sequestosome 1 (SQSTM1) is an autophagy adaptor that serves to bridge ubiquitinated cargo and the autophagosome. It binds ubiquitinated cargo via its UBA domain. SQSTM1 in the cytosol recognizes and binds with ubiquitinated Peroxisomal targeting signal 1 receptor (PEX5) in the peroxisomal membrane (Zhang et al. 2015).

Preceded by: ATM dimer:p-PEX5 ubiquitinates to form ATM dimer:Ub-p-PEX5

Followed by: MAP1LC3B binds ATM dimer:Ub-p-PEX5:SQSTM1, NBR1 binds ATM:Ub-p-PEX5:SQSTM1

Literature references

Kim, J., Walker, CL., Pandita, TK., Charaka, VK., Jing, J., Dere, R. et al. (2015). ATM functions at the peroxisome to induce pexophagy in response to ROS. *Nat. Cell Biol., 17*, 1259-69. ↗

Editions

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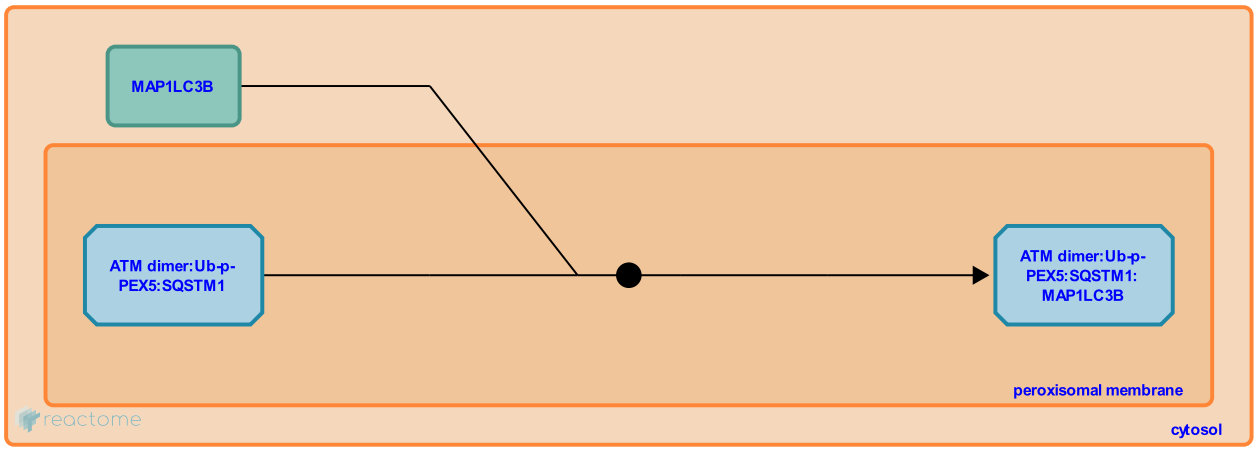
MAP1LC3B binds ATM dimer:Ub-p-PEX5:SQSTM1 ↗

Location: Pexophagy

Stable identifier: R-HSA-9664855

Type: binding

Compartments: peroxisomal membrane



Sequestosome 1 (SQSTM1) is an autophagic receptor that recruits ubiquitinated cargo to the autophagosome. SQSTM1 contains a ubiquitin associated (UBA) domain that binds to monoubiquitinated Peroxisomal targeting signal 1 receptor (PEX5) in the peroxisome and an LC3 interacting region (LIR) that binds to Microtubule associated proteins 1A/1B light chain 3B (MAP1LC3B)/LC3 associated with the nascent autophagosome (Pankiv S et al. 2007). Subsequently, the peroxisome is degraded by the autophagy machinery.

Preceded by: SQSTM1 binds ATM dimer:Ub-p-PEX5

Literature references

Bruun, JA., Clausen, TH., Pankiv, S., Lamark, T., Brech, A., Johansen, T. et al. (2007). p62/SQSTM1 binds directly to Atg8/LC3 to facilitate degradation of ubiquitinated protein aggregates by autophagy. *J. Biol. Chem., 282*, 24131-45. ↗

Editions

2019-10-29	Authored	Varusai, TM.
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NBR1 translocates from cytosol to perixosomal membrane ↗

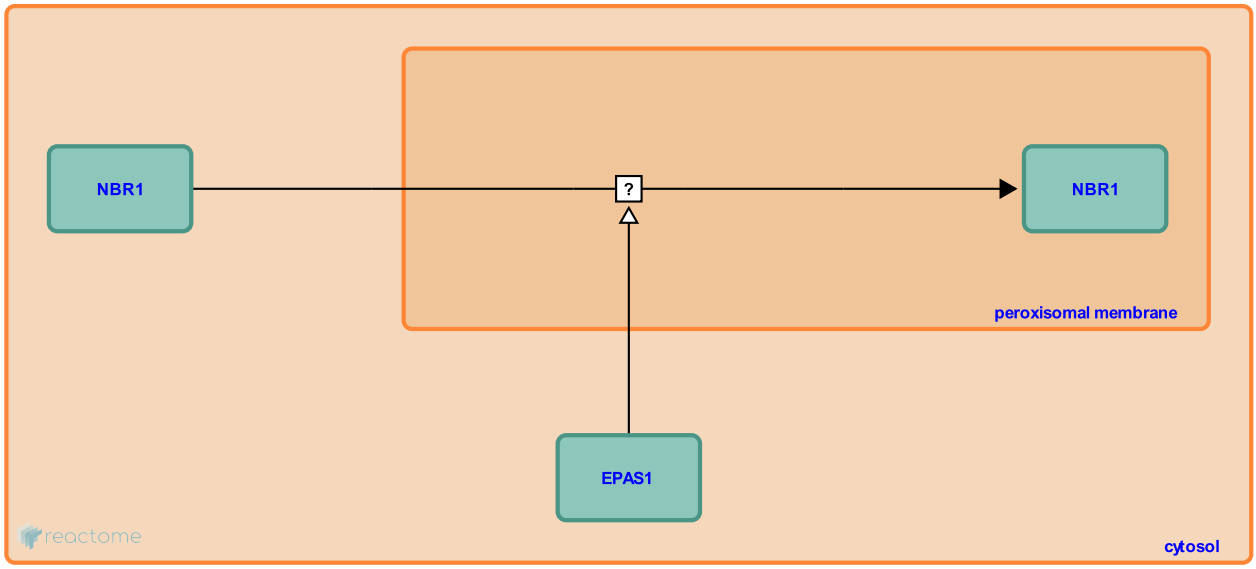
Location: Pexophagy

Stable identifier: R-HSA-9664871

Type: uncertain

Compartments: peroxisomal membrane, cytosol

Inferred from: Nbr1 translocates from cytosol to perixosomal membrane (Mus musculus)



Pexophagy is known to be regulated by molecular oxygen stress as a means of adaptive response. Low oxygen tension stabilizes Endothelial PAS domain containing protein 1 (EPAS1), which positively regulates the translocation of Next to BRCA1 gene 1 protein (NBR1) from the cytosol to the peroxisomal membrane. NBR1 binds peroxisomes through its JUBA domain (Walter KM et al. 2014).

Followed by: NBR1 binds MAP1LC3B, NBR1 binds ATM:Ub-p-PEX5:SQSTM1

Literature references

Kovacs, WJ., Walter, KM., Trötzmüller, M., Krek, W., Moser, AB., Lucas, MS. et al. (2014). Hif-2α promotes degradation of mammalian peroxisomes by selective autophagy. *Cell Metab., 20*, 882-897. ↗

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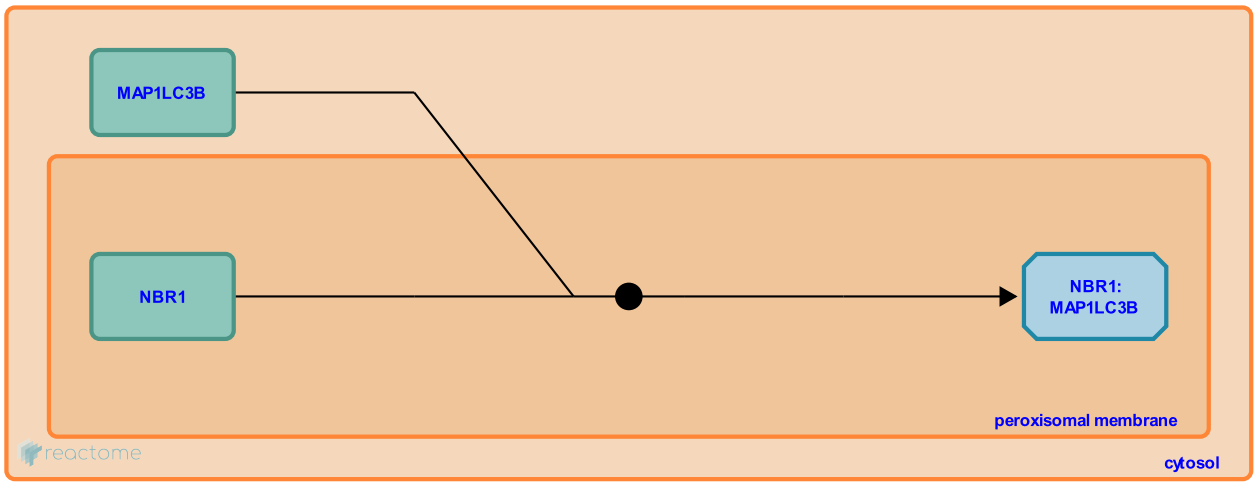
NBR1 binds MAP1LC3B ↗

Location: Pexophagy

Stable identifier: R-HSA-9664867

Type: binding

Compartments: peroxisomal membrane



Once recruited to the peroxisomal membrane, Next to BRCA1 gene 1 protein (NBR1) can bind with Microtubule associated proteins 1A/1B light chain 3B (MAP1LC3B)/LC3 with the help of its LC3 interacting region (LIR) domain (Kirkin V et al. 2009). This targets the peroxisomes to the autophagosomes and the degradation process starts.

Preceded by: NBR1 translocates from cytosol to perixosomal membrane

Literature references

Komatsu, M., Sou, YS., Bilusic, I., Ishii, T., Wild, P., McEwan, DG. et al. (2009). A role for NBR1 in autophagosomal degradation of ubiquitinated substrates. *Mol. Cell, 33*, 505-16. ↗

Editions

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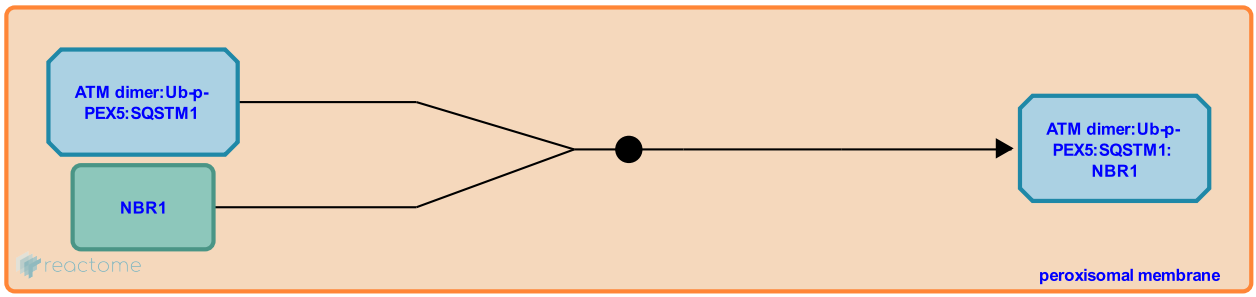
NBR1 binds ATM:Ub-p-PEX5:SQSTM1 ↗

Location: Pexophagy

Stable identifier: R-HSA-9664881

Type: binding

Compartments: peroxisomal membrane



As autophagy receptors, Next to BRCA1 gene 1 protein (NBR1) and Sequestosome 1 (SQSTM1) can cooperate to achieve pexophagy. SQSTM1 supports NBR1 to bind ubiquitinated peroxisomes through its UBA domain and enhances the efficiency of the degradation process (Kirkin V et al. 2009).

Preceded by: SQSTM1 binds ATM dimer:Ub-p-PEX5, NBR1 translocates from cytosol to perixosomal membrane

Followed by: MAP1LC3B binds ATM dimer:Ub-p-PEX5:SQSTM1:NBR1

Literature references

Lamark, T., Johansen, T., Kirkin, V., Dikic, I. (2009). NBR1 cooperates with p62 in selective autophagy of ubiquitinated targets. *Autophagy, 5*, 732-3. ↗

Editions

2019-10-29	Authored	Varusai, TM.
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2020-01-13	Edited	Varusai, TM.

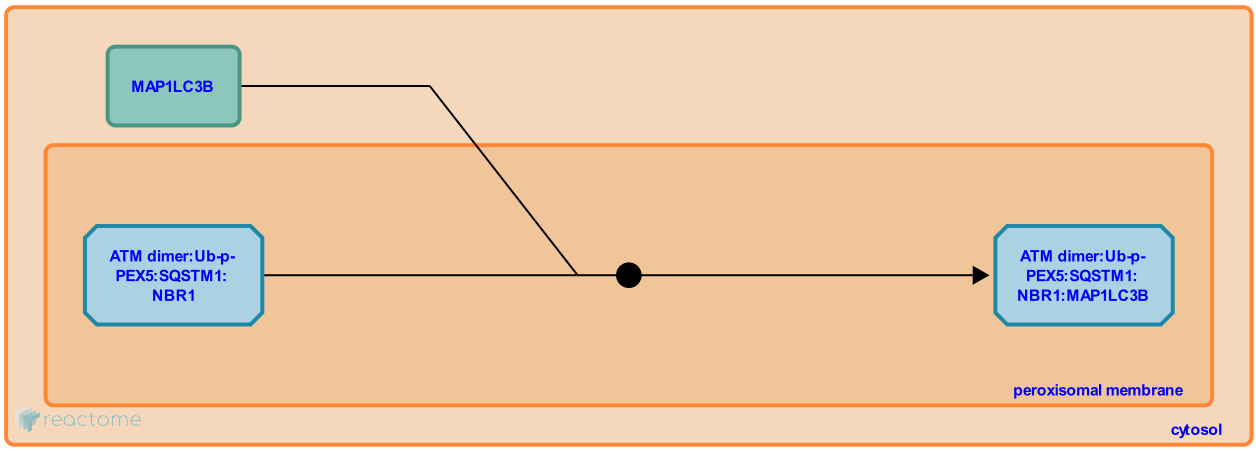
MAP1LC3B binds ATM dimer:Ub-p-PEX5:SQSTM1:NBR1 ↗

Location: Pexophagy

Stable identifier: R-HSA-9664880

Type: binding

Compartments: peroxisomal membrane



Autophagic receptors, Next to BRCA1 gene 1 protein (NBR1) and Sequestosome 1 (SQSTM1) cooperate to bind and recruit ubiquitinated peroxisomes to the autophagy machinery. NBR1 and SQSTM1 have similar protein domain architecture and bind to Microtubule associated proteins 1A/1B light chain 3B (MAP1LC3B)/LC3 via an LC3 interacting region (LIR) (Kirkin V et al. 2009). Subsequently, peroxisomes are engulfed within the autophagosome and degraded.

Preceded by: NBR1 binds ATM:Ub-p-PEX5:SQSTM1

Literature references

Lamark, T., Johansen, T., Kirkin, V., Dikic, I. (2009). NBR1 cooperates with p62 in selective autophagy of ubiquitinated targets. *Autophagy, 5*, 732-3. ↗

Editions

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