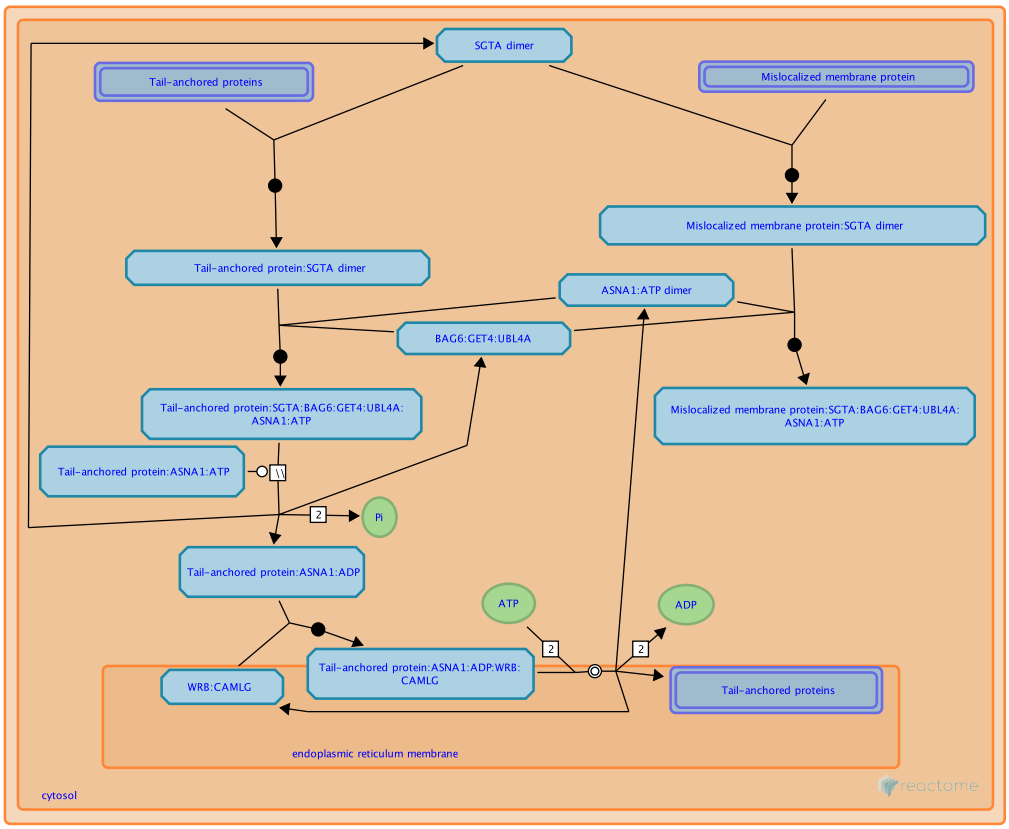
Insertion of tail-anchored proteins into the endoplasmic reticulum membrane



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29/09/2021

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.

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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. ↗

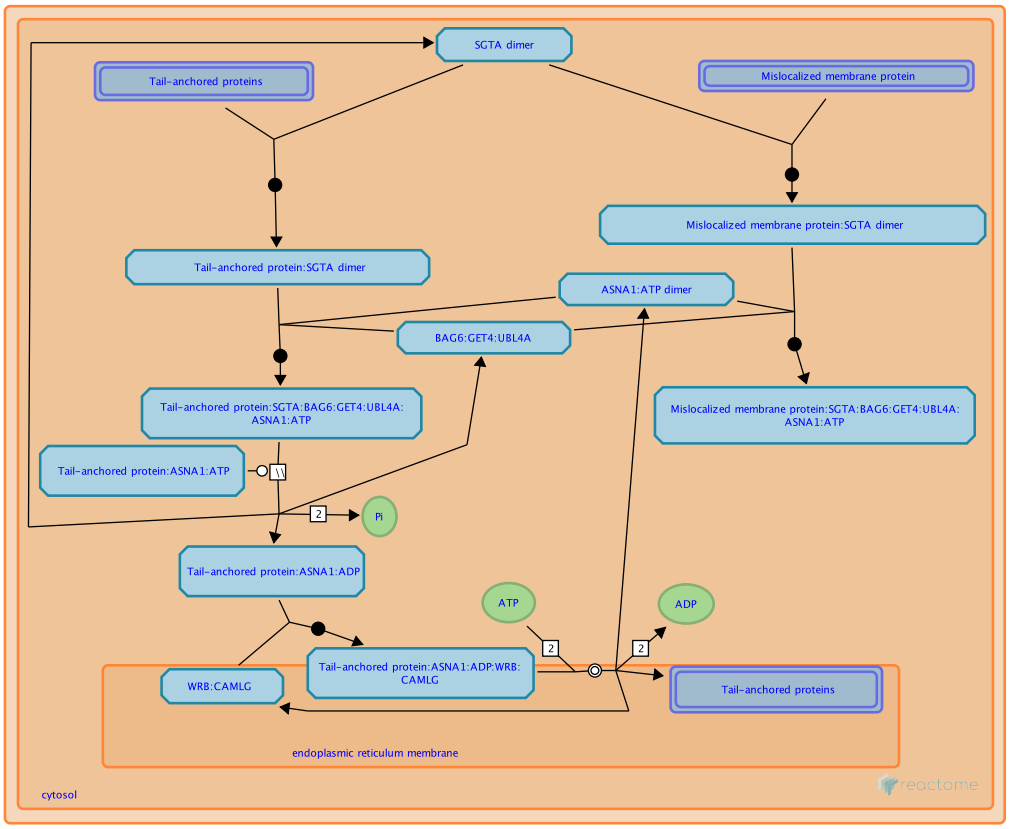
Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

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. ↗

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

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).

Literature references

Casson, J., McKenna, M., High, S. (2016). On the road to nowhere: cross-talk between post-translational protein targeting and cytosolic quality control. *Biochem. Soc. Trans., 44*, 796-801.

Guna, A., Hegde, RS. (2018). Transmembrane Domain Recognition during Membrane Protein Biogenesis and Quality Control. *Curr. Biol., 28*, R498-R511.

Aviram, N., Ast, T., Costa, EA., Arakel, EC., Chuartzman, SG., Jan, CH. et al. (2016). The SND proteins constitute an alternative targeting route to the endoplasmic reticulum. *Nature, 540*, 134-138.

Vilardi, F., Stephan, M., Clancy, A., Janshoff, A., Schwappach, B. (2014). WRB and CAML are necessary and sufficient to mediate tail-anchored protein targeting to the ER membrane. *PLoS ONE, 9*, e85033.

Lee, JG., Ye, Y. (2013). Bag6/Bat3/Scythe: a novel chaperone activity with diverse regulatory functions in protein biogenesis and degradation. *Bioessays, 35*, 377-85.

Editions

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

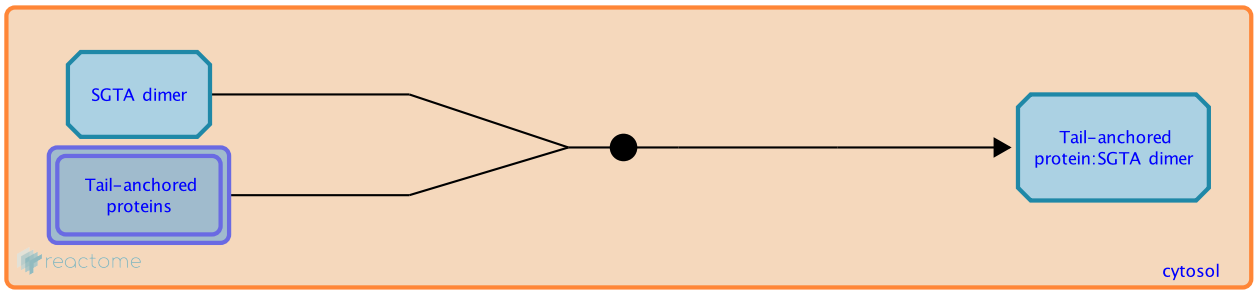
SGTA binds Tail-anchored protein ↗

Location: Insertion of tail-anchored proteins into the endoplasmic reticulum membrane

Stable identifier: R-HSA-9609921

Type: binding

Compartments: cytosol



The C-terminal domains of a SGTA dimer bind the C-terminal hydrophobic transmembrane domain (TMD) of a tail-anchored (TA) protein shortly after it emerges from the ribosome (Liou and Wang 2005, Leznicki et al. 2011, Wunderley et al. 2014, Shao et al. 2017). Binding of SGTA shields the TMD of the TA protein and stabilizes the TA protein by preventing it from being targeted for degradation (Leznicki and High 2012).

Followed by: Tail-anchored protein:SGTA dimer binds BAG6:GET4:UBL4A and ASNA1:ATP

Literature references

Shao, S., Rodrigo-Brenni, MC., Kivlen, MH., Hegde, RS. (2017). Mechanistic basis for a molecular triage reaction. *Science, 355*, 298-302. ↗

Wunderley, L., Leznicki, P., Payapilly, A., High, S. (2014). SGTA regulates the cytosolic quality control of hydrophobic substrates. *J. Cell. Sci., 127*, 4728-39. ↗

Leznicki, P., Warwicker, J., High, S. (2011). A biochemical analysis of the constraints of tail-anchored protein biogenesis. *Biochem. J., 436*, 719-27. ↗

Liou, ST., Wang, C. (2005). Small glutamine-rich tetratricopeptide repeat-containing protein is composed of three structural units with distinct functions. *Arch. Biochem. Biophys., 435*, 253-63. ↗

Leznicki, P., High, S. (2012). SGTA antagonizes BAG6-mediated protein triage. *Proc. Natl. Acad. Sci. U.S.A., 109*, 19214-9. ↗

Editions

2018-06-03	Authored, Edited	May, B.
2018-11-07	Reviewed	Schwappach, B., Farkas, Á., DeLaurentiis, E.

Tail-anchored protein:SGTA dimer binds BAG6:GET4:UBL4A and ASNA1:ATP ↗

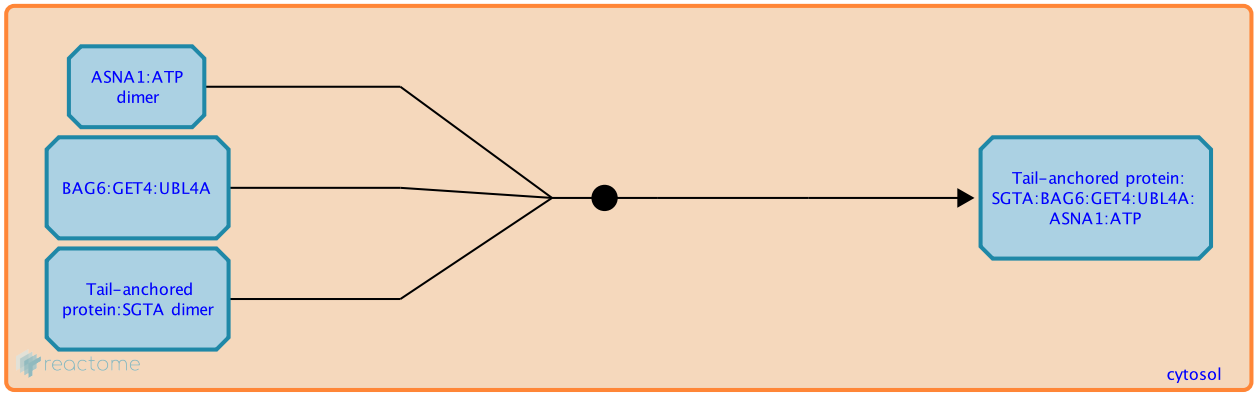
Location: Insertion of tail-anchored proteins into the endoplasmic reticulum membrane

Stable identifier: R-HSA-9610442

Type: binding

Compartments: cytosol

Inferred from: BAG6:GET4:UBL4A binds SEC61B (Homo sapiens)



A SGTA dimer bound to a tail-anchored (TA) protein 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, Darby et al. 2014, Kuwabara et al. 2015, Mock et al. 2015, Shao et al. 2017, also inferred from rabbit homologs in Mariappan et al. 2010). At some point, ASNA1 (TRC40) also binds the complex (Shao et al. 2017). SGTA interacts with the ubiquitin-like domain (UBL) of BAG6 and the UBL of UBL4A competes with BAG6 for binding to SGTA (Chartron et al. 2012, Xu et al. 2012, Leznicki et al. 2013, Darby et al. 2014, Shao et al. 2017).

Preceded by: SGTA binds Tail-anchored protein

Literature references

Leznicki, P., Roebuck, QP., Wunderley, L., Clancy, A., Krysztofinska, EM., Isaacson, RL. et al. (2013). The association of BAG6 with SGTA and tail-anchored proteins. *PLoS ONE, 8*, e59590. ↗

Shao, S., Rodrigo-Brenni, MC., Kivlen, MH., Hegde, RS. (2017). Mechanistic basis for a molecular triage reaction. *Science, 355*, 298-302. ↗

Darby, JF., Krysztofinska, EM., Simpson, PJ., Simon, AC., Leznicki, P., Sriskandarajah, N. et al. (2014). Solution structure of the SGTA dimerisation domain and investigation of its interactions with the ubiquitin-like domains of BAG6 and UBL4A. *PLoS ONE, 9*, e113281. ↗

Xu, Y., Cai, M., Yang, Y., Huang, L., Ye, Y. (2012). SGTA recognizes a noncanonical ubiquitin-like domain in the Bag6-Ubl4A-Trc35 complex to promote endoplasmic reticulum-associated degradation. *Cell Rep, 2*, 1633-44. ↗

Chartron, JW., VanderVelde, DG., Clemons, WM. (2012). Structures of the Sgt2/SGTA dimerization domain with the Get5/UBL4A UBL domain reveal an interaction that forms a conserved dynamic interface. *Cell Rep, 2*, 1620-32. ↗

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2018-06-03	Authored, Edited	May, B.
2018-11-07	Reviewed	Schwappach, B., Farkas, Á., DeLaurentiis, E.

Tail-anchored protein:SGTA:BAG6:GET4:UBL4A:ASNA1:ATP dissociates and ASNA1 hydrolyzes ATP yielding Tail-anchored protein:ASNA1:ADP ↗

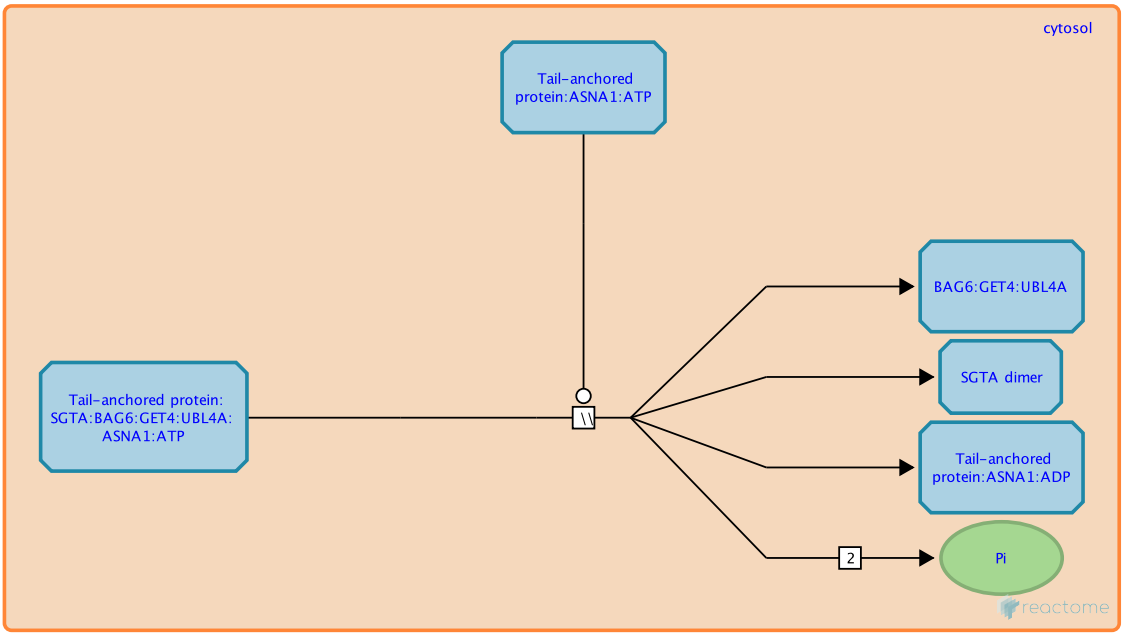
Location: Insertion of tail-anchored proteins into the endoplasmic reticulum membrane

Stable identifier: R-HSA-9609860

Type: omitted

Compartments: cytosol

Inferred from: SBH1:GET3:ATP:GET4:MDY2:SGT2 dissociates and GET3 hydrolyzes ATP yielding SBH1:GET3:ADP (Saccharomyces cerevisiae)



A properly folded tail-anchored (TA) protein is transferred from SGTA to ASNA1 via the BAG6 complex (BAG6:UBL4A:GET4 also known at BAT3:GET5:TRC35) (Marriapan et al. 2010, Leznicki et al. 2011, Mock et al. 2015, Shao et al. 2017, Guna et al. 2018). The TA protein bound to ASNA1 is then presumed to dissociate from the BAG6 complex (inferred from yeast homologs). At some point during or shortly after dissociation, ASNA1 hydrolyzes bound ATP to yield ADP (inferred from yeast homologs).

Improperly folded proteins and improperly localized hydrophobic proteins are transferred from SGTA to BAG6 rather than to ASNA1 (Shao et al. 2017). BAG6 then recruits RNF126 and facilitates the ubiquitination and consequent degradation of the defective protein. The selection of transferring a substrate protein from SGTA to ASNA1 or to BAG6 thereby acts as a "molecular triage". Proteins with less hydrophobic tail-anchors appear to be inserted into the endoplasmic reticulum membrane by a separate system comprising calmodulin and the ER membrane protein complex (Guna et al. 2018).

Followed by: Tail-anchored protein:ASNA1:ADP binds WRB:CAMLG at the endoplasmic reticulum membrane

Literature references

Guna, A., Volkmar, N., Christianson, JC., Hegde, RS. (2018). The ER membrane protein complex is a transmembrane domain insertase. *Science, 359*, 470-473. ↗

Leznicki, P., Warwicker, J., High, S. (2011). A biochemical analysis of the constraints of tail-anchored protein biogenesis. *Biochem. J., 436*, 719-27. ↗

Shao, S., Rodrigo-Brenni, MC., Kivlen, MH., Hegde, RS. (2017). Mechanistic basis for a molecular triage reaction. *Science, 355*, 298-302. ↗

Mock, JY., Chartron, JW., Zaslaver, M., Xu, Y., Ye, Y., Clemons, WM. (2015). Bag6 complex contains a minimal tail-anchor-targeting module and a mock BAG domain. *Proc. Natl. Acad. Sci. U.S.A., 112*, 106-11. ↗

Mariappan, M., Li, X., Stefanovic, S., Sharma, A., Mateja, A., Keenan, RJ. et al. (2010). A ribosome-associating factor chaperones tail-anchored membrane proteins. *Nature, 466*, 1120-4. ↗

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2018-06-03	Authored, Edited	May, B.
2018-11-07	Reviewed	Schwappach, B., Farkas, Á., DeLaurentiis, E.
2018-11-19	Reviewed	DeLaurentiis, E.

Tail-anchored protein:ASNA1:ADP binds WRB:CAMLG at the endoplasmic reticulum membrane ↗

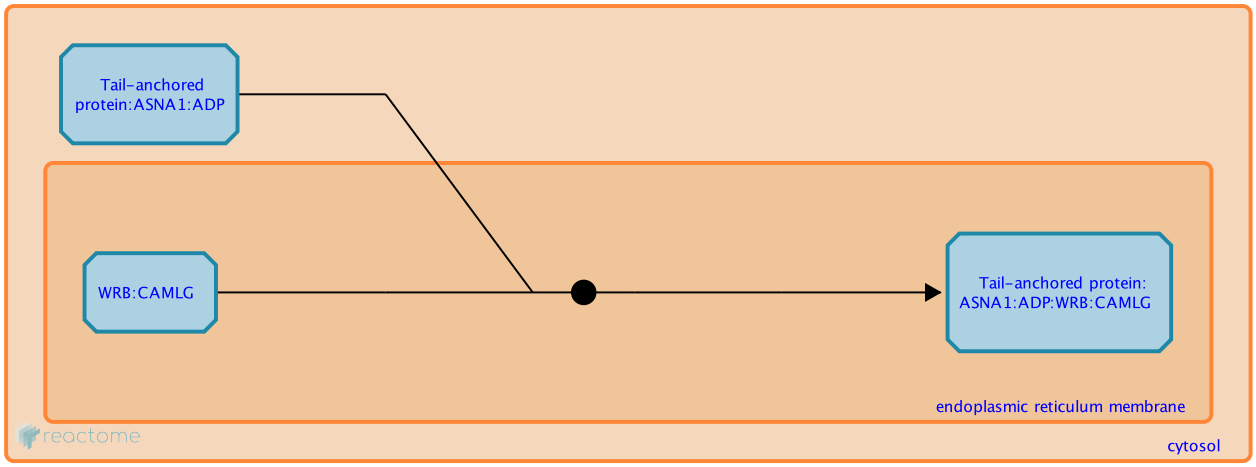
Location: Insertion of tail-anchored proteins into the endoplasmic reticulum membrane

Stable identifier: R-HSA-9609899

Type: binding

Compartments: endoplasmic reticulum membrane

Inferred from: SBH1:GET3:ADP binds GET1:GET2 (Saccharomyces cerevisiae)



A tail-anchored protein bound to ASNA1 dimer (TRC40 dimer) in the cytosol (Stefanovic and Hegde 2007, Favaloro et al. 2008, Favaloro et al. 2010) docks at the WRB:CAMLG complex located in the endoplasmic reticulum membrane (Vilardi et al. 2011, Yamamoto and Sakisaka 2012, Vilardi et al. 2014, Colombo et al. 2016, Pfaff et al. 2016, Vogl et al. 2016). The cytoplasmic coiled coil domain of WRB and the cytoplasmic N-terminal domain of CAMLG compete for binding to ASNA1 (Vilardi et al. 2011, Yamamoto and Sakisaka 2012). As inferred from yeast homologs, ASNA1 hydrolyzes bound ATP at some point, resulting in a change of conformation of ASNA1. This may transfer the tail-anchored protein to WRB:CAMLG, which functions as an insertase.

Preceded by: Tail-anchored protein:SGTA:BAG6:GET4:UBL4A:ASNA1:ATP dissociates and ASNA1 hydrolyzes ATP yielding Tail-anchored protein:ASNA1:ADP

Followed by: Tail-anchored protein:ASNA1:ADP:WRB:CAMLG dissociates yielding Tail-anchored protein in the endoplasmic reticulum membrane

Literature references

Stefanovic, S., Hegde, RS. (2007). Identification of a targeting factor for posttranslational membrane protein insertion into the ER. *Cell, 128*, 1147-59. ↗

Favaloro, V., Spasic, M., Schwappach, B., Dobberstein, B. (2008). Distinct targeting pathways for the membrane insertion of tail-anchored (TA) proteins. *J. Cell. Sci., 121*, 1832-40. ↗

Favaloro, V., Vilardi, F., Schlecht, R., Mayer, MP., Dobberstein, B. (2010). Asna1/TRC40-mediated membrane insertion of tail-anchored proteins. *J. Cell. Sci., 123*, 1522-30. ↗

Yamamoto, Y., Sakisaka, T. (2012). Molecular machinery for insertion of tail-anchored membrane proteins into the endoplasmic reticulum membrane in mammalian cells. *Mol. Cell, 48*, 387-97. ↗

Vilardi, F., Lorenz, H., Dobberstein, B. (2011). WRB is the receptor for TRC40/Asna1-mediated insertion of tail-anchored proteins into the ER membrane. *J. Cell. Sci., 124*, 1301-7. ↗

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2018-11-19	Reviewed	DeLaurentiis, E.

Tail-anchored protein:ASNA1:ADP:WRB:CAMLG dissociates yielding Tail-anchored protein in the endoplasmic reticulum membrane ↗

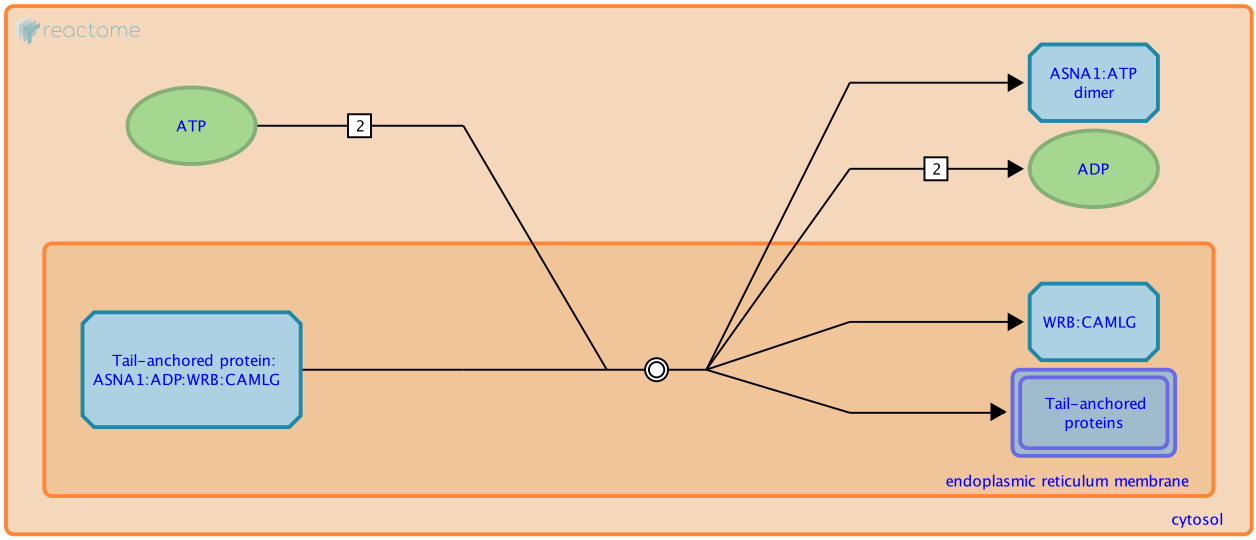
Location: Insertion of tail-anchored proteins into the endoplasmic reticulum membrane

Stable identifier: R-HSA-9609917

Type: dissociation

Compartments: endoplasmic reticulum membrane

Inferred from: SBH1:GET3:ADP:GET1:GET2 dissociates yielding SBH1 in the endoplasmic reticulum membrane (Saccharomyces cerevisiae)



A tail-anchored protein bound to ASNA1 (TRC40) (Stefanovic and Hegde 2007, Favaloro et al. 2008, Favaloro et al. 2010) docked at the WRB:CAMLG complex (also known as the WRB:CAML complex) located in the endoplasmic reticulum membrane is released into the ER membrane in an incompletely characterized reaction (Vilardi et al. 2011, Yamamoto and Sakisaka 2012, Vilardi et al. 2014, Colombo et al. 2016, Pfaff et al. 2016, Vogl et al. 2016). Experiments with yeast homologs (GET1 is the homologue of WRB and GET2 is the homologue of CAMLG) indicate that docking of ASNA1:ADP with WRB:CAMLG results in a conformational change in ASNA1 that causes release of the tail-anchored protein to WRB:CAMLG and then into the membrane (inferred from yeast homologs), ADP dissociates from ASNA1 at some point during the reaction. Exchange of ADP for ATP by ASNA1 then recycles ASNA1 back into the cytosol (inferred from yeast homologs).

Preceded by: Tail-anchored protein:ASNA1:ADP binds WRB:CAMLG at the endoplasmic reticulum membrane

Literature references

Stefanovic, S., Hegde, RS. (2007). Identification of a targeting factor for posttranslational membrane protein insertion into the ER. *Cell, 128*, 1147-59. ↗

Favaloro, V., Spasic, M., Schwappach, B., Dobberstein, B. (2008). Distinct targeting pathways for the membrane insertion of tail-anchored (TA) proteins. *J. Cell. Sci., 121*, 1832-40. ↗

Favaloro, V., Vilardi, F., Schlecht, R., Mayer, MP., Dobberstein, B. (2010). Asna1/TRC40-mediated membrane insertion of tail-anchored proteins. *J. Cell. Sci., 123*, 1522-30. ↗

Yamamoto, Y., Sakisaka, T. (2012). Molecular machinery for insertion of tail-anchored membrane proteins into the endoplasmic reticulum membrane in mammalian cells. *Mol. Cell, 48*, 387-97. ↗

Vilardi, F., Lorenz, H., Dobberstein, B. (2011). WRB is the receptor for TRC40/Asna1-mediated insertion of tail-anchored proteins into the ER membrane. *J. Cell. Sci., 124*, 1301-7. ↗

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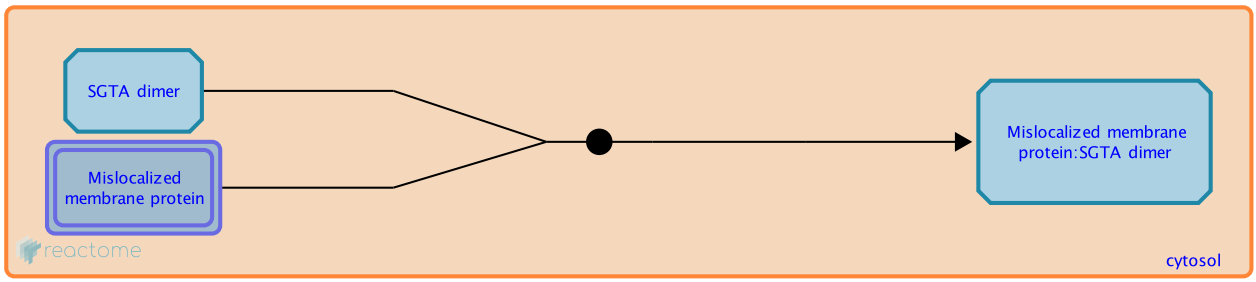
SGTA binds mislocalized membrane protein ↗

Location: Insertion of tail-anchored proteins into the endoplasmic reticulum membrane

Stable identifier: R-HSA-9617595

Type: binding

Compartments: cytosol



Membrane proteins are not delivered to membranes with complete efficiency and a portion can end up mislocalized to the cytosol. SGTA binds the hydrophobic regions of such mislocalized proteins that are exposed to the cytosol (Leznicki and High 2012, Xu et al. 2012, Wunderly et al. 2014, Shao et al. 2017). Client proteins of SGTA include both tail-anchored proteins destined for insertion into the endoplasmic reticulum membrane (Leznicki et al. 2013) and inappropriately localized proteins such as cytosolic PRNP (PrP) (Leznicki and High 2012), which is normally located in the plasma membrane. Mislocalized proteins bound by SGTA can be routed to the proteasome via ubiquitination by the BAG6 complex (BAG6:GET4:UBL4A) (Shao et al. 2017).

Literature references

Shao, S., Rodrigo-Brenni, MC., Kivlen, MH., Hegde, RS. (2017). Mechanistic basis for a molecular triage reaction. *Science, 355*, 298-302. ↗

Leznicki, P., High, S. (2012). SGTA antagonizes BAG6-mediated protein triage. *Proc. Natl. Acad. Sci. U.S.A., 109*, 19214-9. ↗

Xu, Y., Cai, M., Yang, Y., Huang, L., Ye, Y. (2012). SGTA recognizes a noncanonical ubiquitin-like domain in the Bag6-Ubl4A-Trc35 complex to promote endoplasmic reticulum-associated degradation. *Cell Rep, 2*, 1633-44. ↗

Wunderley, L., Leznicki, P., Payapilly, A., High, S. (2014). SGTA regulates the cytosolic quality control of hydrophobic substrates. *J. Cell. Sci., 127*, 4728-39. ↗

Leznicki, P., Roebuck, QP., Wunderley, L., Clancy, A., Krysztofinska, EM., Isaacson, RL. et al. (2013). The association of BAG6 with SGTA and tail-anchored proteins. *PLoS ONE, 8*, e59590. ↗

Editions

2018-08-28	Authored, Edited	May, B.
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BAG6:GET4:UBL4A binds mislocalized membrane protein:SGTA and ASNA1:ATP ↗

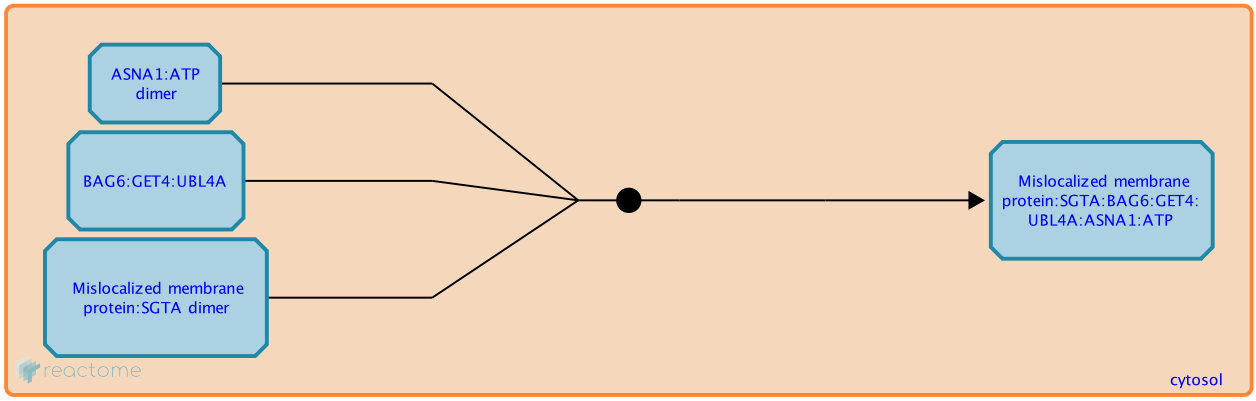
Location: Insertion of tail-anchored proteins into the endoplasmic reticulum membrane

Stable identifier: R-HSA-9617596

Type: binding

Compartments: cytosol

Inferred from: BAG6:GET4:UBL4A binds SEC61B (Homo sapiens)



SGTA is believed to initially bind exposed hydrophobic regions of proteins (client proteins) in the cytosol and then associate with the BAG6 complex (BAG6:GET4:UBL4A) and ASNA1 (Mariappan et al. 2010, Hessa et al. 2011, Leznicki et al. 2012, Wunderly et al. 2014, Shao et al. 2017). If the client protein is not efficiently transferred to ASNA1 then the client protein is transferred to BAG6 (Shao et al. 2017), which has been demonstrated to bind hydrophobic regions of proteins and appears to prevent their aggregation prior to proteasomal degradation (Wang et al. 2011). The efficiency of transfer of a client protein to ASNA1 appears to be determined by the sequence of the hydrophobic domain (Hessa et al. 2011). SGTA is not a stable component of the BAG6 complex (Marriapan et al. 2010) and SGTA and RNF126 compete for the same binding site on BAG6 (Krysztofinska et al. 2016).

Literature references

Leznicki, P., High, S. (2012). SGTA antagonizes BAG6-mediated protein triage. *Proc. Natl. Acad. Sci. U.S.A., 109*, 19214-9. ↗

Wunderley, L., Leznicki, P., Payapilly, A., High, S. (2014). SGTA regulates the cytosolic quality control of hydrophobic substrates. *J. Cell. Sci., 127*, 4728-39. ↗

Shao, S., Rodrigo-Brenni, MC., Kivlen, MH., Hegde, RS. (2017). Mechanistic basis for a molecular triage reaction. *Science, 355*, 298-302. ↗

Krysztofinska, EM., Martínez-Lumbreras, S., Thapaliya, A., Evans, NJ., High, S., Isaacson, RL. (2016). Structural and functional insights into the E3 ligase, RNF126. *Sci Rep, 6*, 26433. ↗

Hessa, T., Sharma, A., Mariappan, M., Eshleman, HD., Gutierrez, E., Hegde, RS. (2011). Protein targeting and degradation are coupled for elimination of mislocalized proteins. *Nature, 475*, 394-7. ↗

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2018-11-07	Reviewed	Schwappach, B., Farkas, Á., DeLaurentiis, E.

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