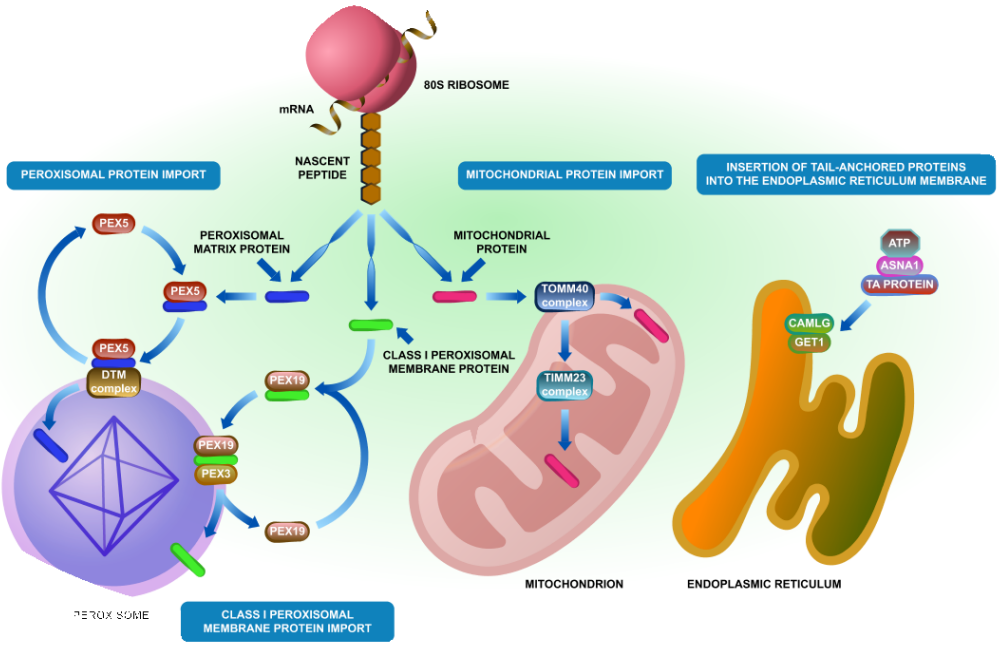
Protein localization



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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).

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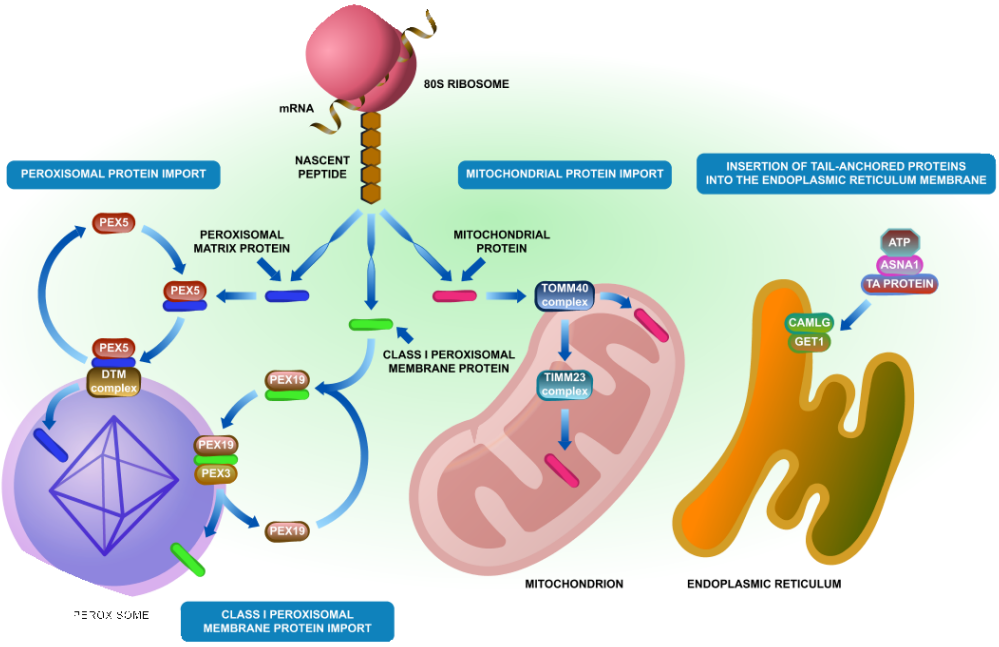
Protein localization ↗

Stable identifier: R-HSA-9609507



Protein localization encompasses the processes that establish and maintain proteins at specific locations. Mechanisms that target proteins to particular locations in the cell typically involve a motif in the targeted protein that interacts with proteins located at the destination (reviewed in Bauer et al. 2015).

Mitochondrial proteins encoded in the nucleus may be targeted to the outer membrane, intermembrane space, inner membrane, or the matrix (reviewed in Kutik et al. 2007, Milenkovic et al. 2007, Bolender et al. 2008, Ender and Yamano 2009, Wiedemann and Pfanner 2017, Kang et al. 2018). A presequence or an internal targeting sequence causes a protein in the cytosol to interact with the TOMM40:TOMM70 complex in the outer mitochondrial membrane. After passage across the outer membrane, sequence motifs cause proteins to be targeted to the outer membrane via the SAMM50 complex, to the inner membrane via the TIMM22 or TIMM23 complexes, to the matrix via the TIMM23 complex, or proteins may fold and remain in the intermembrane space.

All of the proteins contained in the 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 (reviewed in Ma et al. 2011, Fujiki et al. 2014, Francisco et al. 2017). In the cytosol, receptor proteins, PEX5 and PEX7, bind to specific sequence motifs in cargo proteins and then interact with a protein complex containing PEX13, PEX14, PEX2, PEX10, and PEX12 in the peroxisome membrane. The cargo proteins then pass through a proteinaceous channel in the membrane and PEX5 is recycled by a mechanism involving ubiquitination and deubiquitination.

Most peroxisomal membrane proteins (PMPs) are inserted into the peroxisomal membrane by the receptor-chaperone PEX19 and the docking receptor PEX3 (reviewed in Ma et al. 2011, Fujiki et al. 2014). PEX19 binds the PMP as it is translated in the cytosol. The PEX19:PMP complex then interacts with PEX3 located in the peroxisomal membrane. Through a mechanism that is not yet clear, the PMP is inserted into the peroxisomal membrane and PEX19 dissociates from PEX3.

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Editions

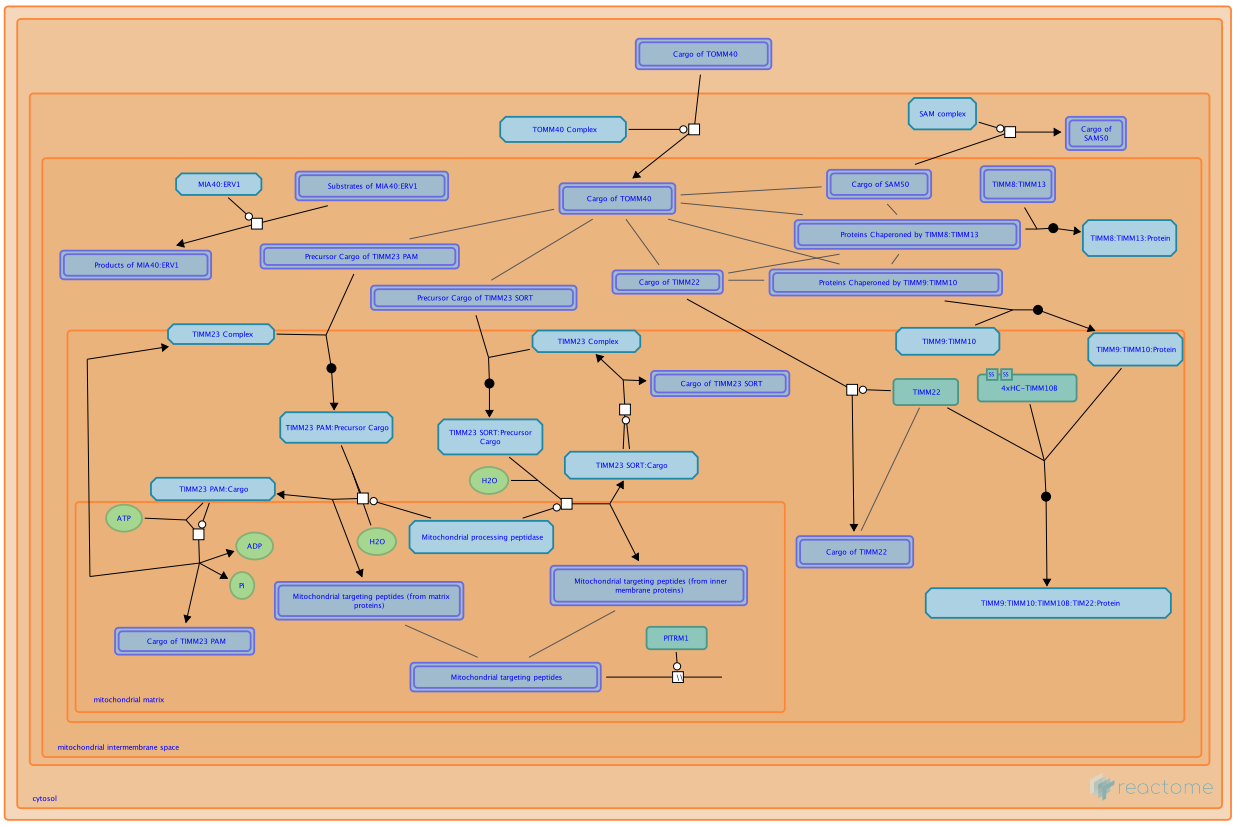
2018-05-26	Authored, Edited	May, B.

Mitochondrial protein import ↗

Location: Protein localization

Stable identifier: R-HSA-1268020

Compartments: cytosol, mitochondrial inner membrane, mitochondrial intermembrane space, mitochondrial matrix, mitochondrial outer membrane



A human mitochondrion contains about 1500 proteins, more than 99% of which are encoded in the nucleus, synthesized in the cytosol and imported into the mitochondrion. Proteins are targeted to four locations (outer membrane, intermembrane space, inner membrane, and matrix) and must be sorted accordingly (reviewed in Kutik et al. 2007, Milenkovic et al. 2007, Bolender et al. 2008, Endo and Yamano 2009, Wiedemann and Pfanner 2017, Kang et al. 2018). Newly synthesized proteins are transported from the cytosol across the outer membrane by the TOMM40:TOMM70 complex. Proteins that contain presequences first interact with the TOMM20 subunit of the complex while proteins that contain internal targeting elements first interact with the TOMM70 subunit. After initial interaction the protein is conducted across the outer membrane by TOMM40 subunits. In yeast some proteins such as Aco1, Atp1, Cit1, Idh1, and Atp2 have both presequences that interact with TOM20 and mature regions that interact with TOM70 (Yamamoto et al. 2009).

After passage across the outer membrane, proteins may be targeted to the outer membrane via the SAMM50 complex, to the inner membrane via the TIMM22 or TIMM23 complexes (reviewed in van der Laan et al. 2010), to the matrix via the TIMM23 complex (reviewed in van der Laan et al. 2010), or proteins may fold and remain in the intermembrane space (reviewed in Stojanovski et al. 2008, Deponte and Hell 2009, Sideris and Tokatlidis 2010). Presequences on matrix and inner membrane proteins cause interaction with TIMM23 complexes; internal targeting sequences cause outer membrane proteins to interact with the SAMM50 complex and inner membrane proteins to interact with the TIMM22 complex. While in the intermembrane space hydrophobic proteins are chaperoned by the TIMM8:TIMM13 com-

plex and/or the TIMM9:TIMM10:FXC1 complex.

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Editions

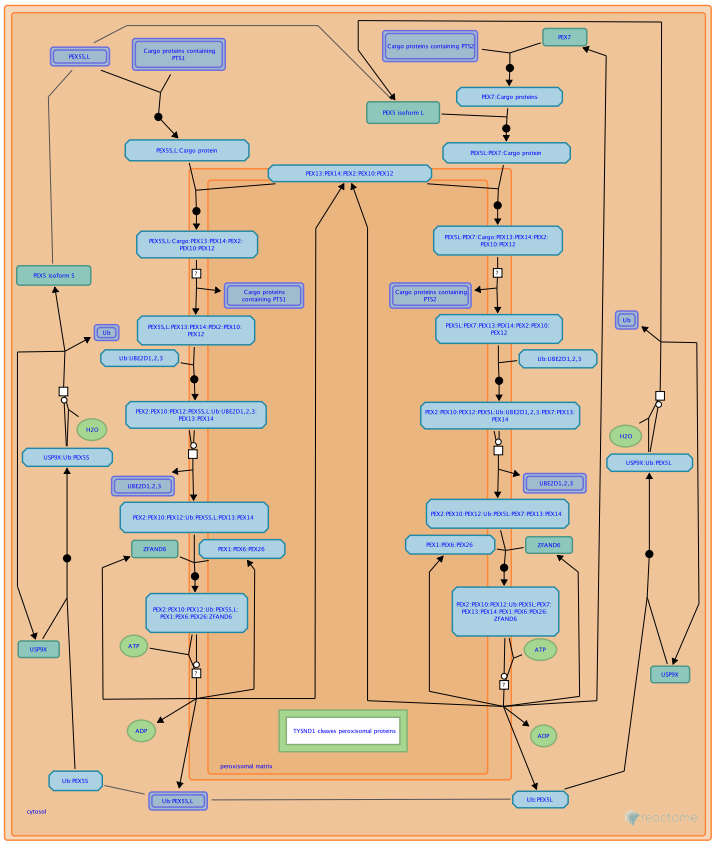
2011-05-03	Authored, Edited	May, B.
2011-11-02	Reviewed	D'Eustachio, P.
2012-02-12	Reviewed	Endo, T.

Peroxisomal protein import ↗

Location: Protein localization

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).

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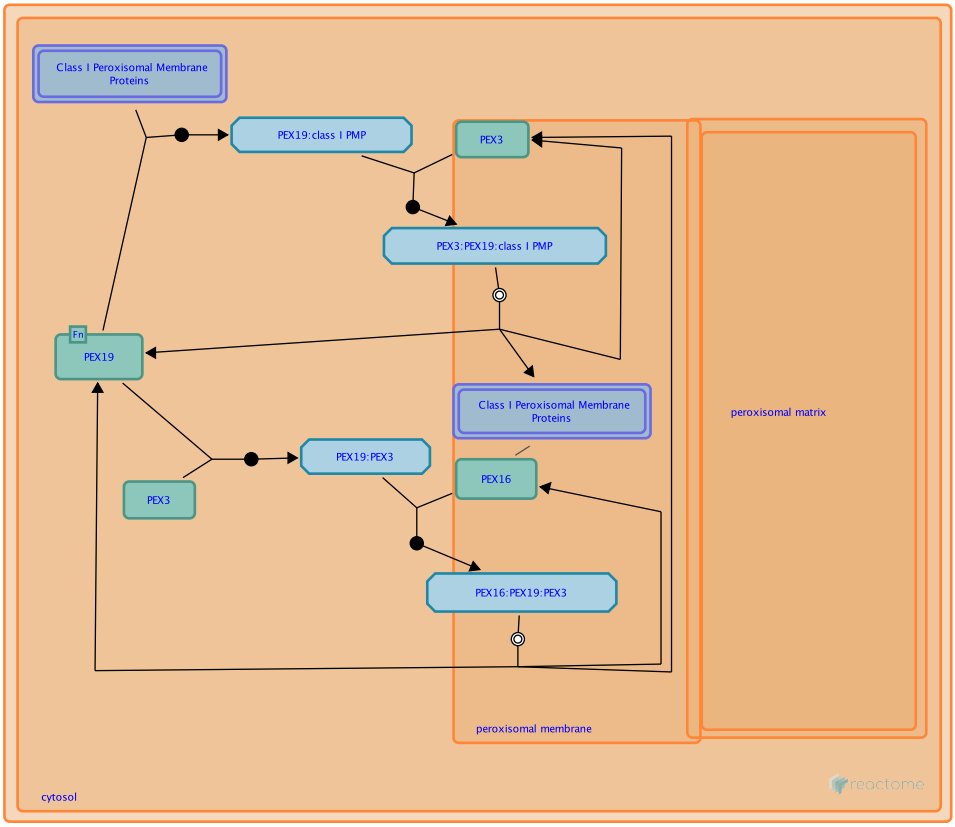
Editions

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

Class I peroxisomal membrane protein import ↗

Location: Protein localization

Stable identifier: R-HSA-9603798



Most peroxisomal membrane proteins (PMPs) are inserted into the peroxisomal membrane by the receptor-chaperone PEX19 and the docking receptor PEX3 (Soukupova et al. 1999, Muntau et al. 2003, Fang et al. 2004, Fujiki et al. 2006, Matsuzono and Fujiki 2006, Matsuzono et al. 2006, Pinto et al. 2006, Sato et al. 2008, Sato et al. 2010, Schmidt et al. 2010, Hattula et al. 2014, reviewed in Fujiki et al. 2014, Mayerhofer 2016). PEX19 binds the PMP as it is translated in the cytosol. Recognition of the PMP by PEX 19 appears to depend on positively charged residues in the transmembrane domain of the PMP (Costello et al. 2017). The PEX19:PMP complex then interacts with PEX3 located in the peroxisomal membrane. Through a mechanism that is not yet clear, the PMP is inserted into the peroxisomal membrane and PEX19 dissociates from PEX3. A current model involves transfer of the PMP from PEX19 to a hydrophobic region of PEX3 followed by insertion of the PMP into the membrane (Chen et al. 2014, reviewed by Giannopoulou et al. 2016). The process does not appear to require hydrolysis of ATP or GTP (Pinto et al. 2006).

Unlike other PMPs, PEX3 is inserted into the peroxisomal membrane by binding PEX19 and then docking with PEX16 (Matsuzaki and Fujiki 2008). Both PEX3 and PEX16 can also be co-translationally inserted into the endoplasmic reticulum membrane (Kim et al. 2006, Yonekawa et al. 2011, Aranovich et al. 2014, Hua et al. 2015, Mayerhofer et al. 2016). This region of the ER membrane then buds to contribute to new peroxisomes. PEX3 is also observed to insert into the mitochondrial outer membrane (Sugiura et al. 2017). Regions of the ER membrane and mitochondrial outer membrane are then released to form pre-peroxisomal vesicles which fuse to form new peroxisomes (Sugiura et al. 2017). Peroxisomes therefore appear to arise from fission of existing peroxisomes and production of new peroxisomes from precursors derived from mitochondria and the ER (Sugiura et al. 2017, reviewed in Fujiki et al. 2014, Hua and Kim 2016).

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Chen, Y., Pieuchot, L., Loh, RA., Yang, J., Kari, TM., Wong, JY. et al. (2014). Hydrophobic handoff for direct delivery of peroxisome tail-anchored proteins. *Nat Commun, 5*, 5790.

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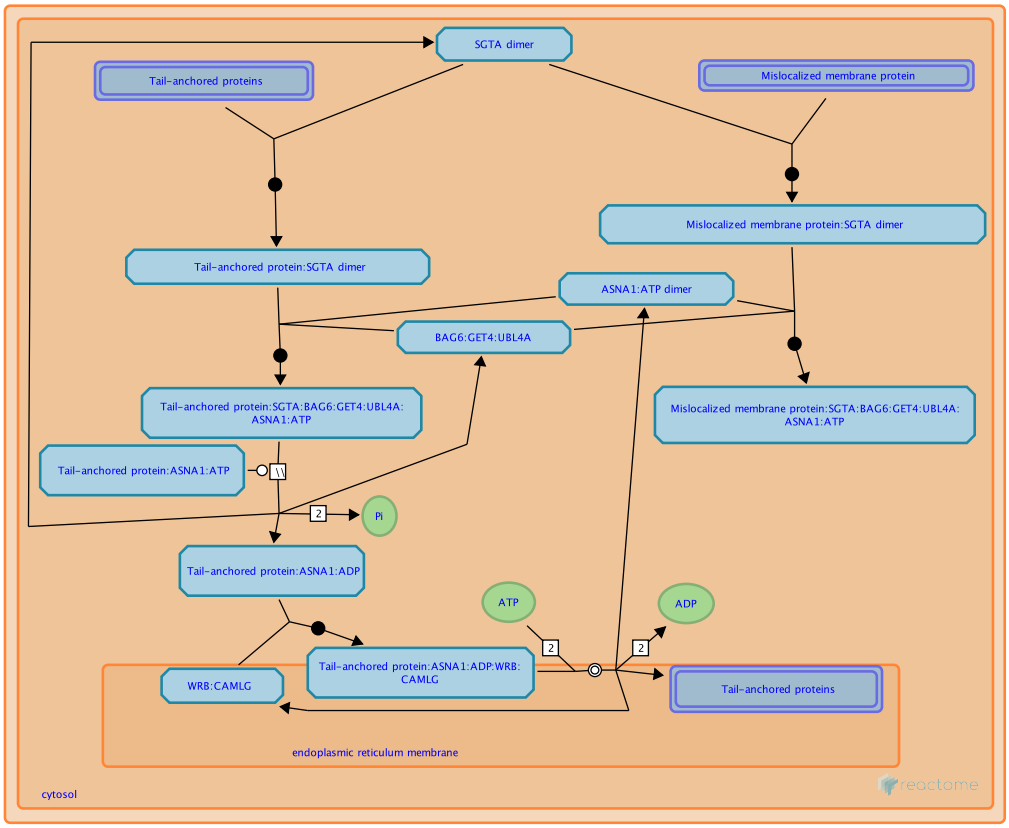
Editions

2018-03-19	Authored, Edited	May, B.
2019-01-28	Reviewed	Fransen, M.

Insertion of tail-anchored proteins into the endoplasmic reticulum membrane ↗

Location: Protein localization

Stable identifier: R-HSA-9609523



Tail-anchored (TA) proteins have a hydrophobic transmembrane domain (TMD) located near the C-terminus ("tail") of the protein. Depending on the nature of the TMD, TA proteins can be inserted into the endoplasmic reticulum (ER) membrane by at least 4 mechanisms: cotranslational insertion by the signal recognition particle (SRP), post-translational insertion by ASNA1 (TRC40), post-translational insertion by the SRP, and post-translational insertion by a SRP-independent mechanism (SND) (Casson et al. 2017, reviewed in Borgese and Fasana 2011, Casson et al. 2016, Aviram et al. 2016, Chio et al. 2017). Much of the information about the mammalian system of insertion by ASNA1 (TRC40) has been inferred from the Saccharomyces cerevisiae homologue Get3.

Prior to post-translational insertion by ASNA1, SGTA binds the transmembrane domain of the substrate TA protein immediately after translation (Leznicki et al. 2011, Leznicki and High 2012, Xu et al. 2012, Wunderly et al. 2014, Shao et al. 2017), the SGTA:TA protein complex then binds the BAG6 complex (BAG6:GET4:UBL4A) via UBL4A (Winnefeld et al. 2006, Chartron et al. 2012, Xu et al. 2012, Leznicki et al. 2013, Mock et al. 2015, Kuwabara et al. 2015, Shao et al. 2017), and the TA protein is transferred to ASNA1 (Mariappan et al. 2010, Leznicki et al. 2011, Shao et al. 2017), also bound by the BAG6 complex via UBL4A. The ASNA1:TA protein complex then docks at the WRB:CAMLG (WRB:CAML) complex located in the ER membrane and the TA protein is inserted into the ER membrane by an uncharacterized mechanism that involves ATP and the transmembrane domain insertase activity of the WRB:CAML complex (Vilardi et al. 2011, Vilardi et al. 2014, Vogl et al. 2016, and inferred from yeast in Wang et al. 2014).

Misfolded TA proteins, overexpressed TA proteins, and membrane proteins mislocalized in the cytosol bind SGTA but are not efficiently transferred to ASNA1 and, instead, are retained by BAG6 which recruits RNF126 to ubiquitinate them, targeting them for degradation by the proteasome (Wang et al. 2011,

Leznicki and High 2012, Xu et al. 2012, Rodrigo-Brenni et al. 2014, Wunderly et al. 2014, Shao et al. 2017, reviewed in Lee and Ye 2013, Casson et al. 2016, Krysztofinska et al. 2016, Guna and Hegde 2018).

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Editions

2018-05-28	Authored, Edited	May, B.
2018-11-07	Reviewed	Schwappach, B., Farkas, Á., DeLaurentiis, E.

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