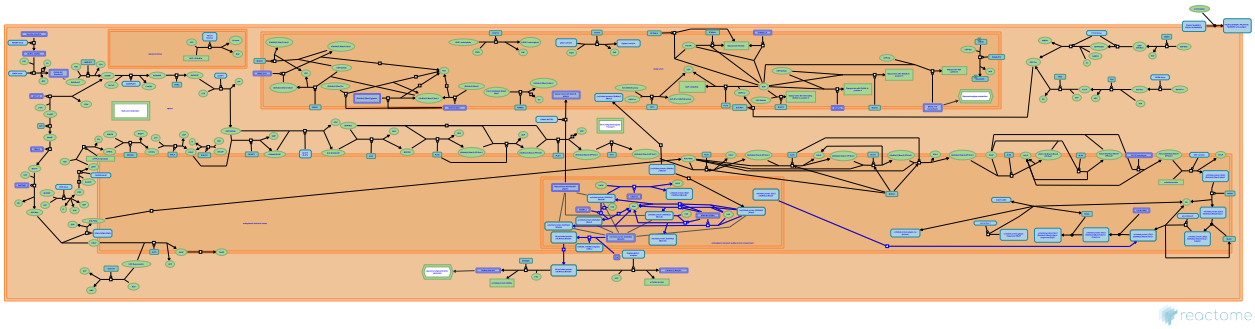
ER Quality Control Compartment (ERQC)



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This is just an excerpt of a full-length report for this pathway. To access the complete report, please download it at the Reactome Textbook.

06/05/2024

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. ↗

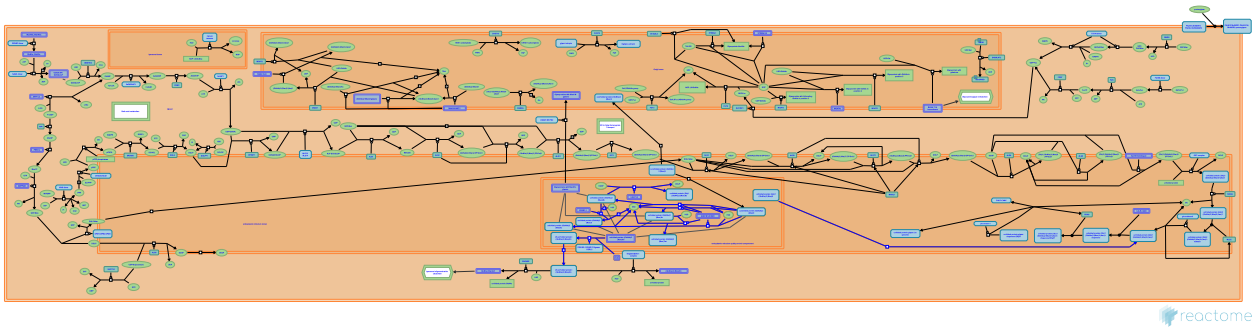
Fabregat, A., Korninger, F., Viteri, G., Sidiropoulos, K., Marin-Garcia, P., Ping, P. et al. (2018). Reactome graph database: Efficient access to complex pathway data. *PLoS computational biology, 14*, e1005968. ↗

Reactome database release: 88

This document contains 1 pathway and 9 reactions (see Table of Contents)

ER Quality Control Compartment (ERQC) ↗

Stable identifier: R-HSA-901032



Proteins that are released from the CNX or CRT complex with folding defects accumulate in a compartment of the ER called ERQC (Kamhi-Nesher et al. 2001). Here, the enzymes UGGG1 or UGGG2 are able to recognize glycoproteins with minor folding process and re-add the glucose on the alpha,1,3 branch; this is a signal for the transport of these glycoproteins back to the ER, where they can interact again with CNX or CRT in order to achieve a correct folding. At the same time that the glycoprotein is in the ERQC, the enzyme ER mannosidase I progressively removes the mannoses at positions 1A, 2A, B, C on N-glycans; when the mannose on 1A is trimmed, UDP-Glc:glycoprotein glucosyltransferases 1 and 2 (UGGT1 and 2) are no longer able to re-add the glucose, and therefore the protein is destined for ERAD. Glycoproteins subject to endoplasmic reticulum-associated degradation (ERAD) undergo reglucosylation, deglucosylation, and mannose trimming to yield Man6GlcNAc2 and Man5GlcNAc2. These structures lack the mannose residue that is the acceptor of glucose transferred by UGGT1 and 2. For years it has been thought that the removal of the mannose in position B of the N-glycan was the signal to direct proteins to degradation. However, this mechanism has been described better by Avezov et al (Avezov et al. 2008) and it has been demonstrated that even glycoproteins with Man8 or Man7 glycans can be re-glucosylated and interact again with CNX or CRT (for a review on this topic, see Lederkremer 2009 and Maattanen P et al, 2010).

Literature references

Lederkremer, GZ. (2009). Glycoprotein folding, quality control and ER-associated degradation. *Curr Opin Struct Biol, 19*, 515-23. ↗

Thomas, DY., Bergeron, JJ., Gehring, K., Määttänen, P. (2010). Protein quality control in the ER: the recognition of misfolded proteins. *Semin Cell Dev Biol, 21*, 500-11. ↗

Herscovics, A., Ehrlich, M., Lederkremer, GZ., Avezov, E., Frenkel, Z. (2008). Endoplasmic reticulum (ER) mannosidase I is compartmentalized and required for N-glycan trimming to Man5-6GlcNAc2 in glycoprotein ER-associated degradation. *Mol Biol Cell, 19*, 216-25. ↗

Fromm, SV., Ehrlich, R., Lederkremer, GZ., Shenkman, M., Kamhi-Nesher, S., Tolchinsky, S. (2001). A novel quality control compartment derived from the endoplasmic reticulum. *Mol Biol Cell, 12*, 1711-23. ↗

Editions

2009-11-10	Authored	Dall'Olio, GM.
2010-07-02	Edited	Jassal, B.
2010-11-18	Reviewed	Gagneux, P.
2015-06-03	Revised	Jassal, B.

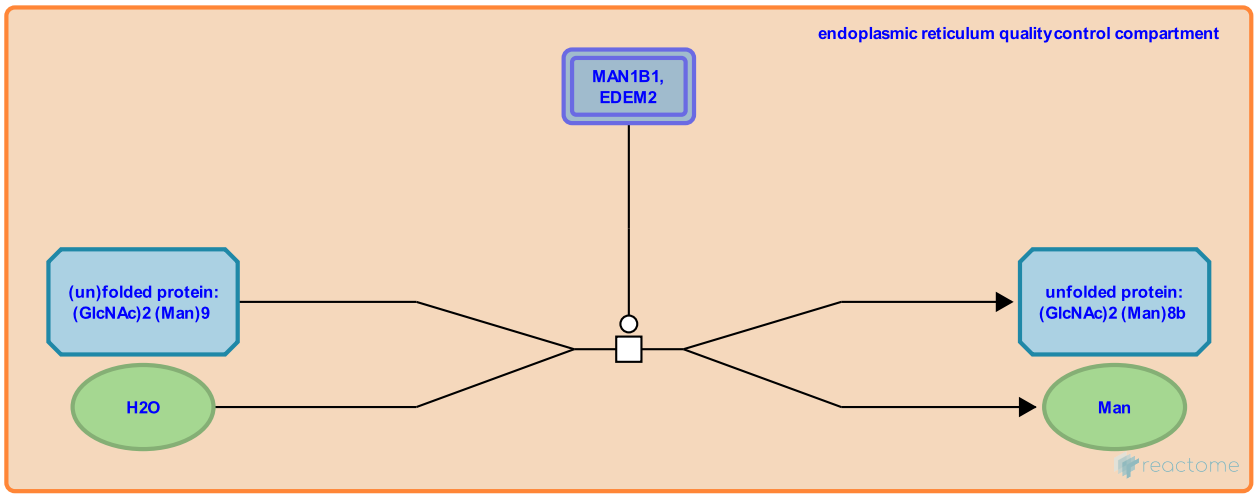
MAN1B1,EDEM2 hydrolyse 1,2-linked mannose (b branch)

Location: ER Quality Control Compartment (ERQC)

Stable identifier: R-HSA-901074

Type: transition

Compartments: endoplasmic reticulum quality control compartment



The enzyme ER Man I can slowly trim up to four of the mannoses on the N-glycan on unfolded proteins accumulated in the ER. This step describes the removal of the mannose in the B position (Gonzalez et al. 1999, Karaveg et al. 2005, Avezov et al. 2008). The ER degradation-enhancing alpha-mannosidase-like protein 2 (EDEM2) is also able to hydrolyse the alpha-1,2-mannose from (GlcNAc)2 (Man)9 to form (GlcNAc)2 (Man)8b (Ninagawa et al. 2014).

Followed by: UGGT1,2 transfers glucose from DbGP to (un)folded protein:(GlcNAc)2 (Man)8b

Literature references

Herscovics, A., Ehrlich, M., Lederkremer, GZ., Avezov, E., Frenkel, Z. (2008). Endoplasmic reticulum (ER) mannosidase I is compartmentalized and required for N-glycan trimming to Man5-6GlcNAc2 in glycoprotein ER-associated degradation. *Mol Biol Cell, 19*, 216-25.

Karaveg, K., Gonzalez, DS., Moremen, KW., Lal, A., Vandersall-Nairn, AS. (1999). Identification, expression, and characterization of a cDNA encoding human endoplasmic reticulum mannosidase I, the enzyme that catalyzes the first mannose trimming step in mammalian Asn-linked oligosaccharide biosynthesis. *J Biol Chem, 274*, 21375-86.

Liu, ZJ., Karaveg, K., Moremen, KW., Glushka, J., Tempel, W., Wang, BC. et al. (2005). Mechanism of class 1 (glycosylhydrolase family 47) {alpha}-mannosidases involved in N-glycan processing and endoplasmic reticulum quality control. *J. Biol. Chem., 280*, 16197-207.

Kamiya, Y., Takeda, S., Ishikawa, T., Sakuma, T., Sumitomo, Y., Okada, T. et al. (2014). EDEM2 initiates mammalian glycoprotein ERAD by catalyzing the first mannose trimming step. *J. Cell Biol., 206*, 347-56.

Editions

2009-11-10	Authored	Dall'Olio, GM.
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2015-06-03	Revised	Jassal, B.

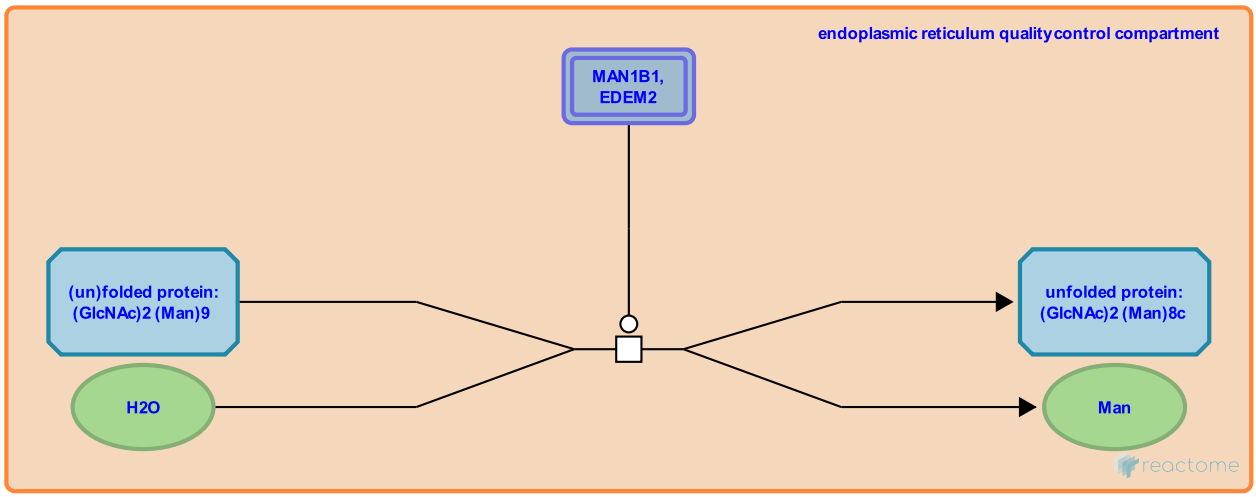
MAN1B1 hydrolyses 1,2-linked mannose (c branch) ↗

Location: ER Quality Control Compartment (ERQC)

Stable identifier: R-HSA-901039

Type: transition

Compartments: endoplasmic reticulum quality control compartment



The enzyme ER Man I can slowly trim up to four of the mannoses on the N-glycan on unfolded proteins accumulated in the ER. This step describes the removal of the mannose in the C position (Gonzalez et al. 1999, Karaveg et al. 2005, Avezov et al. 2008).

Followed by: UGGT1,2 transfers glucose from DbGP to (un)folded protein:(GlcNAc)2 (Man)8b

Literature references

Herscovics, A., Ehrlich, M., Lederkremer, GZ., Avezov, E., Frenkel, Z. (2008). Endoplasmic reticulum (ER) mannosidase I is compartmentalized and required for N-glycan trimming to Man5-6GlcNAc2 in glycoprotein ER-associated degradation. *Mol Biol Cell, 19*, 216-25. ↗

Karaveg, K., Gonzalez, DS., Moremen, KW., Lal, A., Vandersall-Nairn, AS. (1999). Identification, expression, and characterization of a cDNA encoding human endoplasmic reticulum mannosidase I, the enzyme that catalyzes the first mannose trimming step in mammalian Asn-linked oligosaccharide biosynthesis. *J Biol Chem, 274*, 21375-86. ↗

Liu, ZJ., Karaveg, K., Moremen, KW., Glushka, J., Tempel, W., Wang, BC. et al. (2005). Mechanism of class 1 (glycosylhydrolase family 47) {alpha}-mannosidases involved in N-glycan processing and endoplasmic reticulum quality control. *J. Biol. Chem., 280*, 16197-207. ↗

Editions

2009-11-10	Authored	Dall'Olio, GM.
2010-07-02	Edited	Jassal, B.
2010-11-18	Reviewed	Gagneux, P.
2015-06-03	Revised	Jassal, B.

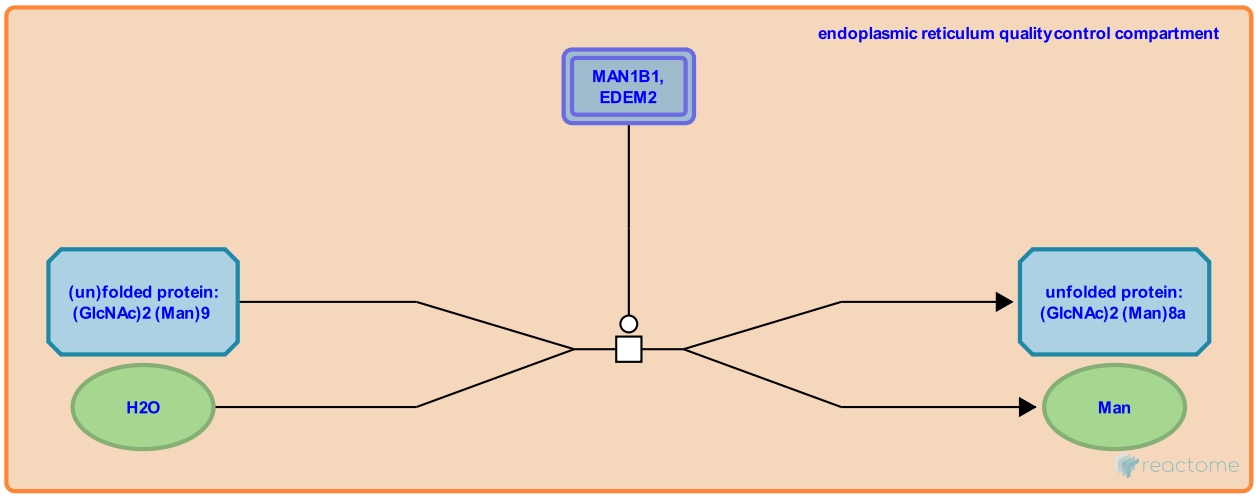
MAN1B1 hydrolyses 1,2-linked mannose (a branch) ↗

Location: ER Quality Control Compartment (ERQC)

Stable identifier: R-HSA-901024

Type: transition

Compartments: endoplasmic reticulum quality control compartment



The enzyme ER Man I can slowly trim up to four of the mannoses on the N-glycan on unfolded proteins accumulated in the ER. This step describes the removal of the mannose in the A position (Hirao et al, 2006; Frenkel et al, 2003).

Followed by: MAN1B1 hydrolyses a second 1,2-linked mannose (a branch)

Literature references

Herscovics, A., Ehrlich, M., Lederkremer, GZ., Avezov, E., Frenkel, Z. (2008). Endoplasmic reticulum (ER) mannosidase I is compartmentalized and required for N-glycan trimming to Man5-6GlcNAc2 in glycoprotein ER-associated degradation. *Mol Biol Cell, 19*, 216-25. ↗

Karaveg, K., Gonzalez, DS., Moremen, KW., Lal, A., Vandersall-Nairn, AS. (1999). Identification, expression, and characterization of a cDNA encoding human endoplasmic reticulum mannosidase I, the enzyme that catalyzes the first mannose trimming step in mammalian Asn-linked oligosaccharide biosynthesis. *J Biol Chem, 274*, 21375-86. ↗

Liu, ZJ., Karaveg, K., Moremen, KW., Glushka, J., Tempel, W., Wang, BC. et al. (2005). Mechanism of class 1 (glycosylhydrolase family 47) {alpha}-mannosidases involved in N-glycan processing and endoplasmic reticulum quality control. *J. Biol. Chem., 280*, 16197-207. ↗

Editions

2009-11-10	Authored	Dall'Olio, GM.
2010-07-02	Edited	Jassal, B.
2010-11-18	Reviewed	Gagneux, P.
2015-06-03	Revised	Jassal, B.

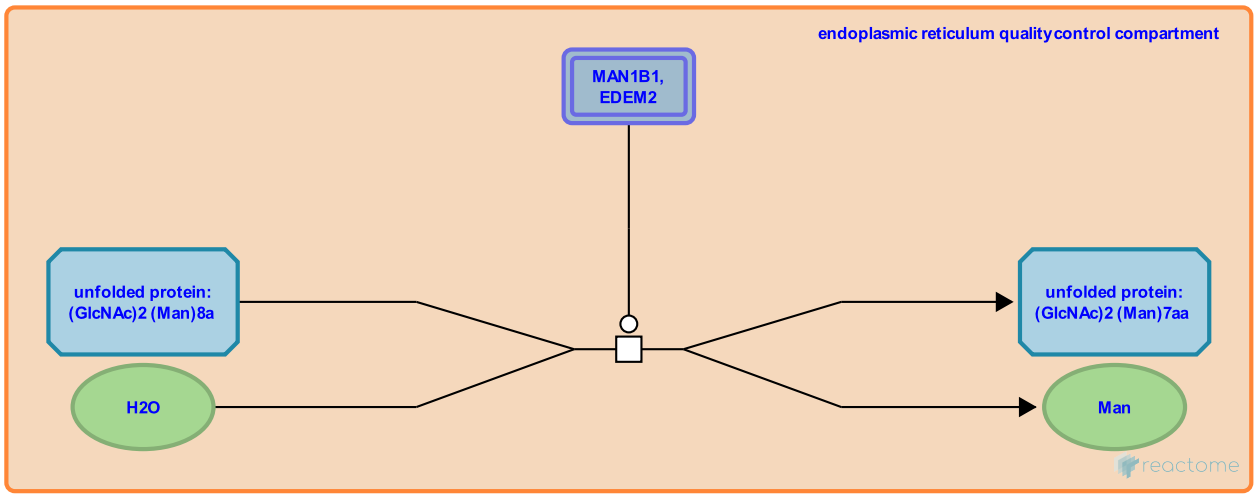
MAN1B1 hydrolyses a second 1,2-linked mannose (a branch) ↗

Location: ER Quality Control Compartment (ERQC)

Stable identifier: R-HSA-901036

Type: transition

Compartments: endoplasmic reticulum quality control compartment



Removal of the second mannose on the alpha 1,3 branch (Frenzel Z et al, 2003).

Preceded by: MAN1B1 hydrolyses 1,2-linked mannose (a branch)

Literature references

Herscovics, A., Ehrlich, M., Lederkremer, GZ., Avezov, E., Frenkel, Z. (2008). Endoplasmic reticulum (ER) mannosidase I is compartmentalized and required for N-glycan trimming to Man5-6GlcNAc2 in glycoprotein ER-associated degradation. *Mol Biol Cell, 19*, 216-25. ↗

Karaveg, K., Gonzalez, DS., Moremen, KW., Lal, A., Vandersall-Nairn, AS. (1999). Identification, expression, and characterization of a cDNA encoding human endoplasmic reticulum mannosidase I, the enzyme that catalyzes the first mannose trimming step in mammalian Asn-linked oligosaccharide biosynthesis. *J Biol Chem, 274*, 21375-86. ↗

Liu, ZJ., Karaveg, K., Moremen, KW., Glushka, J., Tempel, W., Wang, BC. et al. (2005). Mechanism of class 1 (glycosylhydrolase family 47) {alpha}-mannosidases involved in N-glycan processing and endoplasmic reticulum quality control. *J. Biol. Chem., 280*, 16197-207. ↗

Editions

2009-11-10	Authored	Dall'Olio, GM.
2010-07-02	Edited	Jassal, B.
2010-11-18	Reviewed	Gagneux, P.
2015-06-03	Revised	Jassal, B.

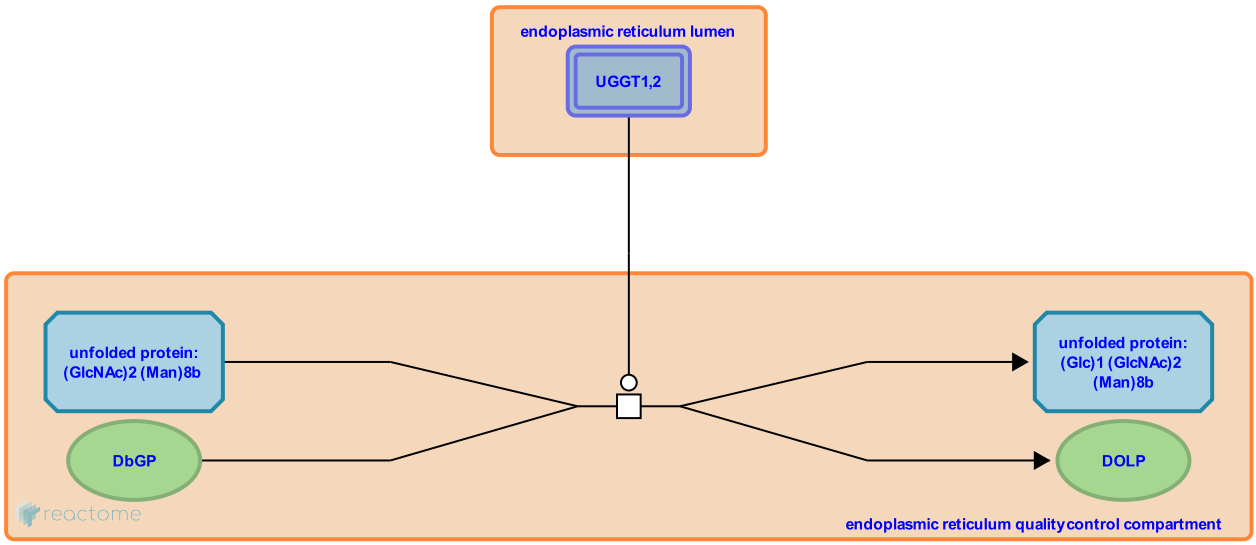
UGGT1,2 transfers glucose from DbGP to (un)folded protein:(GlcNAc)2 (Man)8b ↗

Location: ER Quality Control Compartment (ERQC)

Stable identifier: R-HSA-548884

Type: transition

Compartments: endoplasmic reticulum quality control compartment



The UDP-glucose:glycoprotein glucosyltransferases 1 and 2 (UGGT1 and 2) are able to distinguish proteins with minor folding defects in the ERQC and reglucosylate them, by transferring a glucose (from dolichyl beta-D-glucosyl phosphate, DbGP) onto the alpha 1,3 mannose of the b (or c, not shown here) branch (Arnold et al. 2000, Arnold et al. 2003). The major affinity of these enzymes for proteins with minor folding defects has been demonstrated, but the exact mechanism that enable them to distinguish proteins with major and minor defects is still unknown (Pearse et al. 2008).

Preceded by: MAN1B1,EDEM2 hydrolyse 1,2-linked mannose (b branch), MAN1B1 hydrolyses 1,2-linked mannose (c branch)

Followed by: Glycoproteins with lesser folding defects get transported back to the ER and the CNX/CRT complex

Literature references

Kaufman, RJ., Arnold, SM. (2003). The noncatalytic portion of human UDP-glucose: glycoprotein glucosyltransferase I confers UDP-glucose binding and transferase function to the catalytic domain. *J Biol Chem, 278*, 43320-8. ↗

Fessler, JH., Kaufman, RJ., Fessler, LI., Arnold, SM. (2000). Two homologues encoding human UDP-glucose:glycoprotein glucosyltransferase differ in mRNA expression and enzymatic activity. *Biochemistry, 39*, 2149-63. ↗

Pearse, BR., Wang, N., Gabriel, L., Hebert, DN. (2008). A cell-based reglucosylation assay demonstrates the role of GT1 in the quality control of a maturing glycoprotein. *J Cell Biol, 181*, 309-20. ↗

Editions

2009-11-10	Authored	Dall'Olio, GM.
2010-03-15	Edited	Jassal, B.
2010-11-18	Reviewed	Gagneux, P.
2015-06-03	Revised	Jassal, B.

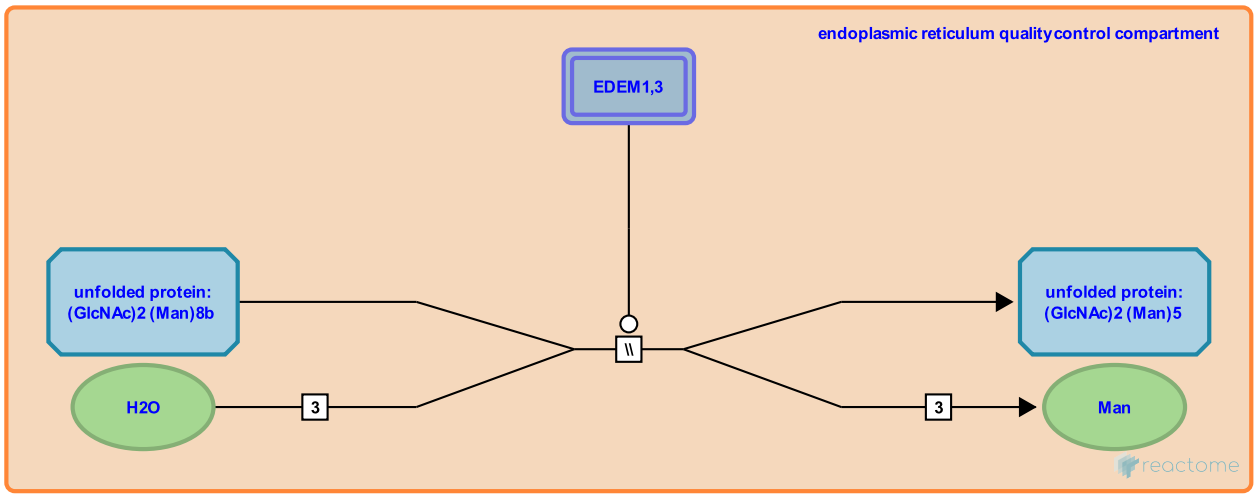
EDEM1,3 hydrolyse (GlcNAc)2 (Man)8b to (GlcNAc)2 (Man)5 ↗

Location: ER Quality Control Compartment (ERQC)

Stable identifier: R-HSA-6782685

Type: omitted

Compartments: endoplasmic reticulum quality control compartment



Proteins with major folding defects are extracted from futile folding cycles in the calnexin chaperone system and the ER Quality Control Compartment, and are translocated back to the cytosol for degradation. The ER degradation-enhancing alpha-mannosidase-like proteins 1 and 3 (EDEM1 and 3) can catalyse the sequential hydrolysis of (GlcNAc)2 (Man)8 to (GlcNAc)2 (Man)7-5. The products are recognised by quality control proteins and become targets for ER-associated degradation (ERAD) (Ninagawa et al. 2014, Hirao et al. 2006).

Followed by: OS9:SEL1:ERAD E3 ligase:DERL2 ubiquitinates unfolded protein:(GlcNAc)2 (Man)9-5

Literature references

Kamiya, Y., Takeda, S., Ishikawa, T., Sakuma, T., Sumitomo, Y., Okada, T. et al. (2014). EDEM2 initiates mammalian glycoprotein ERAD by catalyzing the first mannose trimming step. *J. Cell Biol., 206*, 347-56. ↗

Romero, P., Hosokawa, N., Herscovics, A., Wada, I., Nagata, K., Sleno, B. et al. (2006). EDEM3, a soluble EDEM homolog, enhances glycoprotein endoplasmic reticulum-associated degradation and mannose trimming. *J Biol Chem, 281*, 9650-8. ↗

Editions

2015-06-08	Authored, Edited	Jassal, B.
2015-06-22	Reviewed	Dall'Olio, GM.

OS9:SEL1:ERAD E3 ligase:DERL2 ubiquitinates unfolded protein:(GlcNAc)2 (Man)9-5

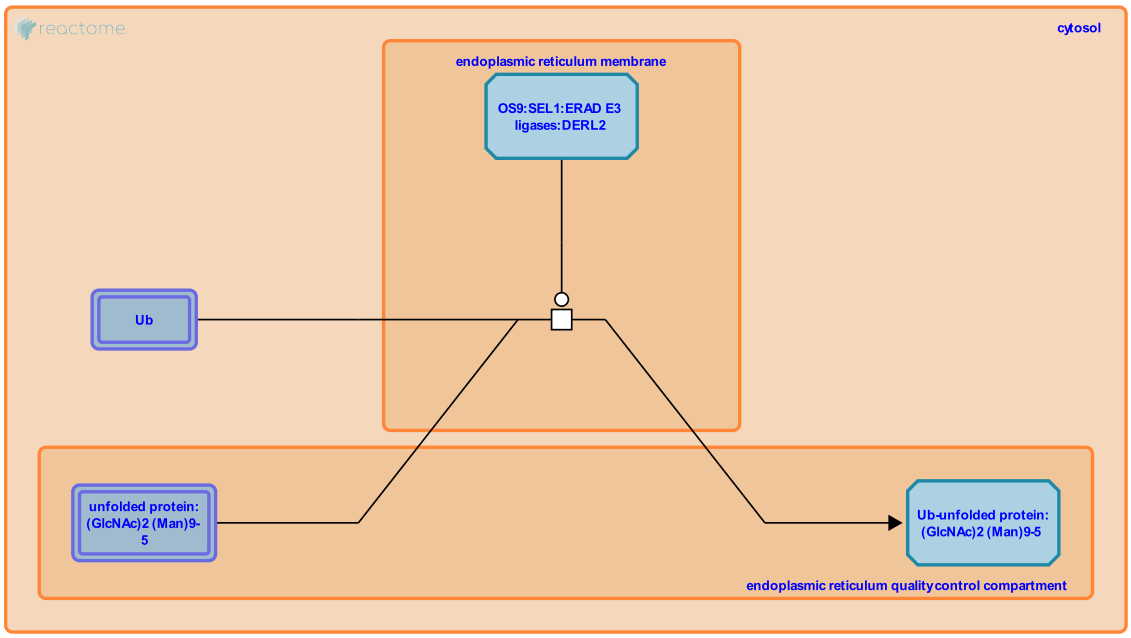
↗

Location: ER Quality Control Compartment (ERQC)

Stable identifier: R-HSA-8867288

Type: transition

Compartments: endoplasmic reticulum membrane, endoplasmic reticulum quality control compartment, cytosol



Proteins with major folding defects are extracted from futile folding cycles in the calnexin chaperone system and the ER Quality Control Compartment, and are translocated back to the cytosol for ER-associated degradation (ERAD). The N-glycan is used as a signal to distinguish proteins to be degraded, by direct binding to a ubiquitin ligase complex composed of, minimally, an E3 ubiquitin-protein ligase, protein sel-1 homolog 1 (SEL1L), derlin-2 (DERL2) and protein OS-9 (OS9) (Christianson et al. 2008, Bernasconi et al. 2008, Alcock & Swanton 2009; review Olzmann et al. 2013).

Preceded by: EDEM1,3 hydrolyse (GlcNAc)2 (Man)8b to (GlcNAc)2 (Man)5

Followed by: Ub-unfolded protein:(GlcNAc)2 (Man)9-5 translocates from ERQC to cytosol

Literature references

Alcock, F., Swanton, E. (2009). Mammalian OS-9 is upregulated in response to endoplasmic reticulum stress and facilitates ubiquitination of misfolded glycoproteins. *J. Mol. Biol., 385*, 1032-42. ↗

Christianson, JC., Kopito, RR., Olzmann, JA. (2013). The mammalian endoplasmic reticulum-associated degradation system. *Cold Spring Harb Perspect Biol, 5*. ↗

Tyler, RE., Christianson, JC., Kopito, RR., Shaler, TA. (2008). OS-9 and GRP94 deliver mutant alpha1-antitrypsin to the Hrd1-SEL1L ubiquitin ligase complex for ERAD. *Nat. Cell Biol., 10*, 272-82. ↗

Molinari, M., Luban, J., Pertel, T., Bernasconi, R. (2008). A dual task for the Xbp1-responsive OS-9 variants in the mammalian endoplasmic reticulum: inhibiting secretion of misfolded protein conformers and enhancing their disposal. *J. Biol. Chem., 283*, 16446-54. ↗

Editions

2010-11-17	Authored, Edited	Jassal, B.
2015-06-22	Reviewed	Dall'Olio, GM.

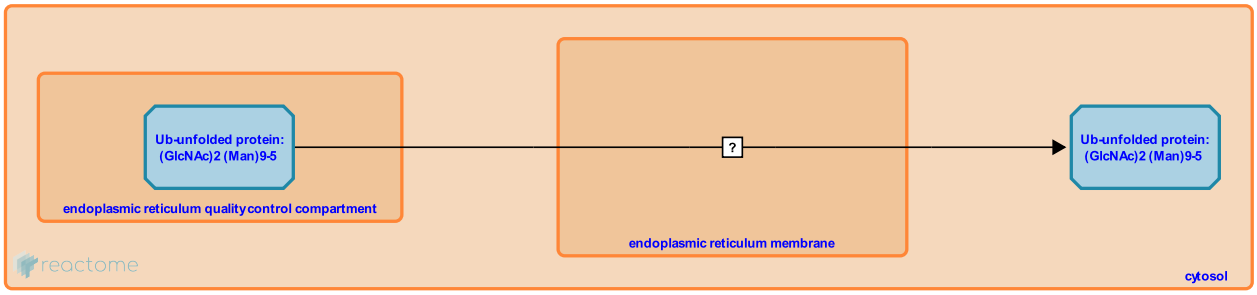
Ub-unfolded protein:(GlcNAc)2 (Man)9-5 translocates from ERQC to cytosol ↗

Location: ER Quality Control Compartment (ERQC)

Stable identifier: R-HSA-1022127

Type: uncertain

Compartments: endoplasmic reticulum membrane, endoplasmic reticulum quality control compartment, cytosol



Proteins with major folding defects are extracted from futile folding cycles in the calnexin chaperone system and the ER Quality Control Compartment, and are translocated back to the cytosol for ER-associated degradation (ERAD). The N-glycan is used as a signal to distinguish proteins to be degraded, by direct binding to a ubiquitin ligase complex composed of, minimally, an E3 ubiquitin-protein ligase, protein sel-1 homolog 1 (SEL1L), derlin-2 (DERL2) and protein OS-9 (OS9) (Christianson et al. 2008, Bernasconi et al. 2008, Alcock & Swanton 2009; review Olzmann et al. 2013). The mechanism of translocation is unknown.

Preceded by: OS9:SEL1:ERAD E3 ligase:DERL2 ubiquitinates unfolded protein:(GlcNAc)2 (Man)9-5

Literature references

Alcock, F., Swanton, E. (2009). Mammalian OS-9 is upregulated in response to endoplasmic reticulum stress and facilitates ubiquitination of misfolded glycoproteins. *J. Mol. Biol., 385*, 1032-42. ↗

Christianson, JC., Kopito, RR., Olzmann, JA. (2013). The mammalian endoplasmic reticulum-associated degradation system. *Cold Spring Harb Perspect Biol, 5*. ↗

Tyler, RE., Christianson, JC., Kopito, RR., Shaler, TA. (2008). OS-9 and GRP94 deliver mutant alpha1-antitrypsin to the Hrd1-SEL1L ubiquitin ligase complex for ERAD. *Nat. Cell Biol., 10*, 272-82. ↗

Molinari, M., Luban, J., Pertel, T., Bernasconi, R. (2008). A dual task for the Xbp1-responsive OS-9 variants in the mammalian endoplasmic reticulum: inhibiting secretion of misfolded protein conformers and enhancing their disposal. *J. Biol. Chem., 283*, 16446-54. ↗

Editions

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2015-06-22	Reviewed	Dall'Olio, GM.

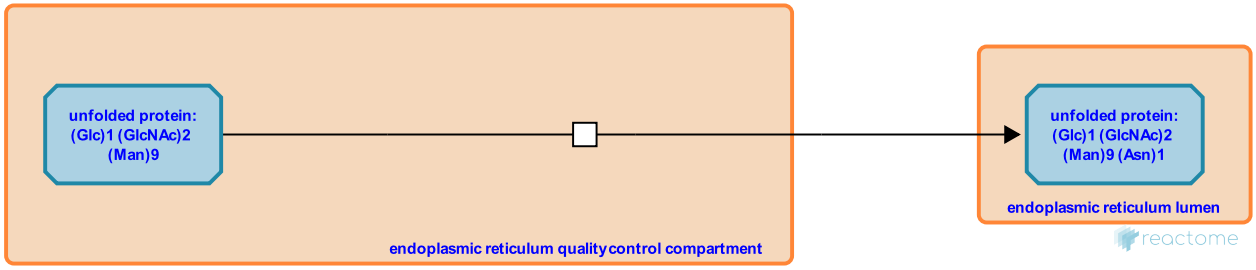
Glycoproteins with lesser folding defects get transported back to the ER and the CNX/CRT complex ↗

Location: ER Quality Control Compartment (ERQC)

Stable identifier: R-HSA-1017228

Type: transition

Compartments: endoplasmic reticulum quality control compartment, endoplasmic reticulum lumen



Glycoproteins with lesser folding defects get transported back to the ER and the CNX/CRT complex (Lederkremer, 2009).

Preceded by: UGGT1,2 transfers glucose from DbGP to (un)folded protein:(GlcNAc)2 (Man)8b

Literature references

Lederkremer, GZ. (2009). Glycoprotein folding, quality control and ER-associated degradation. *Curr Opin Struct Biol, 19*, 515-23. ↗

Editions

2010-11-16	Edited	Jassal, B.
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2010-11-18	Reviewed	Gagneux, P.
2015-06-03	Revised	Jassal, B.

Table of Contents