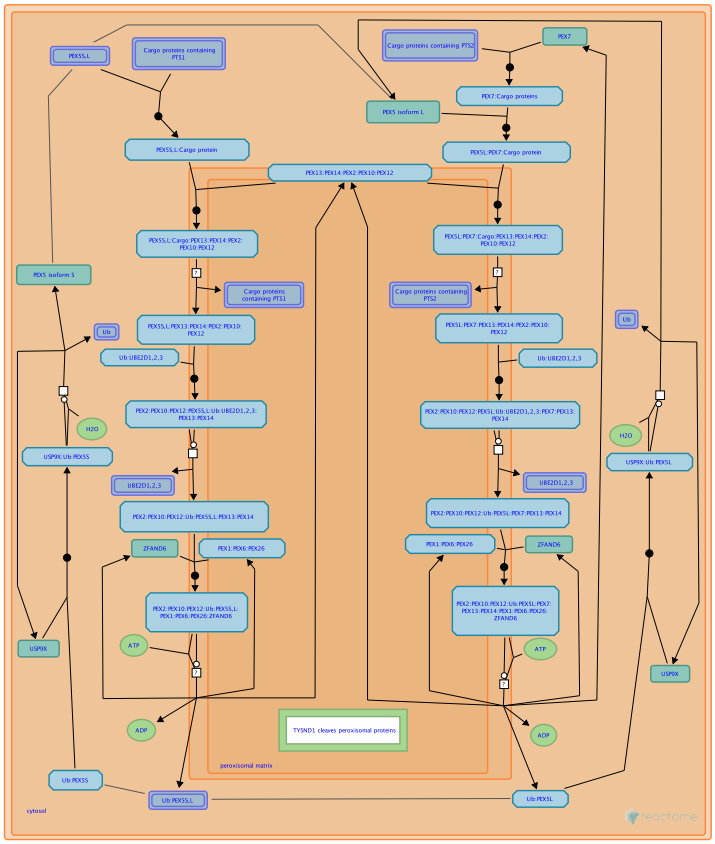
Peroxisomal protein import



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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.

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Literature references

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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. ↗

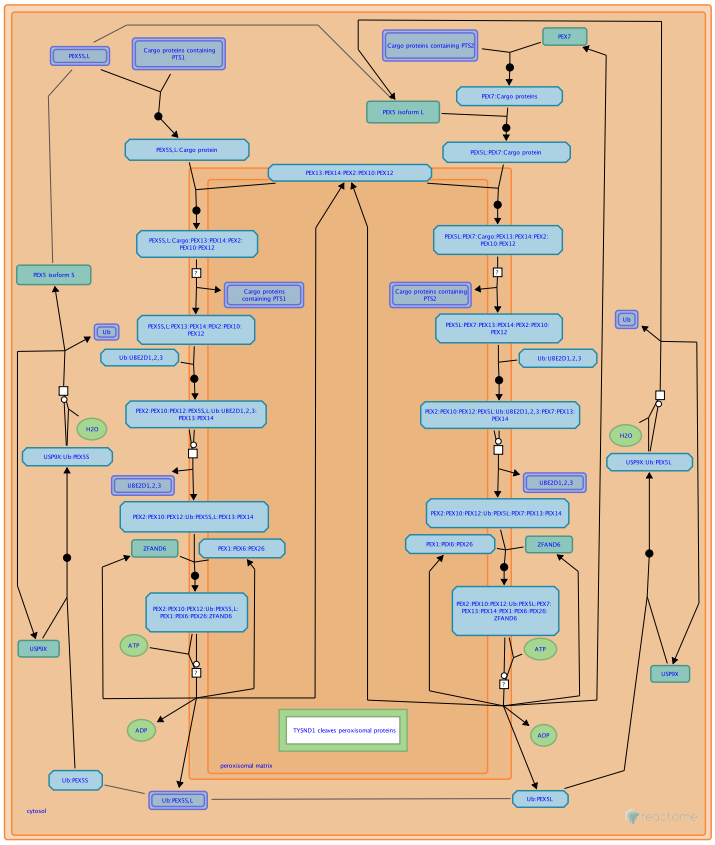
Reactome database release: 77

This document contains 2 pathways and 19 reactions (see Table of Contents)

Peroxisomal protein import ↗

Stable identifier: R-HSA-9033241

Compartments: cytosol, peroxisomal matrix, peroxisomal membrane



Peroxisomes are small cellular organelles that are bounded by a single membrane and contain variable compositions of proteins depending on cell type. Peroxisomes function in oxidation of fatty acids, detoxification of glyoxylate, and synthesis of plasmalogens, glycerophospholipids containing an alcohol with a vinyl-ether bond (reviewed in Lohdi and Semenkovich 2014). All of the approximately 46 proteins contained in peroxisomal matrix are imported from the cytosol by a unique mechanism that does not require the imported proteins to be unfolded as they cross the membrane (Walton et al. 1995, reviewed in Ma et al. 2011, Fujiki et al. 2014, Baker et al. 2016, Dias et al 2016, Emmanoulidis et al. 2016, Erdmann 2016, Francisco et al. 2017). The incompletely characterized process appears to involve the transport of the proteins through a variably sized pore in the membrane comprising at least PEX5 and PEX14 (inferred from the yeast homologs in Meinecke et al. 2010, the yeast pore is reviewed in Meinecke et al. 2016). Oligomeric proteins are also observed to cross the peroxisomal membrane (Otera and Fujiki 2012) but their transport appears to be less efficient than monomeric proteins (Freitas et al. 2011, inferred from mouse homologs in Freitas et al. 2015, reviewed in Dias et al. 2016).

In the cytosol, receptor proteins, PEX5 and PEX7, bind to specific sequence motifs in cargo proteins (Dodt et al. 1995, Wiemer et al. 1995, Braverman et al. 1997). The long and short isoforms of PEX5 (PEX5L and PEX5S) bind peroxisome targeting sequence 1 (PTS1, originally identified in firefly luciferase by Gould et al. 1989) found on most peroxisomal matrix proteins; PEX7 binds PTS2 (originally identified in rat 3-ketoacyl-CoA thiolase by Swinkels et al. 1991) found on 3 imported proteins thus far in humans. The long isoform of PEX5, PEX5L, then binds the PEX7:cargo protein complex (Braverman et al. 1998, Otera et al. 2000). PEX5S,L bound to a cargo protein or PEX5L bound to PEX7:cargo protein then interacts with a complex comprising PEX13, PEX14, PEX2, PEX10, and PEX12 at the peroxisomal membrane (Gould et al. 1996, Fransen et al. 1998, inferred from rat homologs in Reguenga et al. 2001).

The ensuing step in which the cargo protein is translocated across the membrane is not completely understood. During translocation, PEX5 and PEX7 become inserted into the membrane (Wiemer et al. 1995, Dodt et al. 1995, Oliveira et al. 2003) and expose a portion of their polypeptide chains to the organellar matrix (Rodrigues et al. 2015). One current model envisages PEX5 as a plunger that inserts into a transmembrane barrel formed by PEX14, PEX13, PEX2, PEX10, and PEX12 (the Docking-Translocation Module) (Francisco et al. 2017).

After delivering cargo to the matrix, PEX5 and PEX7 are recycled back to the cytosol by a process requiring mono-ubiquitination of PEX5 and ATP hydrolysis (Imanaka et al. 1987, Thoms and Erdmann 2006, Carvalho et al. 2007). PEX7 is not ubiquitinated but its recycling requires PEX5 mono-ubiquitination. A subcomplex of the Docking-Translocation Module comprising the RING-finger proteins PEX2, PEX10, and PEX12 conjugates a single ubiquitin to a cysteine residue of PEX5 (Carvalho et al. 2007, reviewed in Platta et al. 2016). The mono-ubiquitinated PEX5 and associated PEX7 are then extracted by the exportomer complex consisting of PEX1, PEX6, PEX26, and ZFAND6 (inferred from rat homologs in Miyata et al. 2012). PEX1 and PEX6 are members of the ATPases Associated with diverse cellular Activities (AAA) family, a group of proteins that use the energy of ATP hydrolysis to remodel molecular complexes. PEX1 and PEX6 form a hetero-hexameric ring, best described as a trimer of PEX1/PEX6 dimers (inferred from yeast in Platta et al. 2005, yeast homologs reviewed in Schwerter et al. 2017). Data on the yeast PEX1:PEX6 complex suggest that these ATPases use a substrate-threading mechanism to disrupt protein-protein interactions (Gardner et al. 2018). PEX7 is also then returned to the cytosol (Rodrigues et al. 2014). Once in the cytosol, ubiquitinated PEX5 is enzymatically deubiquitinated by USP9X and may also be non-enzymatically deubiquitinated by nucleophilic attack of the thioester bond between ubiquitin and the cysteine residue of PEX5 by small metabolites such as glutathione (Grou et al. 2012).

Defects in peroxisomal import cause human diseases: Zellweger syndrome, neonatal adrenoleukodystrophy, infantile Refsum disease and rhizomelic chondrodysplasia punctata types 1 and 5 (Barøy et al. 2015, reviewed in Nagotu et al. 2012, Braverman et al. 2013, Wanders 2014, Fujiki 2016, Waterham et al. 2016).

Literature references

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Baker, A., Lanyon-Hogg, T., Warriner, SL. (2016). Peroxisome protein import: a complex journey. *Biochem. Soc. Trans., 44*, 783-9. ↗

Rodrigues, TA., Alencastre, IS., Francisco, T., Brites, P., Fransen, M., Grou, CP. et al. (2014). A PEX7-centered perspective on the peroxisomal targeting signal type 2-mediated protein import pathway. *Mol. Cell. Biol., 34*, 2917-28. ↗

Walton, PA., Hill, PE., Subramani, S. (1995). Import of stably folded proteins into peroxisomes. *Mol. Biol. Cell, 6*, 675-83. ↗

Imanaka, T., Small, GM., Lazarow, PB. (1987). Translocation of acyl-CoA oxidase into peroxisomes requires ATP hydrolysis but not a membrane potential. *J. Cell Biol., 105*, 2915-22. ↗

Editions

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2018-03-12	Reviewed	Azevedo, JE.

PEX5S,L binds cargo proteins containing PTS1 ↗

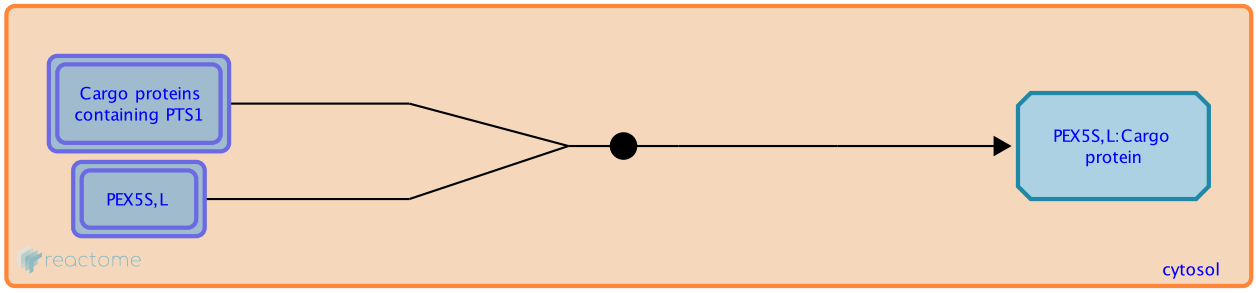
Location: Peroxisomal protein import

Stable identifier: R-HSA-9033233

Type: binding

Compartments: cytosol

Inferred from: Pex5l binds Acox1 or Uox (Mus musculus)



It is unclear how the long isoform of PEX5 (PEX5L) and the short isoform of PEX5 (PEX5S) are generated. A current hypothesis suggests alternative mRNA splicing. Both isoforms can bind the peroxisome targeting signal 1 (PTS1) located at the C-terminus of most of the proteins that are targeted to the peroxisomal matrix (Dodt et al. 1995, Fransen et al. 1995, Wiemer et al. 1995, Gatto et al. 2000, Brocard et al. 2003, Gatto et al. 2003, Harper et al. 2003, Ghosh and Berg 2010, Freitas et al. 2011, Okumoto et al. 2011). PTS1 typically contains Ser-Lys-Leu (SKL) at the C-terminus but substantial variation in sequences and affinities for PEX5 are observed and upstream residues can modulate binding to PEX5 (Lametschwandtner et al. 1998, Ghosh and Berg 2010, reviewed in Brocard and Hartig 2006).

A minority of peroxisomal matrix proteins contain PTS2. While the PEX5S isoform binds proteins containing PTS1, the PEX5L isoform binds either proteins containing PTS1 or PEX7 bound to proteins containing PTS2 (Braverman et al. 1998). Some proteins appear to be imported as oligomers, however this is rather inefficient as PEX5 appears to have a preference for monomeric substrates (Otera and Fujiki 2012, Freitas et al. 2011, Freitas et al. 2015, also inferred from mouse homologs). Mutations in PEX5 cause defects in peroxisomal import and comprise complementation group 2 of peroxisomal biogenesis disorders (also called Zellweger spectrum disorders) (Dodt et al. 1995, Wiemer et al. 1995). A specific mutation affecting only the PEX5L isoform is the cause of rhizomelic chondrodysplasia punctate type 5 (Barøy et al. 2015).

Followed by: PEX5S,L:Cargo binds PEX13:PEX14:PEX2:PEX10:PEX12 (Docking and Translocation Module)

Literature references

Gatto, GJ., Maynard, EL., Guerrerio, AL., Geisbrecht, BV., Gould, SJ., Berg, JM. (2003). Correlating structure and affinity for PEX5:PTS1 complexes. *Biochemistry, 42*, 1660-6. ↗

Harper, CC., Berg, JM., Gould, SJ. (2003). PEX5 binds the PTS1 independently of Hsp70 and the peroxin PEX12. *J. Biol. Chem., 278*, 7897-901. ↗

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Dodt, G., Braverman, N., Wong, C., Moser, A., Moser, HW., Watkins, P. et al. (1995). Mutations in the PTS1 receptor gene, PXR1, define complementation group 2 of the peroxisome biogenesis disorders. *Nat. Genet., 9*, 115-25. ↗

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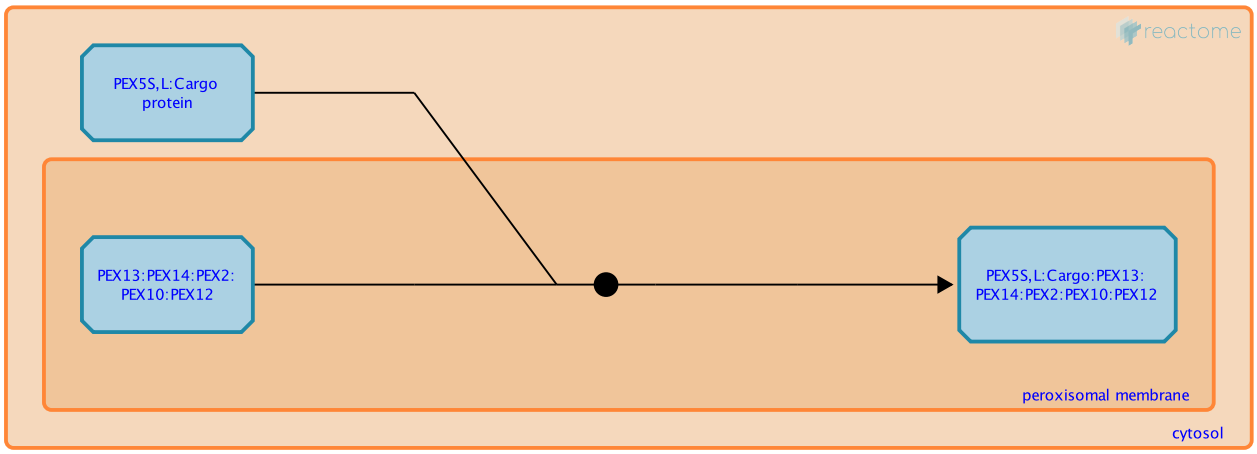
PEX5S,L:Cargo binds PEX13:PEX14:PEX2:PEX10:PEX12 (Docking and Translocation Module) ↗

Location: Peroxisomal protein import

Stable identifier: R-HSA-9033236

Type: binding

Compartments: peroxisomal membrane



PEX5S or PEX5L bound to cargo proteins containing PTS1 interacts with the Docking and Translocation Module (PEX13:PEX14:PEX2:PEX10:PEX12) (Gould et al. 1996, Fransen et al. 1998, Will et al. 1999, Neufeld et al. 2009, Shiozawa et al. 2009, Freitas et al. 2011, Francisco et al. 2013, Neufeld et al. 2014, Dias et al. 2017).

Preceded by: PEX5S,L binds cargo proteins containing PTS1

Followed by: Cargo of PEX5S,L translocates from the cytosol to the peroxisomal matrix

Literature references

Fransen, M., Terlecky, SR., Subramani, S. (1998). Identification of a human PTS1 receptor docking protein directly required for peroxisomal protein import. *Proc. Natl. Acad. Sci. U.S.A., 95*, 8087-92. ↗

Dias, AF., Rodrigues, TA., Pedrosa, AG., Barros-Barbosa, A., Francisco, T., Azevedo, JE. (2017). The peroxisomal matrix protein translocon is a large cavity-forming protein assembly into which PEX5 protein enters to release its cargo. *J. Biol. Chem., 292*, 15287-15300. ↗

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Freitas, MO., Francisco, T., Rodrigues, TA., Alencastre, IS., Pinto, MP., Grou, CP. et al. (2011). PEX5 protein binds monomeric catalase blocking its tetramerization and releases it upon binding the N-terminal domain of PEX14. *J. Biol. Chem., 286*, 40509-19. ↗

Shiozawa, K., Konarev, PV., Neufeld, C., Wilmanns, M., Svergun, DI. (2009). Solution structure of human Pex5.Pex14.PTS1 protein complexes obtained by small angle X-ray scattering. *J. Biol. Chem., 284*, 25334-42. ↗

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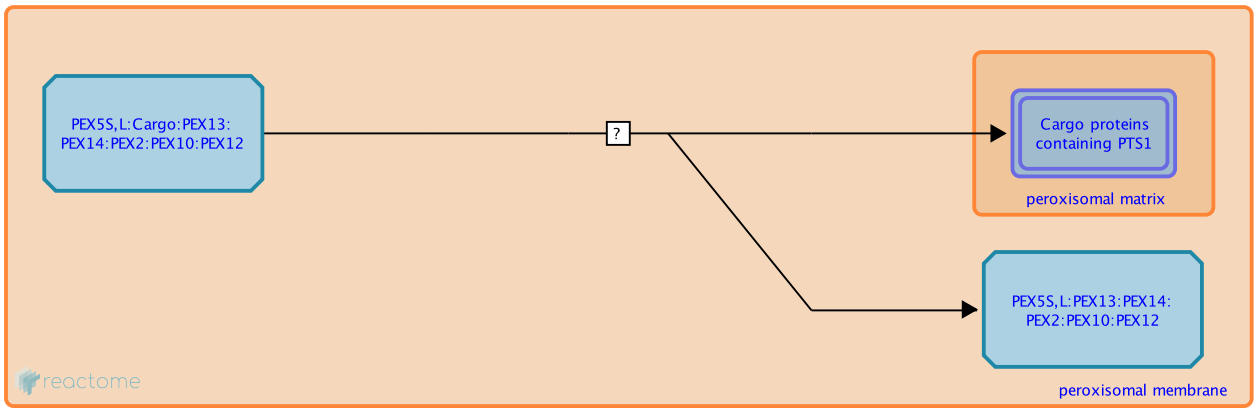
Cargo of PEX5S,L translocates from the cytosol to the peroxisomal matrix ↗

Location: Peroxisomal protein import

Stable identifier: R-HSA-9033235

Type: uncertain

Compartments: peroxisomal membrane



After binding the Docking and Translocation Module comprising PEX14, PEX13, PEX2, PEX10 and PEX12 , PEX5S or PEX5L bound to a cargo protein becomes localized to the membrane (Dodt et al. 1995, Wiemer et al. 1995, Alencastre et al. 2009, Francisco et al. 2013, Dias et al. 2017). In a reaction that is not yet fully characterized, the cargo protein is released into the peroxisomal matrix while PEX5S or PEX5L remains in the membrane (Dodt et al. 1995, Wiemer et al. 1995, Alencastre et al. 2009, Franscisco et al. 2013). One model for the reaction hypothesizes that PEX13:PEX14 (associated with PEX2:PEX10:PEX12) forms a barrel in the peroxisomal membrane while PEX5S or PEX5L acts as a plunger to guide the cargo through the barrel (Dias et al. 2017, Francisco et al. 2017). Notably, the reaction does not require a source of energy such as ATP (Oliveira et al. 2003). Mutations in PEX5 cause defects in import of PTS1-containing proteins or PTS2-containing proteins or both (Eberrink et al. 2009, Barøy et al. 2015).

Preceded by: PEX5S,L:Cargo binds PEX13:PEX14:PEX2:PEX10:PEX12 (Docking and Translocation Module)

Followed by: PEX2:PEX10:PEX12 binds PEX5S,L (in PEX5S:PEX13:PEX14) and Ub:UBE2D1,2,3

Literature references

Francisco, T., Rodrigues, TA., Freitas, MO., Grou, CP., Carvalho, AF., Sá-Miranda, C. et al. (2013). A cargo-centered perspective on the PEX5 receptor-mediated peroxisomal protein import pathway. *J. Biol. Chem., 288*, 29151-9. ↗

Alencastre, IS., Rodrigues, TA., Grou, CP., Fransen, M., Sá-Miranda, C., Azevedo, JE. (2009). Mapping the cargo protein membrane translocation step into the PEX5 cycling pathway. *J. Biol. Chem., 284*, 27243-51. ↗

Wiemer, EA., Nuttley, WM., Bertolaet, BL., Li, X., Francke, U., Wheelock, MJ. et al. (1995). Human peroxisomal targeting signal-1 receptor restores peroxisomal protein import in cells from patients with fatal peroxisomal disorders. *J. Cell Biol., 130*, 51-65. ↗

Oliveira, ME., Gouveia, AM., Pinto, RA., Sá-Miranda, C., Azevedo, JE. (2003). The energetics of Pex5p-mediated peroxisomal protein import. *J. Biol. Chem., 278*, 39483-8. ↗

Ebberink, MS., Mooyer, PA., Koster, J., Dekker, CJ., Eyskens, FJ., Dionisi-Vici, C. et al. (2009). Genotype-phenotype correlation in PEX5-deficient peroxisome biogenesis defective cell lines. *Hum. Mutat., 30*, 93-8. ↗

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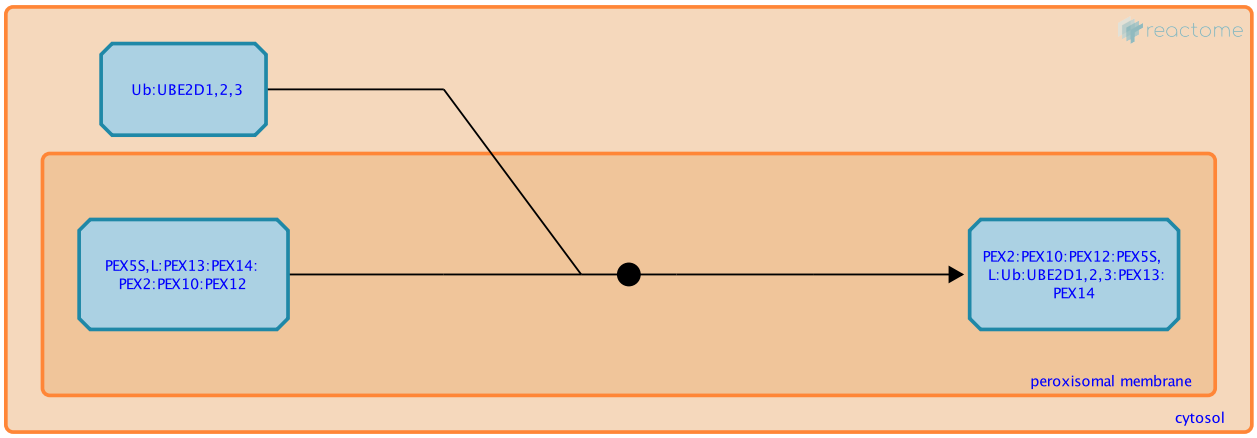
PEX2:PEX10:PEX12 binds PEX5S,L (in PEX5S:PEX13:PEX14) and Ub:UBE2D1,2,3 ↗

Location: Peroxisomal protein import

Stable identifier: R-HSA-8953917

Type: binding

Compartments: peroxisomal membrane



A RING E3 ubiquitin ligase complex containing PEX10, PEX12, and PEX2 ubiquitinates PEX5L. The PEX2:PEX10:PEX12 complex is believed to bind an activated E2-ubiquitin conjugate (one of Ub:UBE2D1, Ub:UBE2D2, Ub:UBE2D3) and PEX5L in a complex that also contains PEX13 and PEX14 (Chang et al. 1999, Carvalho et al. 2007, Grou et al. 2008, Grou et al. 2009, Okumoto et al. 2011). The short isoform of PEX5, PEX5S, is inferred to undergo the same reaction.

Preceded by: Cargo of PEX5S,L translocates from the cytosol to the peroxisomal matrix

Followed by: PEX2:PEX10:PEX12 monoubiquitinates PEX5S,L at cysteine-11

Literature references

Grou, CP., Carvalho, AF., Pinto, MP., Wiese, S., Piechura, H., Meyer, HE. et al. (2008). Members of the E2D (UbcH5) family mediate the ubiquitination of the conserved cysteine of Pex5p, the peroxisomal import receptor. *J. Biol. Chem., 283*, 14190-7. ↗

Grou, CP., Carvalho, AF., Pinto, MP., Huybrechts, SJ., Sá-Miranda, C., Fransen, M. et al. (2009). Properties of the ubiquitin-pex5p thiol ester conjugate. *J. Biol. Chem., 284*, 10504-13. ↗

Okumoto, K., Misono, S., Miyata, N., Matsumoto, Y., Mukai, S., Fujiki, Y. (2011). Cysteine ubiquitination of PTS1 receptor Pex5p regulates Pex5p recycling. *Traffic, 12*, 1067-83. ↗

Carvalho, AF., Pinto, MP., Grou, CP., Alencastre, IS., Fransen, M., Sá-Miranda, C. et al. (2007). Ubiquitination of mammalian Pex5p, the peroxisomal import receptor. *J. Biol. Chem., 282*, 31267-72. ↗

Chang, CC., Warren, DS., Sacksteder, KA., Gould, SJ. (1999). PEX12 interacts with PEX5 and PEX10 and acts downstream of receptor docking in peroxisomal matrix protein import. *J. Cell Biol., 147*, 761-74. ↗

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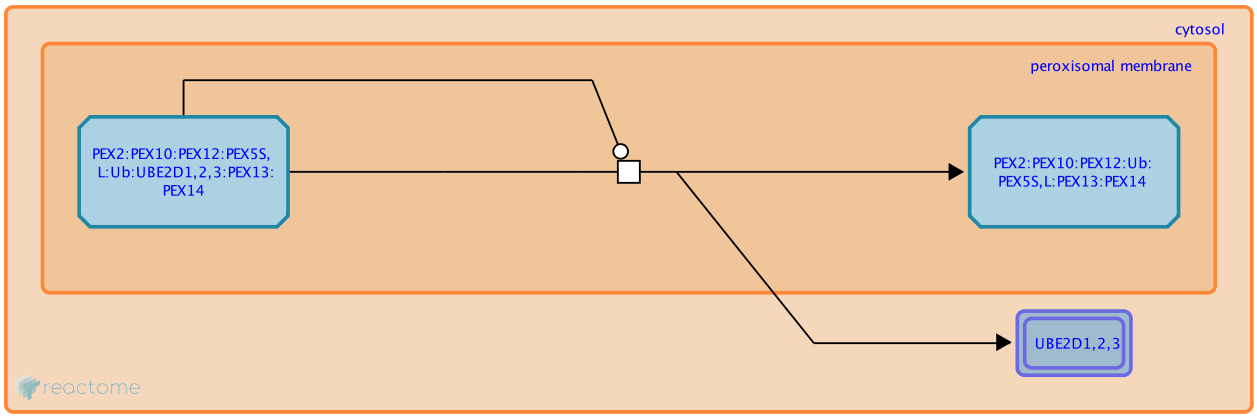
PEX2:PEX10:PEX12 monoubiquitinates PEX5S,L at cysteine-11 ↗

Location: Peroxisomal protein import

Stable identifier: R-HSA-8953946

Type: transition

Compartments: peroxisomal membrane



The RING-type E3 ubiquitin ligase sub-complex PEX2:PEX10:PEX12 catalyzes the transfer of ubiquitin from an E2-ubiquitin conjugate (one of Ub:UBE2D1, Ub:UBE2D2, or Ub:UBE2D3) to the cysteine-11 residue of the substrate PEX5L, the peroxisomal matrix protein shuttling receptor (Carvalho et al. 2007; Grou et al. 2008, Okumoto et al. 2011, Sargent et al. 2016, inferred from yeast in Dodt and Gould 1996). The thiol ester bond between ubiquitin and the cysteine residue of PEX5 is unusual among ubiquitin substrates, which usually have isopeptide bonds between ubiquitin and a lysine residue. Monoubiquitination of PEX5 at cysteine-11 is an integral and mandatory step in the PEX5-mediated peroxisomal protein transport pathway; in its absence, PEX5 cannot be extracted from the peroxisomal membrane docking/translocation machinery (the peroxisomal protein translocon), and thus transport of newly synthesized peroxisomal matrix proteins to the organelle matrix stops (Grou et al. 2009). In addition to monoubiquitinating PEX5 during peroxisomal protein import, the PEX2:PEX10:PEX12 complex has also been implicated in pexophagy, a type of selective autophagy targeting peroxisomes. Pexophagy seems to be triggered mainly by ubiquitination of PEX5, which, in this case, can occur either at its cysteine-11 or lysine-209 residues, but ubiquitination of ABCD3 (also known as PMP70) and other peroxisomal membrane proteins may also be involved (Zhang et al. 2015, inferred from mouse in Nordgren et al. 2015, Sargent et al. 2016).

Preceded by: PEX2:PEX10:PEX12 binds PEX5S,L (in PEX5S:PEX13:PEX14) and Ub:UBE2D1,2,3

Followed by: PEX2:PEX10:PEX12:Ub:PEX5S,L:PEX13:PEX14 binds PEX1:PEX6:PEX26 and ZFAND6

Literature references

Grou, CP., Carvalho, AF., Pinto, MP., Wiese, S., Piechura, H., Meyer, HE. et al. (2008). Members of the E2D (UbcH5) family mediate the ubiquitination of the conserved cysteine of Pex5p, the peroxisomal import receptor. *J. Biol. Chem., 283*, 14190-7. ↗

Grou, CP., Carvalho, AF., Pinto, MP., Huybrechts, SJ., Sá-Miranda, C., Fransen, M. et al. (2009). Properties of the ubiquitin-pex5p thiol ester conjugate. *J. Biol. Chem., 284*, 10504-13. ↗

Okumoto, K., Misono, S., Miyata, N., Matsumoto, Y., Mukai, S., Fujiki, Y. (2011). Cysteine ubiquitination of PTS1 receptor Pex5p regulates Pex5p recycling. *Traffic, 12*, 1067-83. ↗

Dodt, G., Gould, SJ. (1996). Multiple PEX genes are required for proper subcellular distribution and stability of Pex5p, the PTS1 receptor: evidence that PTS1 protein import is mediated by a cycling receptor. *J. Cell Biol., 135*, 1763-74. ↗

Nordgren, M., Francisco, T., Lismont, C., Hennebel, L., Brees, C., Wang, B. et al. (2015). Export-deficient monoubiquitinated PEX5 triggers peroxisome removal in SV40 large T antigen-transformed mouse embryonic fibroblasts. *Autophagy, 11*, 1326-40. ↗

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PEX2:PEX10:PEX12:Ub:PEX5S,L:PEX13:PEX14 binds PEX1:PEX6:PEX26 and ZFAND6

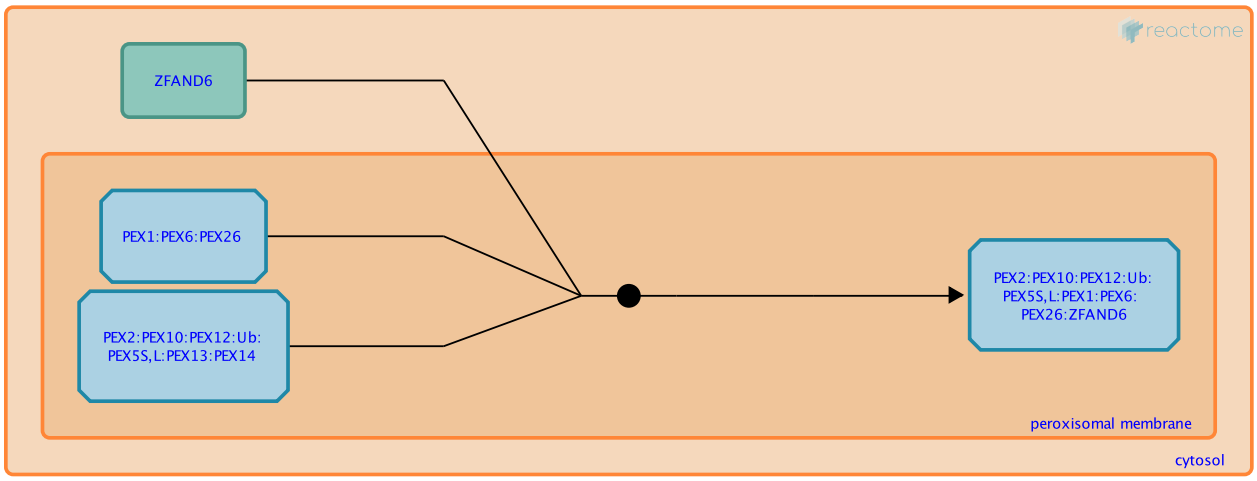
↗

Location: Peroxisomal protein import

Stable identifier: R-HSA-9033533

Type: binding

Compartments: peroxisomal membrane



PEX1:PEX6:PEX26 (also known as the Receptor Export Module or peroxisomal AAA ATPase complex) extracts ubiquitinated PEX5S or PEX5L in the peroxisomal membrane (Tamura et al. 2006, Tamura et al. 2014). PEX1 and PEX6 are soluble proteins that form a hexameric ring bound to PEX26 in the peroxisomal membrane (Matsumoto et al. 2003, Weller et al. 2005). ZFAND6 (AWP1) probably binds to ubiquitinated PEX5 and PEX6 and acts as an export factor (Miyata et al. 2012).

Preceded by: PEX2:PEX10:PEX12 monoubiquitinates PEX5S,L at cysteine-11

Followed by: PEX1:PEX6:PEX26:ZFAND6:Ub:PEX5S,L:PEX14:PEX13:PEX2:PEX10:PEX12 dissociates yielding cytosolic Ub:PEX5S,L and membrane PEX14:PEX13:PEX2:PEX10:PEX12

Literature references

Tamura, S., Yasutake, S., Matsumoto, N., Fujiki, Y. (2006). Dynamic and functional assembly of the AAA peroxins, Pex1p and Pex6p, and their membrane receptor Pex26p. *J. Biol. Chem., 281*, 27693-704. ↗

Miyata, N., Okumoto, K., Mukai, S., Noguchi, M., Fujiki, Y. (2012). AWP1/ZFAND6 functions in Pex5 export by interacting with cys-monoubiquitinated Pex5 and Pex6 AAA ATPase. *Traffic, 13*, 168-83. ↗

Tamura, S., Matsumoto, N., Takeba, R., Fujiki, Y. (2014). AAA peroxins and their recruiter Pex26p modulate the interactions of peroxins involved in peroxisomal protein import. *J. Biol. Chem., 289*, 24336-46. ↗

Weller, S., Cajigas, I., Morrell, J., Obie, C., Steel, G., Gould, SJ. et al. (2005). Alternative splicing suggests extended function of PEX26 in peroxisome biogenesis. *Am. J. Hum. Genet., 76*, 987-1007. ↗

Matsumoto, N., Tamura, S., Fujiki, Y. (2003). The pathogenic peroxin Pex26p recruits the Pex1p-Pex6p AAA ATPase complexes to peroxisomes. *Nat. Cell Biol., 5*, 454-60. ↗

Editions

2017-12-20	Authored, Edited	May, B.
2018-02-13	Reviewed	Van Veldhoven, PP., Fransen, M.
2018-03-12	Reviewed	Azevedo, JE.

PEX1:PEX6:PEX26:ZFAND6:Ub:PEX5S,L:PEX14:PEX13:PEX2:PEX10:PEX12 dissociates yielding cytosolic Ub:PEX5S,L and membrane PEX14:PEX13:PEX2:PEX10:PEX12 ↗

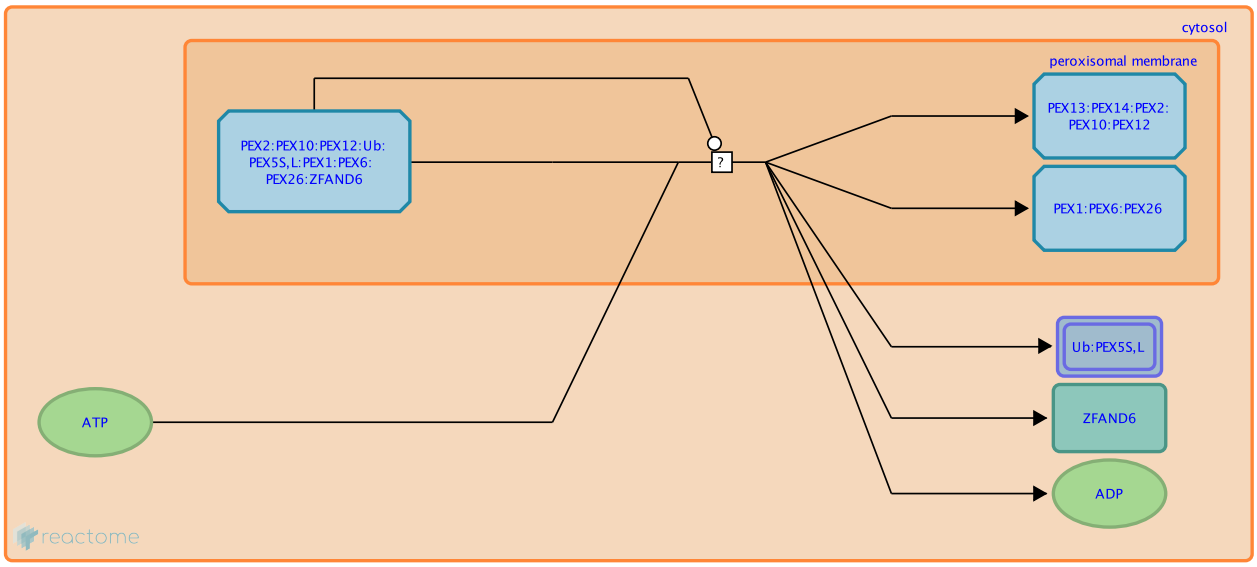
Location: Peroxisomal protein import

Stable identifier: R-HSA-9033505

Type: uncertain

Compartments: peroxisomal membrane

Inferred from: PEX1:PEX6:PEX15:Ub:PEX5:PEX14:PEX13:PEX17:PEX1:PEX6:PEX15 dissociates yielding cytosolic Ub:PEX5S,L and membrane PEX14:PEX13:PEX17:PEX1:PEX6:PEX15 (Saccharomyces cerevisiae)



Ubiquitinated PEX5 isoform S or isoform L (Ub:PEX5S,L) is released from the peroxisomal membrane and interaction with the Docking and Translocation Module by PEX1:PEX6:PEX26:ZFAND6 (the peroxisomal AAA ATPase complex, receptor export module) (Tamura et al. 2014, Law et al. 2017, also inferred from yeast homologs). PEX1 and PEX6 form a cytosolic hexameric ring that is anchored to the peroxisomal membrane by PEX26. Hydrolysis of ATP by PEX1 and PEX6 appears to cause a conformational change in PEX1:PEX6:PEX26:ZFAND6 that releases Ub:PEX5S,L from the peroxisomal membrane and into the cytosol (reviewed in Saffert et al. 2017).

Preceded by: PEX2:PEX10:PEX12:Ub:PEX5S,L:PEX13:PEX14 binds PEX1:PEX6:PEX26 and ZFAND6

Followed by: USP9X binds Ub:PEX5S, USP9X hydrolyzes Ub:PEX5S yielding PEX5S and Ubiquitin, USP9X binds Ub:PEX5L

Literature references

Law, KB., Bronte-Tinkew, D., Di Pietro, E., Snowden, A., Jones, RO., Moser, A. et al. (2017). The peroxisomal AAA ATPase complex prevents pexophagy and development of peroxisome biogenesis disorders. *Autophagy, 13*, 868-884. ↗

Tamura, S., Matsumoto, N., Takeba, R., Fujiki, Y. (2014). AAA peroxins and their recruiter Pex26p modulate the interactions of peroxins involved in peroxisomal protein import. *J. Biol. Chem., 289*, 24336-46. ↗

Saffert, P., Enenkel, C., Wendler, P. (2017). Structure and Function of p97 and Pex1/6 Type II AAA+ Complexes. *Front Mol Biosci, 4*, 33. ↗

Tamura, S., Okumoto, K., Toyama, R., Shimozawa, N., Tsukamoto, T., Suzuki, Y. et al. (1998). Human PEX1 cloned by functional complementation on a CHO cell mutant is responsible for peroxisome-deficient Zellweger syndrome of complementation group I. *Proc. Natl. Acad. Sci. U.S.A., 95*, 4350-5. ↗

Miyata, N., Okumoto, K., Mukai, S., Noguchi, M., Fujiki, Y. (2012). AWP1/ZFAND6 functions in Pex5 export by interacting with cys-monoubiquitinated Pex5 and Pex6 AAA ATPase. *Traffic, 13*, 168-83. ↗

Editions

2017-12-20	Authored, Edited	May, B.
2018-02-13	Reviewed	Van Veldhoven, PP., Fransen, M.
2018-03-12	Reviewed	Azevedo, JE.

USP9X binds Ub:PEX5S ↗

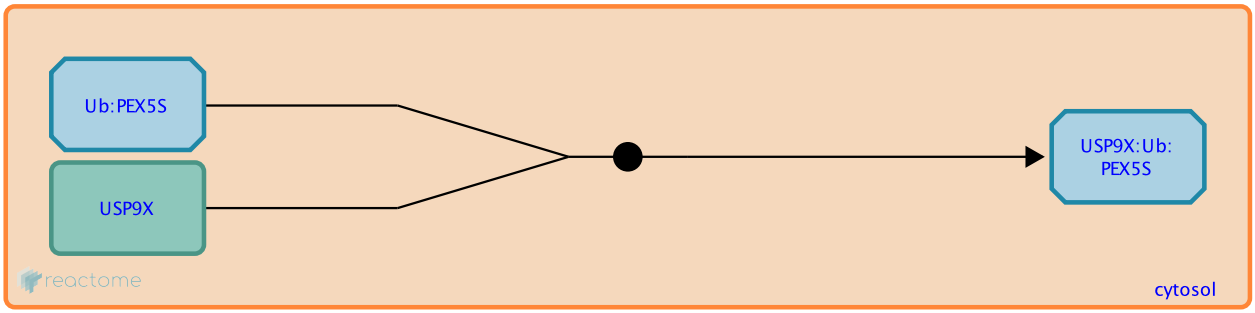
Location: Peroxisomal protein import

Stable identifier: R-HSA-9033526

Type: binding

Compartments: cytosol

Inferred from: USP9X binds Ub:PEX5L (Homo sapiens)



The deubiquitinating enzyme USP9X binds cytosolic ubiquitinated PEX5S (Ub:PEX5S) and then hydrolyzes the thioester bond between the carboxyl terminus of ubiquitin and cysteine-11 of PEX5S (inferred from the large isoform of PEX5 in Grou et al. 2012).

Preceded by: PEX1:PEX6:PEX26:ZFAND6:Ub:PEX5S,L:PEX14:PEX13:PEX2:PEX10:PEX12 dissociates yielding cytosolic Ub:PEX5S,L and membrane PEX14:PEX13:PEX2:PEX10:PEX12

Literature references

Grou, CP., Francisco, T., Rodrigues, TA., Freitas, MO., Pinto, MP., Carvalho, AF. et al. (2012). Identification of ubiquitin-specific protease 9X (USP9X) as a deubiquitinase acting on ubiquitin-peroxin 5 (PEX5) thioester conjugate. *J. Biol. Chem., 287,* 12815-27. ↗

Editions

2017-12-20	Authored, Edited	May, B.
2018-02-13	Reviewed	Van Veldhoven, PP., Fransen, M.
2018-03-12	Reviewed	Azevedo, JE.

USP9X hydrolyzes Ub:PEX5S yielding PEX5S and Ubiquitin ↗

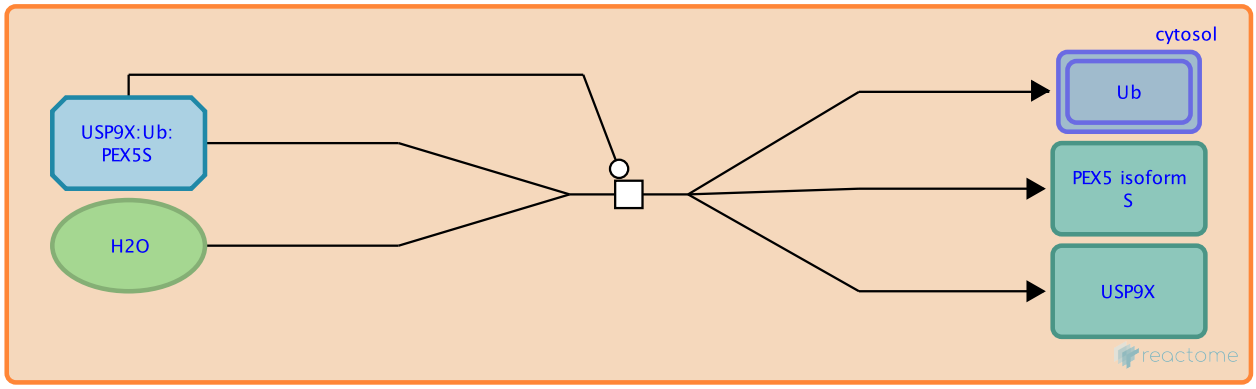
Location: Peroxisomal protein import

Stable identifier: R-HSA-9033478

Type: transition

Compartments: cytosol

Inferred from: USP9X hydrolyzes Ub:PEX5L yielding PEX5L and Ubiquitin (Homo sapiens)



The deubiquitinating enzyme USP9X hydrolyzes the thioester bond between the carboxyl terminus of ubiquitin and cysteine-11 of PEX5S (inferred from the large isoform of PEX5L in Grou et al. 2012). The thioester bond is unstable and appears also to be spontaneously disrupted by nucleophilic attack of small metabolites such as reduced glutathione (Grou et al. 2009).

Preceded by: PEX1:PEX6:PEX26:ZFAND6:Ub:PEX5S,L:PEX14:PEX13:PEX2:PEX10:PEX12 dissociates yielding cytosolic Ub:PEX5S,L and membrane PEX14:PEX13:PEX2:PEX10:PEX12

Literature references

Grou, CP., Francisco, T., Rodrigues, TA., Freitas, MO., Pinto, MP., Carvalho, AF. et al. (2012). Identification of ubiquitin-specific protease 9X (USP9X) as a deubiquitinase acting on ubiquitin-peroxin 5 (PEX5) thioester conjugate. *J. Biol. Chem., 287*, 12815-27. ↗

Grou, CP., Carvalho, AF., Pinto, MP., Huybrechts, SJ., Sá-Miranda, C., Fransen, M. et al. (2009). Properties of the ubiquitin-pex5p thiol ester conjugate. *J. Biol. Chem., 284*, 10504-13. ↗

Editions

2017-12-20	Authored, Edited	May, B.
2018-02-13	Reviewed	Van Veldhoven, PP., Fransen, M.
2018-03-12	Reviewed	Azevedo, JE.

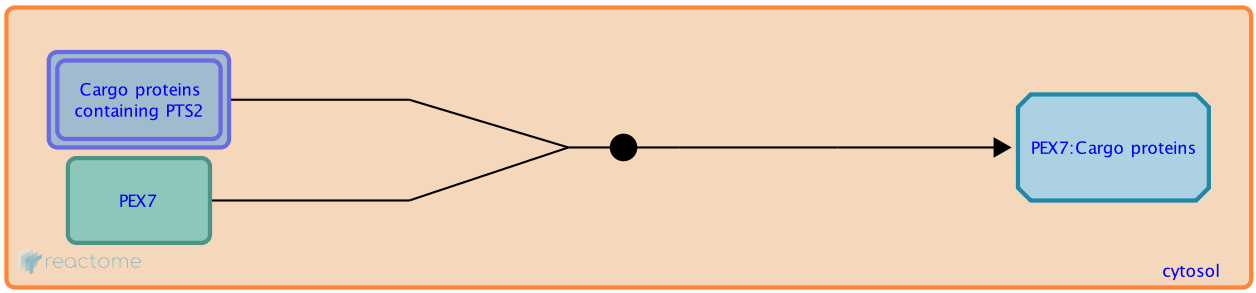
PEX7 binds cargo proteins containing PTS2 ↗

Location: Peroxisomal protein import

Stable identifier: R-HSA-9033232

Type: binding

Compartments: cytosol



Cytosolic PEX7 binds peroxisome targeting signal 2 (PTS2), a sequence of nine amino acid residues functionally identified in 3 human peroxisomal matrix proteins (Braverman et al. 1997, Motley et al. 1997, Purdue et al. 1997, Braverman et al. 2000, Ghys et al. 2002, Motley et al. 2002, Kunze et al. 2011, Kunze et al. 2015). According to molecular modeling, the PTS2 consensus sequence binds a groove in PEX7 (Kunze et al. 2011). Mutations in PEX7 cause rhizomelic chondrodysplasia punctata type 1 (Braverman et al. 1997, Motley et al. 1997, Purdue et al. 1997).

Followed by: PEX5L binds PEX7:Cargo protein

Literature references

Kunze, M., Malkani, N., Maurer-Stroh, S., Wiesinger, C., Schmid, JA., Berger, J. (2015). Mechanistic insights into PTS2-mediated peroxisomal protein import: the co-receptor PEX5L drastically increases the interaction strength between the cargo protein and the receptor PEX7. *J. Biol. Chem., 290*, 4928-40. ↗

Kunze, M., Neuberger, G., Maurer-Stroh, S., Ma, J., Eck, T., Braverman, N. et al. (2011). Structural requirements for interaction of peroxisomal targeting signal 2 and its receptor PEX7. *J. Biol. Chem., 286*, 45048-62. ↗

Braverman, N., Steel, G., Obie, C., Moser, A., Moser, H., Gould, SJ. et al. (1997). Human PEX7 encodes the peroxisomal PTS2 receptor and is responsible for rhizomelic chondrodysplasia punctata. *Nat. Genet., 15*, 369-76. ↗

Braverman, N., Steel, G., Lin, P., Moser, A., Moser, H., Valle, D. (2000). PEX7 gene structure, alternative transcripts, and evidence for a founder haplotype for the frequent RCDP allele, L292ter. *Genomics, 63*, 181-92. ↗

Motley, AM., Hettema, EH., Hogenhout, EM., Brites, P., ten Asbroek, AL., Wijburg, FA. et al. (1997). Rhizomelic chondrodysplasia punctata is a peroxisomal protein targeting disease caused by a non-functional PTS2 receptor. *Nat. Genet., 15*, 377-80. ↗

Editions

2017-12-15	Authored, Edited	May, B.
2018-02-13	Reviewed	Van Veldhoven, PP., Fransen, M.
2018-03-12	Reviewed	Azevedo, JE.

PEX5L binds PEX7:Cargo protein ↗

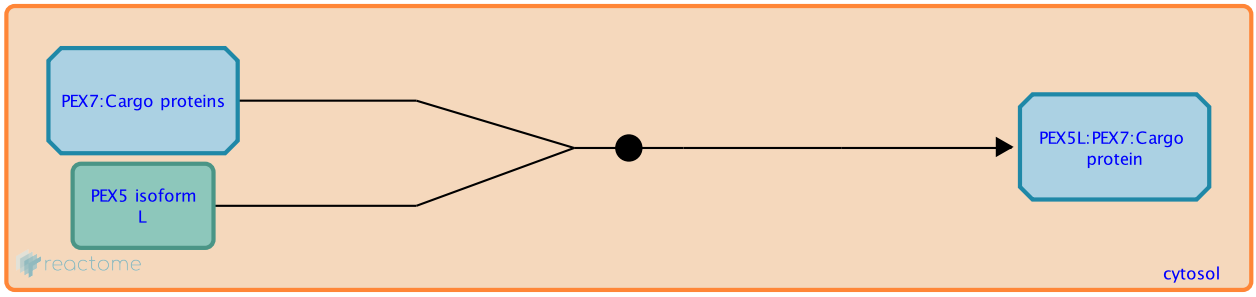
Location: Peroxisomal protein import

Stable identifier: R-HSA-9033240

Type: binding

Compartments: cytosol

Inferred from: PEX5L binds PEX7:Acaa1a (Cricetulus griseus)



The long isoform of PEX5, PEX5L, binds PEX7 that is already bound to a PTS2-containing cargo protein (Braverman et al. 1998, Dodt et al. 2001, Kunze et al. 2015, Rodrigues et al. 2015). The binding of PEX5L to PEX7 increases the affinity of PEX7 for cargo protein (Kunze et al. 2015). Mutations affecting the additional sequence present only in the long isoform of PEX5 cause rhizomelic chondrodysplasia punctata type 5 (Baroy et al. 2015).

Preceded by: PEX7 binds cargo proteins containing PTS2

Followed by: PEX5L:PEX7:Cargo binds PEX13:PEX14:PEX2:PEX10:PEX12 (Docking and Translocation Module)

Literature references

Kunze, M., Malkani, N., Maurer-Stroh, S., Wiesinger, C., Schmid, JA., Berger, J. (2015). Mechanistic insights into PTS2-mediated peroxisomal protein import: the co-receptor PEX5L drastically increases the interaction strength between the cargo protein and the receptor PEX7. *J. Biol. Chem., 290*, 4928-40. ↗

Braverman, N., Dodt, G., Gould, SJ., Valle, D. (1998). An isoform of pex5p, the human PTS1 receptor, is required for the import of PTS2 proteins into peroxisomes. *Hum. Mol. Genet., 7*, 1195-205. ↗

Rodrigues, TA., Grou, CP., Azevedo, JE. (2015). Revisiting the intraperoxisomal pathway of mammalian PEX7. *Sci Rep , 5*, 11806. ↗

Dodt, G., Warren, D., Becker, E., Rehling, P., Gould, SJ. (2001). Domain mapping of human PEX5 reveals functional and structural similarities to Saccharomyces cerevisiae Pex18p and Pex21p. *J. Biol. Chem., 276*, 41769-81. ↗

Barøy, T., Koster, J., Strømme, P., Ebberink, MS., Misceo, D., Ferdinandusse, S. et al. (2015). A novel type of rhizomelic chondrodysplasia punctata, RCDP5, is caused by loss of the PEX5 long isoform. *Hum. Mol. Genet., 24*, 5845-54. ↗

Editions

2017-12-15	Authored, Edited	May, B.
2018-02-13	Reviewed	Van Veldhoven, PP., Fransen, M.
2018-03-12	Reviewed	Azevedo, JE.

PEX5L:PEX7:Cargo binds PEX13:PEX14:PEX2:PEX10:PEX12 (Docking and Translocation Module)

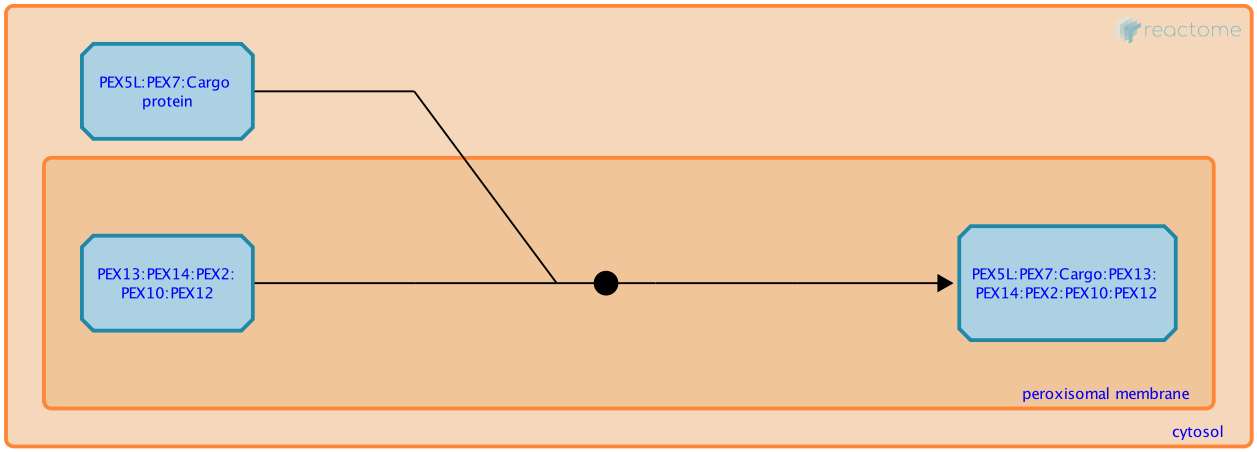
Location: Peroxisomal protein import

Stable identifier: R-HSA-9033238

Type: binding

Compartments: peroxisomal membrane

Inferred from: Pex14 binds PEX5L (in PEX5L:PEX7:Acaa1a) (Cricetulus griseus)



PEX5L bound to PEX7:Cargo interacts with the peroxisomal membrane complex PEX13:PEX14:PEX2:PEX10:PEX12 (the Docking-Translocation Complex) thus bringing PEX7 and its cargo to dock at the peroxisomal membrane (Gould et al. 1996, Fransen et al. 1998, Will et al. 1999, Dodt et al. 2001, Rodrigues et al. 2014, Rodrigues et al. 2015, also inferred from hamster and rat homologues).

Preceded by: PEX5L binds PEX7:Cargo protein

Followed by: Cargo of PEX5L:PEX7 translocates from the cytosol to the peroxisomal matrix

Literature references

Rodrigues, TA., Grou, CP., Azevedo, JE. (2015). Revisiting the intraperoxisomal pathway of mammalian PEX7. *Sci Rep , 5*, 11806.

Rodrigues, TA., Alencastre, IS., Francisco, T., Brites, P., Fransen, M., Grou, CP. et al. (2014). A PEX7-centered perspective on the peroxisomal targeting signal type 2-mediated protein import pathway. *Mol. Cell. Biol., 34*, 2917-28.

Dodt, G., Warren, D., Becker, E., Rehling, P., Gould, SJ. (2001). Domain mapping of human PEX5 reveals functional and structural similarities to Saccharomyces cerevisiae Pex18p and Pex21p. *J. Biol. Chem., 276*, 41769-81.

Fransen, M., Terlecky, SR., Subramani, S. (1998). Identification of a human PTS1 receptor docking protein directly required for peroxisomal protein import. *Proc. Natl. Acad. Sci. U.S.A., 95*, 8087-92.

Will, GK., Soukupova, M., Hong, X., Erdmann, KS., Kiel, JA., Dodt, G. et al. (1999). Identification and characterization of the human orthologue of yeast Pex14p. *Mol. Cell. Biol., 19*, 2265-77.

Editions

2017-12-19	Authored, Edited	May, B.
2018-02-13	Reviewed	Van Veldhoven, PP., Fransen, M.
2018-03-12	Reviewed	Azevedo, JE.

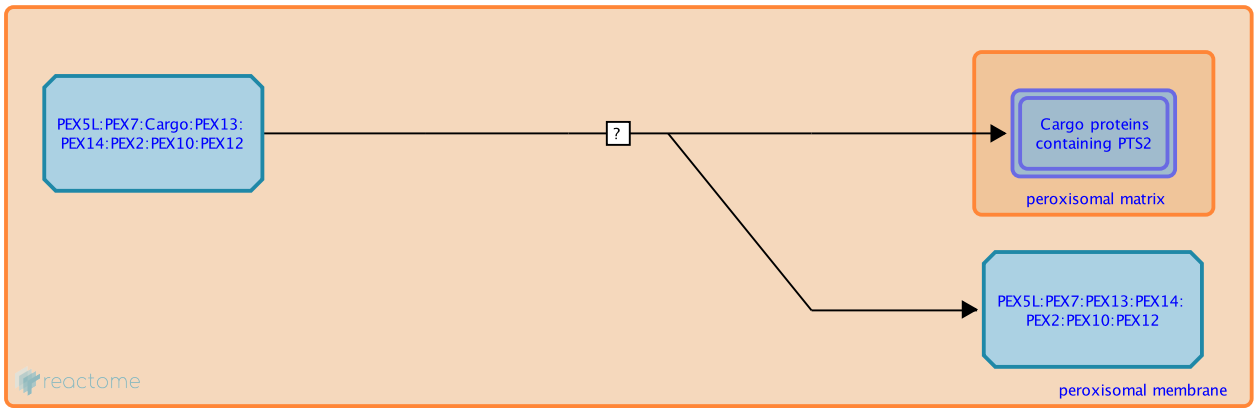
Cargo of PEX5L:PEX7 translocates from the cytosol to the peroxisomal matrix ↗

Location: Peroxisomal protein import

Stable identifier: R-HSA-9033514

Type: uncertain

Compartments: peroxisomal membrane



The cargo protein bound to PEX7 is released from PEX7 into the peroxisomal matrix in a reaction that does not require ATP (Purdue et al. 1997, Dodt et al. 2001, Rodrigues et al. 2014, Rodrigues et al. 2015). PEX7 may also be released into the matrix (inferred from yeast in Nair et al. 2004), however later research indicates that PEX7 remains with PEX5L in the peroxisomal membrane (Rodrigues et al. 2015) apparently in a proteinaceous cavity (Dias et al. 2017). Mutations in PEX5 cause defects in import of PTS1-containing proteins or PTS2-containing proteins or both (Eberrink et al. 2009, Barøy et al. 2015).

Preceded by: PEX5L:PEX7:Cargo binds PEX13:PEX14:PEX2:PEX10:PEX12 (Docking and Translocation Module)

Followed by: PEX2:PEX10:PEX12 binds PEX5L (in PEX5L:PEX7:PEX13:PEX14:PEX2:PEX10:PEX12) and Ub:UBE2D1,2,3

Literature references

Rodrigues, TA., Grou, CP., Azevedo, JE. (2015). Revisiting the intraperoxisomal pathway of mammalian PEX7. *Sci Rep , 5*, 11806. ↗

Rodrigues, TA., Alencastre, IS., Francisco, T., Brites, P., Fransen, M., Grou, CP. et al. (2014). A PEX7-centered perspective on the peroxisomal targeting signal type 2-mediated protein import pathway. *Mol. Cell. Biol., 34*, 2917-28. ↗

Dodt, G., Warren, D., Becker, E., Rehling, P., Gould, SJ. (2001). Domain mapping of human PEX5 reveals functional and structural similarities to Saccharomyces cerevisiae Pex18p and Pex21p. *J. Biol. Chem., 276*, 41769-81. ↗

Purdue, PE., Zhang, JW., Skoneczny, M., Lazarow, PB. (1997). Rhizomelic chondrodysplasia punctata is caused by deficiency of human PEX7, a homologue of the yeast PTS2 receptor. *Nat. Genet., 15*, 381-4. ↗

Ebberink, MS., Mooyer, PA., Koster, J., Dekker, CJ., Eyskens, FJ., Dionisi-Vici, C. et al. (2009). Genotype-phenotype correlation in PEX5-deficient peroxisome biogenesis defective cell lines. *Hum. Mutat., 30*, 93-8. ↗

Editions

2017-12-20	Authored, Edited	May, B.
2018-02-13	Reviewed	Van Veldhoven, PP., Fransen, M.
2018-03-12	Reviewed	Azevedo, JE.

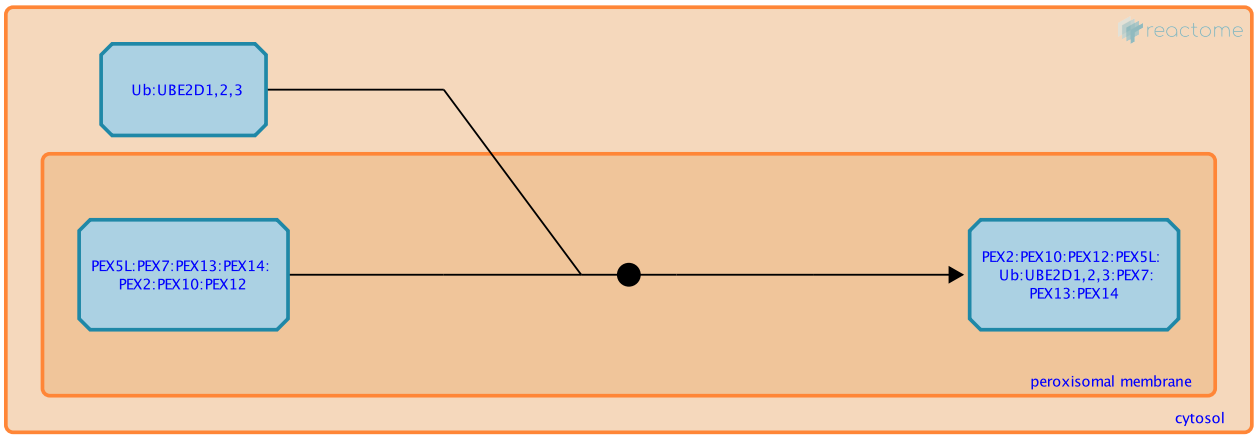
PEX2:PEX10:PEX12 binds PEX5L (in PEX5L:PEX7:PEX13:PEX14:PEX2:PEX10:PEX12) and Ub:UBE2D1,2,3

Location: Peroxisomal protein import

Stable identifier: R-HSA-9033527

Type: binding

Compartments: peroxisomal membrane



A RING E3 ubiquitin ligase sub-complex containing PEX10, PEX12, and PEX2 ubiquitinates PEX5L. PEX10:PEX12:PEX2 is believed to bind an activated E2-ubiquitin conjugate (one of Ub:UBE2D1, Ub:UBE2D2, Ub:UBE2D3) and PEX5L in a complex that also contains PEX13 and PEX14 (Chang et al. 1999, Carvalho et al. 2007, Grou et al. 2008, Grou et al. 2009, Okumoto et al. 2011).

Preceded by: Cargo of PEX5L:PEX7 translocates from the cytosol to the peroxisomal matrix

Followed by: PEX2:PEX10:PEX12 monoubiquitinates PEX5L at cysteine-11

Literature references

Grou, CP., Carvalho, AF., Pinto, MP., Wiese, S., Piechura, H., Meyer, HE. et al. (2008). Members of the E2D (UbcH5) family mediate the ubiquitination of the conserved cysteine of Pex5p, the peroxisomal import receptor. *J. Biol. Chem., 283*, 14190-7.

Grou, CP., Carvalho, AF., Pinto, MP., Huybrechts, SJ., Sá-Miranda, C., Fransen, M. et al. (2009). Properties of the ubiquitin-pex5p thiol ester conjugate. *J. Biol. Chem., 284*, 10504-13.

Okumoto, K., Misono, S., Miyata, N., Matsumoto, Y., Mukai, S., Fujiki, Y. (2011). Cysteine ubiquitination of PTS1 receptor Pex5p regulates Pex5p recycling. *Traffic, 12*, 1067-83.

Carvalho, AF., Pinto, MP., Grou, CP., Alencastre, IS., Fransen, M., Sá-Miranda, C. et al. (2007). Ubiquitination of mammalian Pex5p, the peroxisomal import receptor. *J. Biol. Chem., 282*, 31267-72.

Chang, CC., Warren, DS., Sacksteder, KA., Gould, SJ. (1999). PEX12 interacts with PEX5 and PEX10 and acts downstream of receptor docking in peroxisomal matrix protein import. *J. Cell Biol., 147*, 761-74.

Editions

2017-12-20	Authored, Edited	May, B.
2018-02-13	Reviewed	Van Veldhoven, PP., Fransen, M.
2018-03-12	Reviewed	Azevedo, JE.

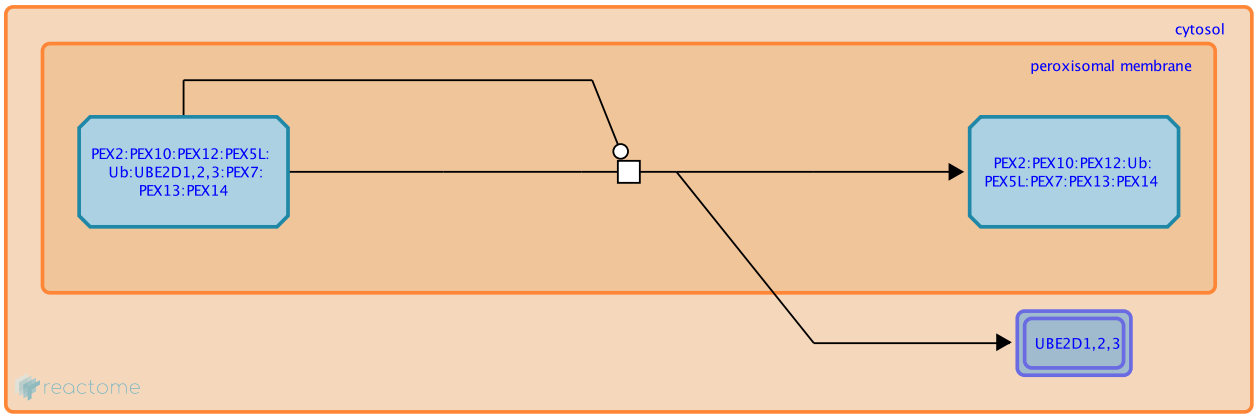
PEX2:PEX10:PEX12 monoubiquitinates PEX5L at cysteine-11 ↗

Location: Peroxisomal protein import

Stable identifier: R-HSA-9033485

Type: transition

Compartments: peroxisomal membrane



The RING-type E3 ubiquitin ligase sub-complex PEX2:PEX10:PEX12 catalyzes the transfer of ubiquitin from an E2-ubiquitin conjugate (one of Ub:UBE2D1, Ub:UBE2D2, or Ub:UBE2D3) to the cysteine-11 residue of the substrate PEX5L, the peroxisomal matrix protein shuttling receptor (Carvalho et al. 2007; Grou et al. 2008, Okumoto et al. 2011, Sargent et al. 2016, inferred from yeast in Dodt and Gould 1996). In contrast to PEX5, PEX7 transiently associated with the docking and translocation module (which comprises PEX14, PEX13, PEX2, PEX10, and PEX12) is not ubiquitinated. The thiol ester bond between ubiquitin and the cysteine residue of PEX5 is unusual among ubiquitin substrates, which usually have isopeptide bonds between ubiquitin and a lysine residue. Monoubiquitination of PEX5 at cysteine-11 is an integral and mandatory step in the PEX5-mediated peroxisomal protein transport pathway; in its absence, PEX5 and PEX7 cannot be extracted from the peroxisomal membrane docking-translocation machinery (the peroxisomal protein translocon), and thus transport of newly synthesized peroxisomal matrix proteins to the organelle matrix stops (Grou et al. 2009). In addition to monoubiquitinating PEX5 during peroxisomal protein import, the PEX2:PEX10:PEX12 sub-complex has also been implicated in pexophagy, a type of selective autophagy targeting peroxisomes. Pexophagy seems to be triggered mainly by ubiquitination of PEX5, which, in this case, can occur either at its cysteine-11 or lysine-209 residues, but ubiquitination of ABCD3 (also known as PMP70) and other peroxisomal membrane proteins may also be involved (Zhang et al. 2015, inferred from mouse in Nordgren et al. 2015, Sargent et al. 2016).

Preceded by: PEX2:PEX10:PEX12 binds PEX5L (in PEX5L:PEX7:PEX13:PEX14:PEX2:PEX10:PEX12) and Ub:UBE2D1,2,3

Followed by: PEX2:PEX10:PEX12:Ub:PEX5L:PEX7:PEX13:PEX14 binds PEX1:PEX6:PEX26 and ZFAND6

Literature references

Grou, CP., Carvalho, AF., Pinto, MP., Wiese, S., Piechura, H., Meyer, HE. et al. (2008). Members of the E2D (UbcH5) family mediate the ubiquitination of the conserved cysteine of Pex5p, the peroxisomal import receptor. *J. Biol. Chem., 283*, 14190-7. ↗

Grou, CP., Carvalho, AF., Pinto, MP., Huybrechts, SJ., Sá-Miranda, C., Fransen, M. et al. (2009). Properties of the ubiquitin-pex5p thiol ester conjugate. *J. Biol. Chem., 284*, 10504-13. ↗

Okumoto, K., Misono, S., Miyata, N., Matsumoto, Y., Mukai, S., Fujiki, Y. (2011). Cysteine ubiquitination of PTS1 receptor Pex5p regulates Pex5p recycling. *Traffic, 12*, 1067-83. ↗

Dodt, G., Gould, SJ. (1996). Multiple PEX genes are required for proper subcellular distribution and stability of Pex5p, the PTS1 receptor: evidence that PTS1 protein import is mediated by a cycling receptor. *J. Cell Biol., 135*, 1763-74. ↗

Nordgren, M., Francisco, T., Lismont, C., Hennebel, L., Brees, C., Wang, B. et al. (2015). Export-deficient monoubiquitinated PEX5 triggers peroxisome removal in SV40 large T antigen-transformed mouse embryonic fibroblasts. *Autophagy, 11*, 1326-40. ↗

Editions

2017-01-01	Authored, Edited	May, B.
2018-02-13	Reviewed	Van Veldhoven, PP., Fransen, M.
2018-03-12	Reviewed	Azevedo, JE.

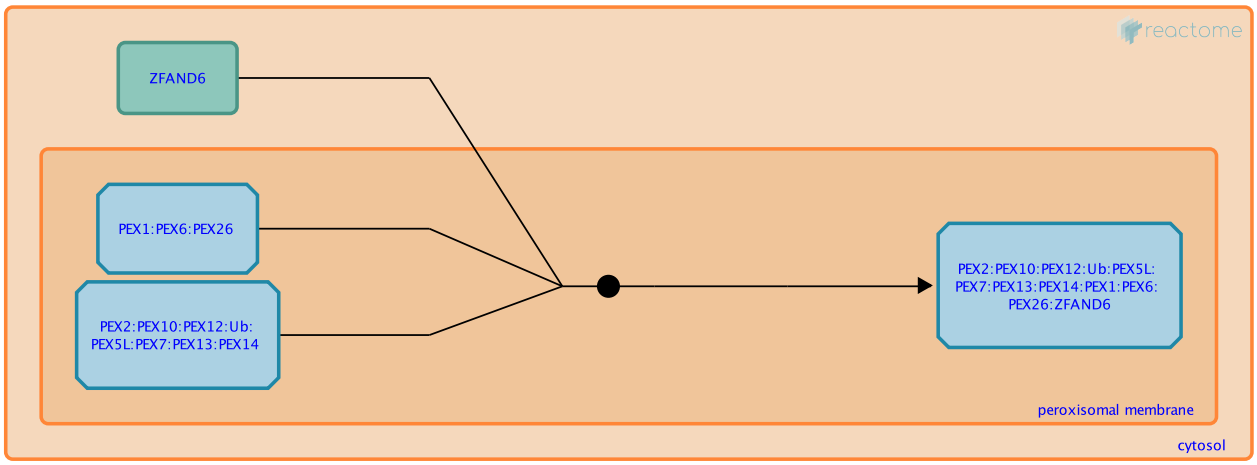
PEX2:PEX10:PEX12:Ub:PEX5L:PEX7:PEX13:PEX14 binds PEX1:PEX6:PEX26 and ZFAND6 ↗

Location: Peroxisomal protein import

Stable identifier: R-HSA-9033516

Type: binding

Compartments: peroxisomal membrane



PEX1:PEX6:PEX26 (known as the Receptor Export Module) extracts ubiquitinated PEX5L from the peroxisomal membrane Docking and Translocation Module (Tamura et al. 2006, Tamura et al. 2014). PEX1 and PEX6 are soluble proteins that form a hexameric ring bound to PEX26 in the peroxisomal membrane (Matsumoto et al. 2003, Welle et al. 2005). ZFAND6 (AWP1) probably binds to ubiquitinated PEX5 and PEX6 and acts as an export factor (Miyata et al. 2012).

Preceded by: PEX2:PEX10:PEX12 monoubiquitinates PEX5L at cysteine-11

Followed by: PEX1:PEX6:PEX26:ZFAND6 dissociates Ub:PEX5L and PEX7 from PEX14:PEX13:PEX2:PEX10:PEX12 and translocates PEX5L and PEX7 from the peroxisomal membrane to the cytosol

Literature references

Tamura, S., Yasutake, S., Matsumoto, N., Fujiki, Y. (2006). Dynamic and functional assembly of the AAA peroxins, Pex1p and Pex6p, and their membrane receptor Pex26p. *J. Biol. Chem., 281*, 27693-704. ↗

Miyata, N., Okumoto, K., Mukai, S., Noguchi, M., Fujiki, Y. (2012). AWP1/ZFAND6 functions in Pex5 export by interacting with cys-monoubiquitinated Pex5 and Pex6 AAA ATPase. *Traffic, 13*, 168-83. ↗

Tamura, S., Matsumoto, N., Takeba, R., Fujiki, Y. (2014). AAA peroxins and their recruiter Pex26p modulate the interactions of peroxins involved in peroxisomal protein import. *J. Biol. Chem., 289*, 24336-46. ↗

Weller, S., Cajigas, I., Morrell, J., Obie, C., Steel, G., Gould, SJ. et al. (2005). Alternative splicing suggests extended function of PEX26 in peroxisome biogenesis. *Am. J. Hum. Genet., 76*, 987-1007. ↗

Matsumoto, N., Tamura, S., Fujiki, Y. (2003). The pathogenic peroxin Pex26p recruits the Pex1p-Pex6p AAA ATPase complexes to peroxisomes. *Nat. Cell Biol., 5*, 454-60. ↗

Editions

2017-12-20	Authored, Edited	May, B.
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2018-03-12	Reviewed	Azevedo, JE.

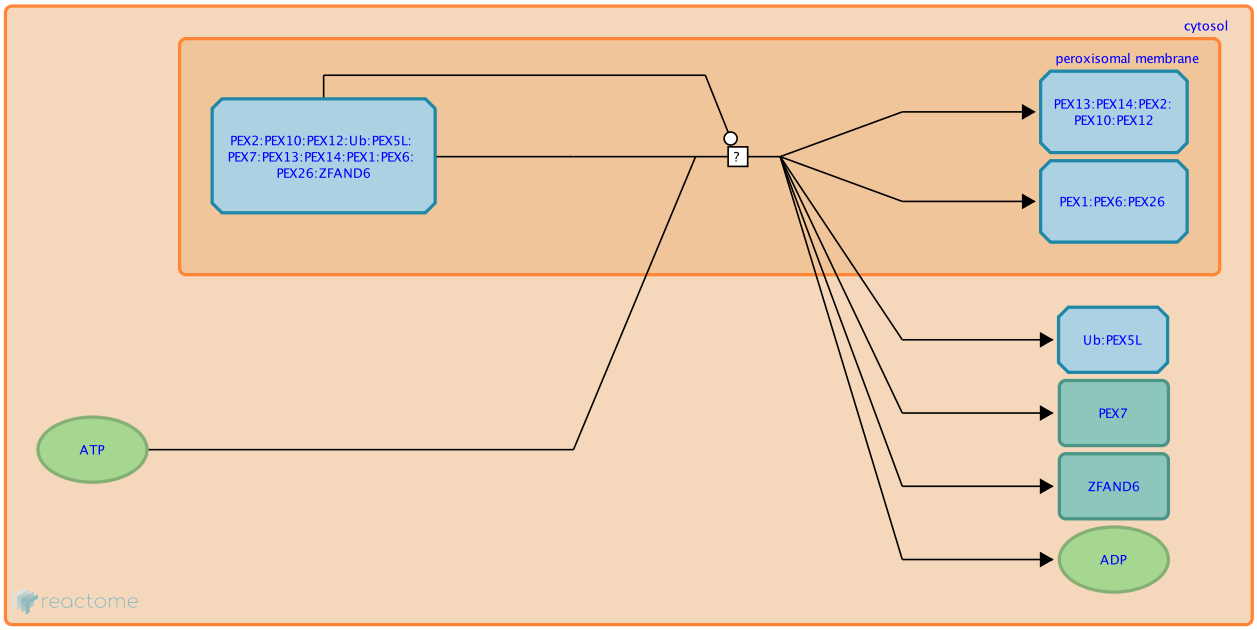
PEX1:PEX6:PEX26:ZFAND6 dissociates Ub:PEX5L and PEX7 from PEX14:PEX13:PEX2:PEX10:PEX12 and translocates PEX5L and PEX7 from the peroxisomal membrane to the cytosol ↗

Location: Peroxisomal protein import

Stable identifier: R-HSA-9033499

Type: uncertain

Compartments: peroxisomal membrane



Ubiquitinated PEX5 isoform L (Ub:PEX5L) is released from the peroxisomal membrane Docking and Translocation Module by PEX1:PEX6:PEX26 (the peroxisomal AAA ATPase complex, receptor export module) (Tamura et al. 2014, Law et al. 2017, also inferred from yeast homologs). PEX1 and PEX6 form a cytosolic hexameric ring that is anchored to the peroxisomal membrane by PEX26. Hydrolysis of ATP by PEX1 and PEX6 appears to cause a conformational change in PEX1:PEX6:PEX26 that removes Ub:PEX5L from the peroxisomal membrane and into the cytosol (reviewed in Saffert et al. 2017). ZFAND6 probably binds ubiquitinated PEX5 and PEX6 and acts as an export factor (Miyata et al. 2012). Export of PEX7 back to the cytosol requires export of PEX5L but PEX7 and PEX5L appear to be exported separately (Rodrigues et al. 2014).

Preceded by: PEX2:PEX10:PEX12:Ub:PEX5L:PEX7:PEX13:PEX14 binds PEX1:PEX6:PEX26 and ZFAND6

Followed by: USP9X binds Ub:PEX5L

Literature references

Law, KB., Bronte-Tinkew, D., Di Pietro, E., Snowden, A., Jones, RO., Moser, A. et al. (2017). The peroxisomal AAA ATPase complex prevents pexophagy and development of peroxisome biogenesis disorders. *Autophagy, 13*, 868-884. ↗

Tamura, S., Matsumoto, N., Takeba, R., Fujiki, Y. (2014). AAA peroxins and their recruiter Pex26p modulate the interactions of peroxins involved in peroxisomal protein import. *J. Biol. Chem., 289*, 24336-46. ↗

Saffert, P., Enenkel, C., Wendler, P. (2017). Structure and Function of p97 and Pex1/6 Type II AAA+ Complexes. *Front Mol Biosci, 4*, 33. ↗

Tamura, S., Okumoto, K., Toyama, R., Shimozawa, N., Tsukamoto, T., Suzuki, Y. et al. (1998). Human PEX1 cloned by functional complementation on a CHO cell mutant is responsible for peroxisome-deficient Zellweger syndrome of complementation group I. *Proc. Natl. Acad. Sci. U.S.A., 95*, 4350-5. ↗

Miyata, N., Okumoto, K., Mukai, S., Noguchi, M., Fujiki, Y. (2012). AWP1/ZFAND6 functions in Pex5 export by interacting with cys-monoubiquitinated Pex5 and Pex6 AAA ATPase. *Traffic, 13*, 168-83. ↗

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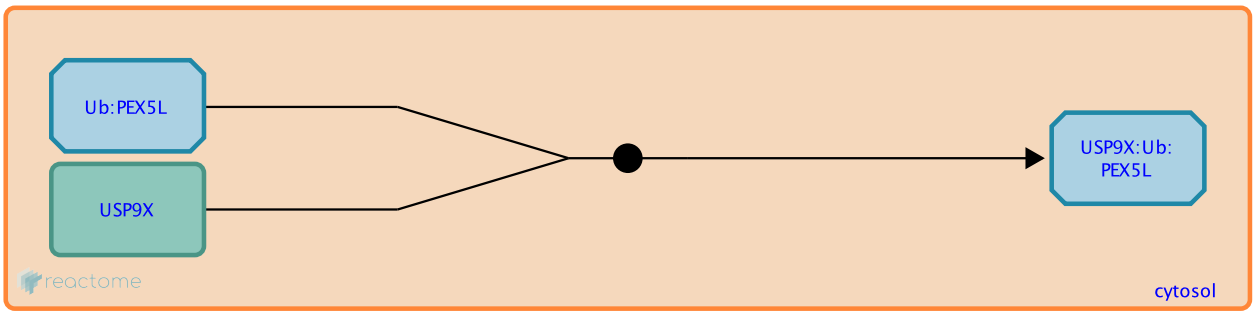
USP9X binds Ub:PEX5L ↗

Location: Peroxisomal protein import

Stable identifier: R-HSA-9033509

Type: binding

Compartments: cytosol



The deubiquitinating enzyme USP9X binds ubiquitinated PEX5L (ubiquitin conjugated to the large isoform of PEX5, Ub:PEX5L) and then hydrolyzes the thioester bond between the carboxyl terminus of ubiquitin and cysteine-11 of PEX5L (Grou et al. 2012).

Preceded by: PEX1:PEX6:PEX26:ZFAND6 dissociates Ub:PEX5L and PEX7 from PEX14:PEX13:PEX2:PEX10:PEX12 and translocates PEX5L and PEX7 from the peroxisomal membrane to the cytosol, PEX1:PEX6:PEX26:ZFAND6:Ub:PEX5S,L:PEX14:PEX13:PEX2:PEX10:PEX12 dissociates yielding cytosolic Ub:PEX5S,L and membrane PEX14:PEX13:PEX2:PEX10:PEX12

Followed by: USP9X hydrolyzes Ub:PEX5L yielding PEX5L and Ubiquitin

Literature references

Grou, CP., Francisco, T., Rodrigues, TA., Freitas, MO., Pinto, MP., Carvalho, AF. et al. (2012). Identification of ubiquitin-specific protease 9X (USP9X) as a deubiquitinase acting on ubiquitin-peroxin 5 (PEX5) thioester conjugate. *J. Biol. Chem., 287*, 12815-27. ↗

Editions

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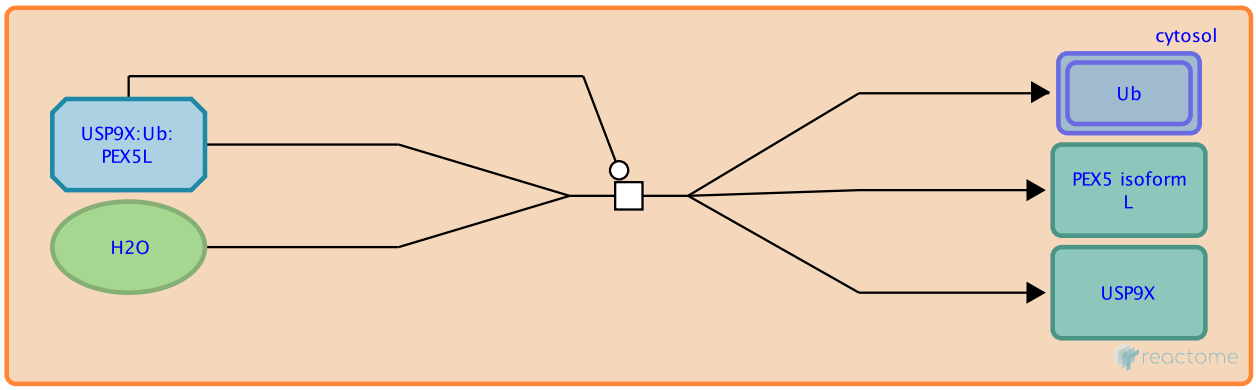
USP9X hydrolyzes Ub:PEX5L yielding PEX5L and Ubiquitin ↗

Location: Peroxisomal protein import

Stable identifier: R-HSA-9033491

Type: transition

Compartments: cytosol



The deubiquitinating enzyme USP9X hydrolyzes the thioester bond between the carboxyl terminus of ubiquitin and cysteine-11 of PEX5L (Grou et al. 2012). The thioester bond is unstable and appears to be also spontaneously (non-enzymatically) disrupted by nucleophilic attack of small metabolites such as reduced glutathione (Grou et al. 2009).

Preceded by: USP9X binds Ub:PEX5L

Literature references

Grou, CP., Francisco, T., Rodrigues, TA., Freitas, MO., Pinto, MP., Carvalho, AF. et al. (2012). Identification of ubiquitin-specific protease 9X (USP9X) as a deubiquitinase acting on ubiquitin-peroxin 5 (PEX5) thioester conjugate. *J. Biol. Chem., 287,* 12815-27. ↗

Grou, CP., Carvalho, AF., Pinto, MP., Huybrechts, SJ., Sá-Miranda, C., Fransen, M. et al. (2009). Properties of the ubiquitin-pex5p thiol ester conjugate. *J. Biol. Chem., 284,* 10504-13. ↗

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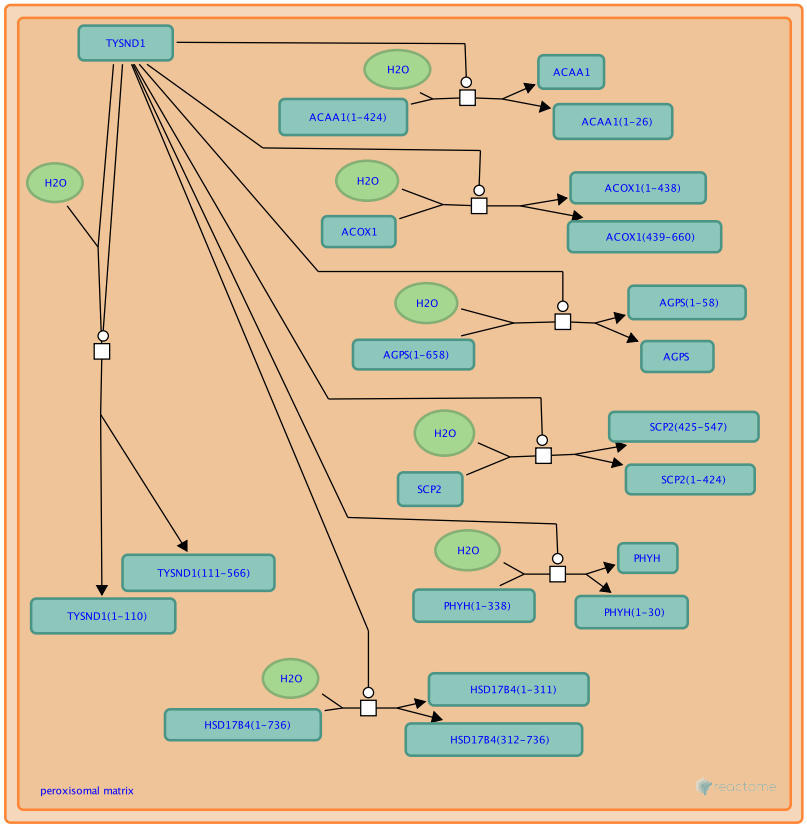
TYSND1 cleaves peroxisomal proteins ↗

Location: Peroxisomal protein import

Stable identifier: R-HSA-9033500

Compartments: peroxisomal matrix



After proteins are imported into the peroxisome a subset of proteins are cleaved by the protease TYSND1 (Okumoto et al. 2011). Based onmutagenesis of human TYSND1 (Okumoto et al. 2011) and the homolog in Arabidopsis (Schuhmann et al. 2008), TYSND1 appears to be a trypsin-like serine protease containing a conserved histidine aspartate serine triad essential for catalysis. Mice lacking Tysnd1 have reduced peroxisomal localization of some peroxisomal enzymes and exhibit reduced beta-oxidation of fatty acids and metabolism of phytanic acid (Mizuno et al. 2013). Male mice lacking Tysnd1 are sterile due to sperm that lack acrosomal caps.

Literature references

Okumoto, K., Kametani, Y., Fujiki, Y. (2011). Two proteases, trypsin domain-containing 1 (Tysnd1) and peroxisomal lon protease (PsLon), cooperatively regulate fatty acid β-oxidation in peroxisomal matrix. *J. Biol. Chem., 286*, 44367-79. ↗

Mizuno, Y., Ninomiya, Y., Nakachi, Y., Iseki, M., Iwasa, H., Akita, M. et al. (2013). Tysnd1 deficiency in mice interferes with the peroxisomal localization of PTS2 enzymes, causing lipid metabolic abnormalities and male infertility. *PLoS Genet., 9*, e1003286. ↗

Schuhmann, H., Huesgen, PF., Gietl, C., Adamska, I. (2008). The DEG15 serine protease cleaves peroxisomal targeting signal 2-containing proteins in Arabidopsis. *Plant Physiol., 148*, 1847-56. ↗

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