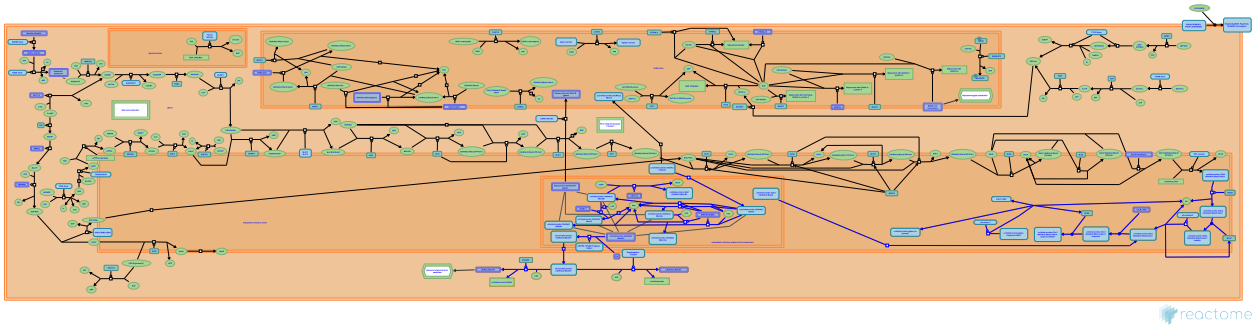
N-glycan trimming in the ER and Calnexin/Calreticulin cycle



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18/05/2024

Introduction

Reactome is open-source, open access, manually curated and peer-reviewed pathway database. Pathway annotations are authored by expert biologists, in collaboration with Reactome editorial staff and cross-referenced to many bioinformatics databases. A system of evidence tracking ensures that all assertions are backed up by the primary literature. Reactome is used by clinicians, geneticists, genomics researchers, and molecular biologists to interpret the results of high-throughput experimental studies, by bioinformaticians seeking to develop novel algorithms for mining knowledge from genomic studies, and by systems biologists building predictive models of normal and disease variant pathways.
The development of Reactome is supported by grants from the US National Institutes of Health (P41 HG003751), University of Toronto (CFREF Medicine by Design), European Union (EU STRP, EMI-CD), and the European Molecular Biology Laboratory (EBI Industry program).

Literature references

Fabregat, A., Sidiropoulos, K., Viteri, G., Forner, O., Marin-Garcia, P., Arnau, V. et al. (2017). Reactome pathway analysis: a high-performance in-memory approach. *BMC bioinformatics, 18*, 142. ↗

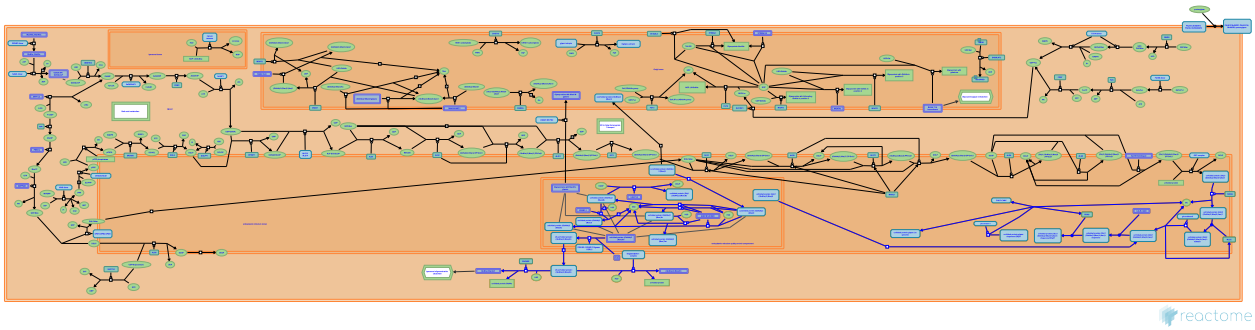
Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

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

Fabregat, A., Korninger, F., Viteri, G., Sidiropoulos, K., Marin-Garcia, P., Ping, P. et al. (2018). Reactome graph database: Efficient access to complex pathway data. *PLoS computational biology, 14*, e1005968. ↗

N-glycan trimming in the ER and Calnexin/Calreticulin cycle ↗

Stable identifier: R-HSA-532668



After being synthesized in the ER membrane the 14-sugars lipid-linked oligosaccharide is co-translationally transferred to an unfolded protein, as described in the previous steps. After this point the N-glycan is progressively trimmed of the three glucoses and some of the mannoses before the protein is transported to the cis-Golgi. The role of these trimming reactions is that the N-glycan attached to an unfolded glycoprotein in the ER assume the role of 'tags' that direct the interactions of the glycoprotein with different elements that mediate its folding. The removal of the two outer glucoses leads to an N-glycan with only one glucose, which is a signal for the binding of either one of two chaperone proteins, calnexin (CNX) and calreticulin (CRT). These chaperones provide an environment where the protein can fold more easily. The interaction with these proteins is not transient and is terminated by the trimming of the last remaining glucose, after which the glycoprotein is released from CNX or CRT and directed to the ER Quality Control compartment (ERQC) if it still has folding defects, or transported to the Golgi if the folding is correct. The involvement of N-glycans in the folding quality control of proteins in the ER explains why this form of glycosylation is so important, and why defects in the enzymes involved in these reactions are frequently associated with congenital diseases. However, there are many unknown points in this process, as it is known that even proteins without N-glycosylation sites can be folded properly (Caramelo JJ and Parodi AJ, 2008).

Literature references

Parodi, AJ., Caramelo, JJ. (2008). Getting in and out from calnexin/calreticulin cycles. *J Biol Chem, 283*, 10221-5. ↗

Editions

2009-11-10	Authored	Dall'Olio, GM.
2010-03-02	Edited	Jassal, B.
2010-08-17	Reviewed	Gagneux, P.

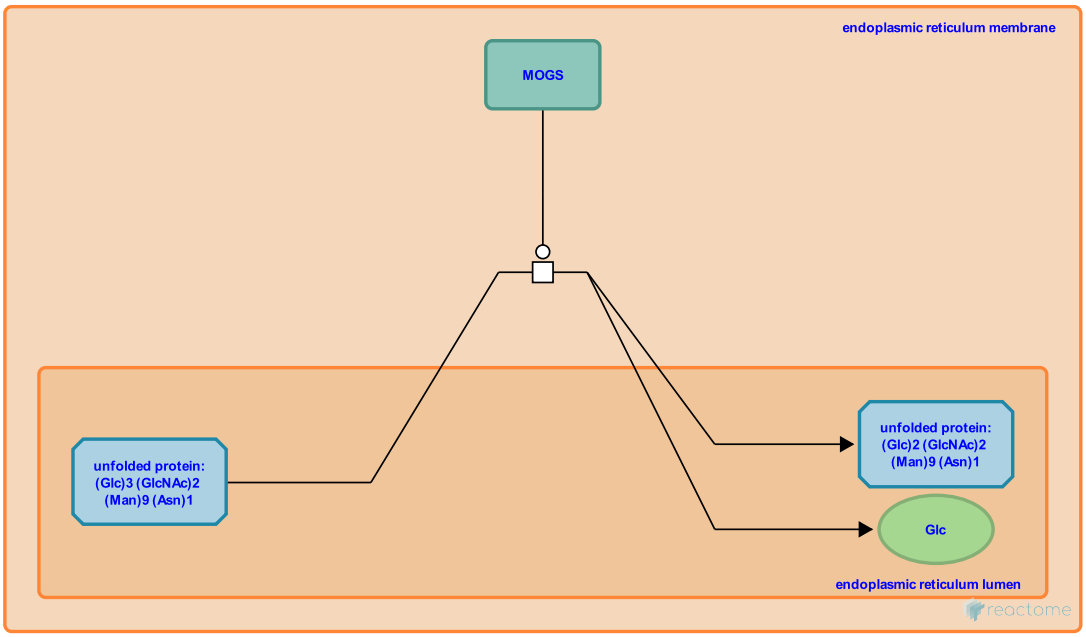
Trimming of the first glucose by by mannosyl-oligosaccharide glucosidase ↗

Location: N-glycan trimming in the ER and Calnexin/Calreticulin cycle

Stable identifier: R-HSA-532678

Type: transition

Compartments: endoplasmic reticulum membrane, endoplasmic reticulum lumen



After the glycosylated precursor is attached to the protein, the outer alpha-1,2-linked glucose is removed by by mannosyl-oligosaccharide glucosidase (MOGS, GCS1 in yeast). This is a mandatory step for the protein folding control and glycan extension, and defects in MOGS are associated with congenital disorder of glycosylation type IIb (CDGIIb) (De Praeter et al. 2000, Völker et al. 2002).

Followed by: Binding of Malectin

Literature references

Espeel, MF., Chan, NW., Nuytinck, LK., Martin, JJ., Gerwig, GJ., Kamerling, JP. et al. (2000). A novel disorder caused by defective biosynthesis of N-linked oligosaccharides due to glucosidase I deficiency. *Am J Hum Genet, 66*, 1744-56. ↗

Hardt, B., Kalz-Füller, B., Bause, E., De Praeter, CM., Breuer, W., Van Coster, RN. et al. (2002). Processing of N-linked carbohydrate chains in a patient with glucosidase I deficiency (CDG type IIb). *Glycobiology, 12*, 473-83. ↗

Editions

2009-11-10	Authored	Dall'Olio, GM.
2010-03-02	Edited	Jassal, B.
2010-08-17	Reviewed	Gagneux, P.

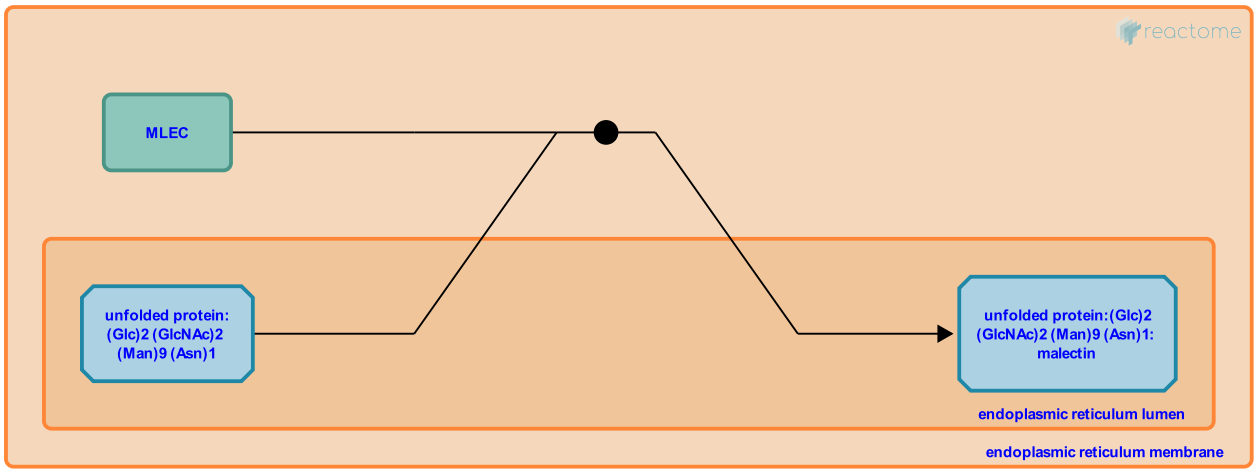
Binding of Malectin ↗

Location: N-glycan trimming in the ER and Calnexin/Calreticulin cycle

Stable identifier: R-HSA-901006

Type: binding

Compartments: endoplasmic reticulum membrane, endoplasmic reticulum lumen



A recently discovered protein called malectin is known to recognize the Glc(2)Man(9)GlcNAc(2) glycan (Schallus T et al, 2008). The exact role of this interaction is not clear but malectin is thought to regulate the availability of this substrate to glucosidase II, or to act as a chaperone to stabilize the unfolded protein.

Preceded by: Trimming of the first glucose by by mannosyl-oligosaccharide glucosidase

Followed by: Removal of the second glucose by glucosidase II

Literature references

Liu, Y., Palma, AS., Simpson, JC., Muhle-Goll, C., Feizi, T., Gibson, TJ. et al. (2008). Malectin: a novel carbohydrate-binding protein of the endoplasmic reticulum and a candidate player in the early steps of protein N-glycosylation . *Mol Biol Cell, 19*, 3404-14. ↗

Editions

2009-11-10	Authored	Dall'Olio, GM.
2010-07-02	Edited	Jassal, B.
2010-08-17	Reviewed	Gagneux, P.

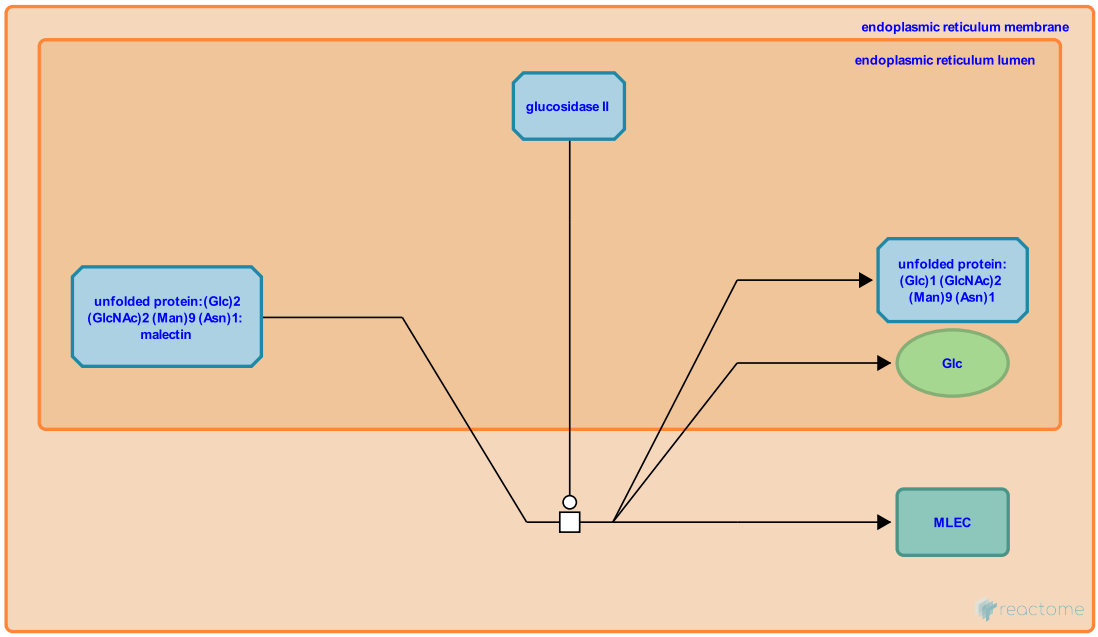
Removal of the second glucose by glucosidase II ↗

Location: N-glycan trimming in the ER and Calnexin/Calreticulin cycle

Stable identifier: R-HSA-532667

Type: transition

Compartments: endoplasmic reticulum membrane, endoplasmic reticulum lumen



A second glucose is removed from the N-linked glycan. The removal of an alpha1,3 glucose moiety is catalyzed by glucosidase II, a complex composed of an alpha subunit (GANAB) with catalytic activity and a beta subunit (GLU2B; PRKCSH), probably with regulatory and recruitment function (Pelletier MF et al, 2000). GANAB can exist in two different isoforms, but both are able to catalyze both of the reactions catalyzed by glucosidase II (Pelletier MF et al, 2000). Defects in PRKCSH are a cause of polycystic liver disease (PCLD).

Preceded by: Binding of Malectin

Literature references

Sevigny, G., Pelletier, MF., Thomas, DY., Menard, R., Marcil, A., Bergeron, JJ. et al. (2000). The heterodimeric structure of glucosidase II is required for its activity, solubility, and localization in vivo. *Glycobiology, 10*, 815-27. ↗

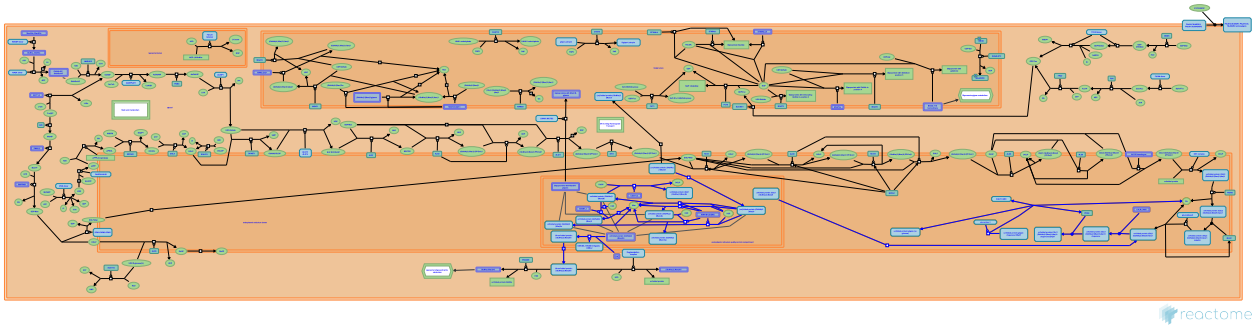
Editions

2009-11-10	Authored	Dall'Olio, GM.
2010-03-02	Edited	Jassal, B.
2010-08-17	Reviewed	Gagneux, P.

Calnexin/calreticulin cycle ↗

Location: N-glycan trimming in the ER and Calnexin/Calreticulin cycle

Stable identifier: R-HSA-901042



The unfolded protein is recognized by a chaperon protein (calnexin or calreticulin) and the folding process starts. The binding of these protein requires a mono-glucosylated glycan (Caramelo JJ and Parodi AJ, 2008) and lectin-based interaction with client proteins is the predominant contributor to chaperone activity of calreticulin (inferred from the mouse homolog in Lum et al. 2016).

Literature references

Kozlov, G., Lum, R., Chapman, DC., Hong, SJ., Williams, DB., Ahmad, S. (2016). Contributions of the Lectin and Polypeptide Binding Sites of Calreticulin to Its Chaperone Functions in Vitro and in Cells. *J Biol Chem, 291*, 19631-41. ↗

Parodi, AJ., Caramelo, JJ. (2008). Getting in and out from calnexin/calreticulin cycles. *J Biol Chem, 283*, 10221-5. ↗

Editions

2009-11-10	Authored	Dall'Olio, GM.
2010-07-02	Edited	Jassal, B.
2010-08-17	Reviewed	Gagneux, P.

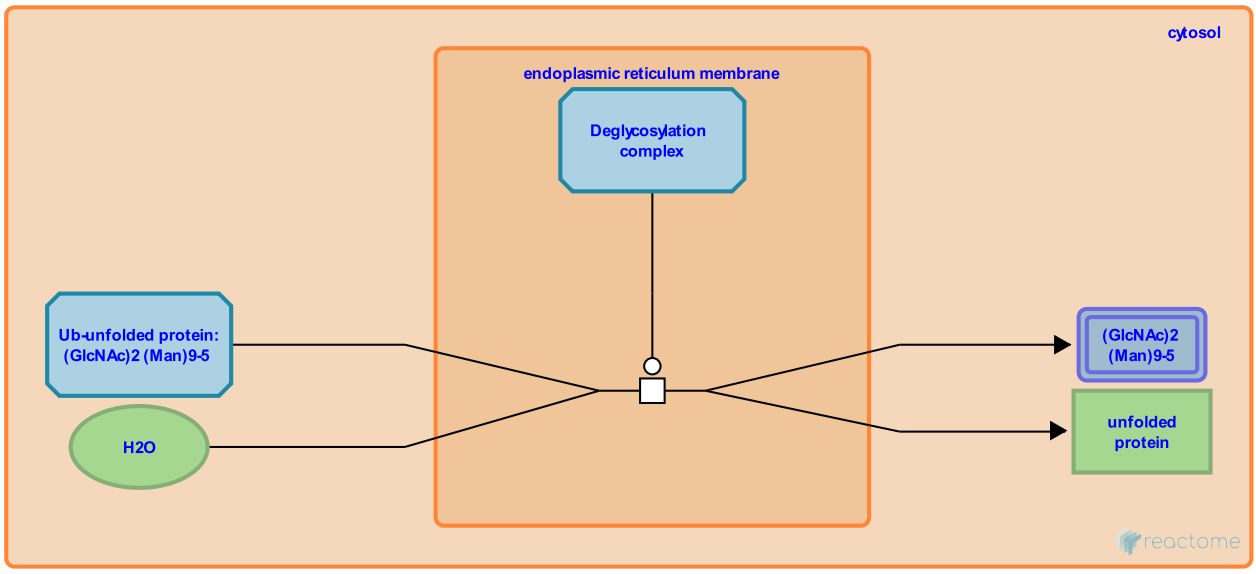
Deglycosylation complex hydrolyses N-glycans from unfolded glycoproteins ↗

Location: N-glycan trimming in the ER and Calnexin/Calreticulin cycle

Stable identifier: R-HSA-8850594

Type: transition

Compartments: endoplasmic reticulum membrane, cytosol



Peptide-N(4)-(N-acetyl-beta-glucosaminyl)asparagine amidase (NGLY1, aka PNGase) is a cytosolic peptide:N-glycanase which acts on N-glycoproteins generating free, unconjugated N-glycans and deglycosylated peptides in which the N-glycosylated asparagine residues are converted to aspartates. It is involved in the quality control system for misfolded glycoproteins exported to the cytosol that need to be targeted for degradation (Suzuki et al. 2016). NGLY1 is part of a complex that couples retrotranslocation, ubiquitination and deglycosylation. It is probably composed of NGLY1, UBX domain-containing protein 1 (UBXN1 aka SAKS1), E3 ubiquitin-protein ligase (AMFR), transitional endoplasmic reticulum ATPase (VCP), derlin-1 (DERL1), 26S protease regulatory subunit 4 (PSMC1) and UV excision repair protein RAD23 homolog B (RAD23B). NGLY1 interacts with the proteasome components RAD23B and PSMC1, directly with VCP and with DERL1, bringing it close to the endoplasmic reticulum membrane (Katiyar & Lennarz 2004, Song et al. 2005, McNeill et al. 2004, Ye et al. 2004, Katiyar et al. 2005).

Literature references

Song, BL., Sever, N., DeBose-Boyd, RA. (2005). Gp78, a membrane-anchored ubiquitin ligase, associates with Insig-1 and couples sterol-regulated ubiquitination to degradation of HMG CoA reductase. *Mol. Cell, 19*, 829-40. ↗

Cohen, P., Arthur, JS., Cuenda, A., Knebel, A., McNeill, H. (2004). A novel UBA and UBX domain protein that binds polyubiquitin and VCP and is a substrate for SAPKs. *Biochem. J., 384*, 391-400. ↗

Huang, C., Fujihira, H., Suzuki, T. (2016). The cytoplasmic peptide:N-glycanase (NGLY1) - Structure, expression and cellular functions. *Gene, 577*, 1-7. ↗

Li, G., Katiyar, S., Lennarz, WJ. (2004). A complex between peptide:N-glycanase and two proteasome-linked proteins suggests a mechanism for the degradation of misfolded glycoproteins. *Proc. Natl. Acad. Sci. U.S.A., 101*, 13774-9. ↗

Joshi, S., Katiyar, S., Lennarz, WJ. (2005). The retrotranslocation protein Derlin-1 binds peptide:N-glycanase to the endoplasmic reticulum. *Mol. Biol. Cell, 16*, 4584-94. ↗

Editions

2015-12-24	Authored, Edited	Jassal, B.
2016-04-05	Reviewed	D'Eustachio, P.

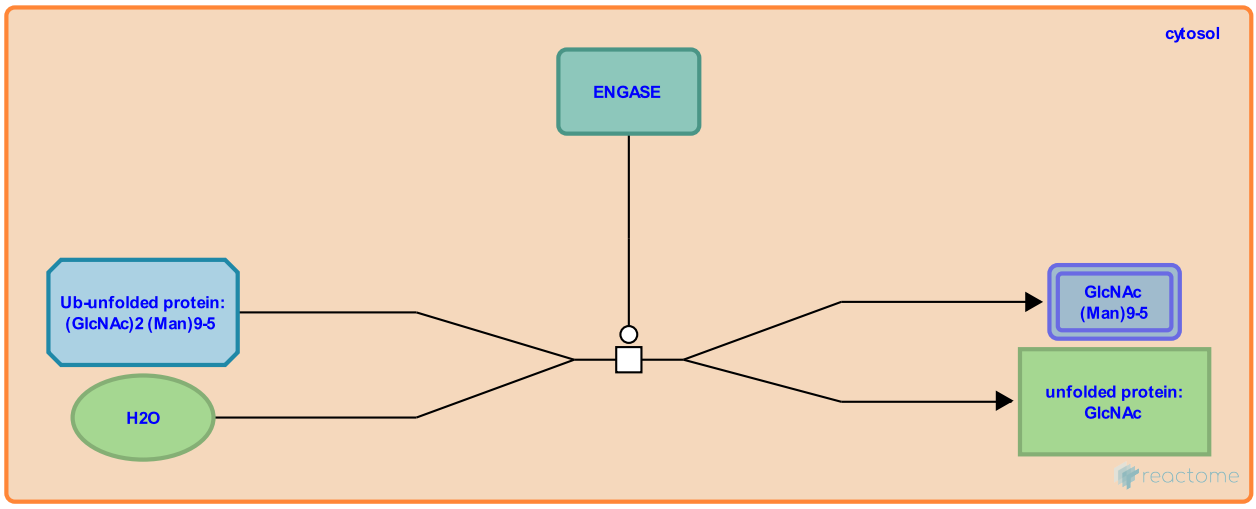
ENGASE hydrolyses unfolded protein:(GlcNAc)2 (Man(9-5) ↗

Location: N-glycan trimming in the ER and Calnexin/Calreticulin cycle

Stable identifier: R-HSA-8853379

Type: transition

Compartments: cytosol



Two cytosolic deglycosylating systems can generate free oligosaccharides from glycoproteins; a deglycosylation complex that hydrolyses the whole glycan from an unfolded protein and cytosolic endo-beta-N-acetylglucosaminidase (ENGASE) that catalyses the endohydrolysis of -(Man(GlcNAc)2)Asn- structures in glycoproteins, leaving one N-acetyl-D-glucosamine (GlcNAc) residue attached to the protein (Suzuki et al. 2002). Glycans with a single GlcNAc at their reducing termini need to be further degraded by a cytosolic alpha-mannosidase, MAN2C1.

Literature references

Emori, Y., Kitajima, K., Inoue, Y., Sugimoto, S., Inoue, S., Yano, K. et al. (2002). Endo-beta-N-acetylglucosaminidase, an enzyme involved in processing of free oligosaccharides in the cytosol. *Proc. Natl. Acad. Sci. U.S.A., 99*, 9691-6. ↗

Editions

2016-01-22	Authored, Edited	Jassal, B.
2016-04-05	Reviewed	D'Eustachio, P.

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