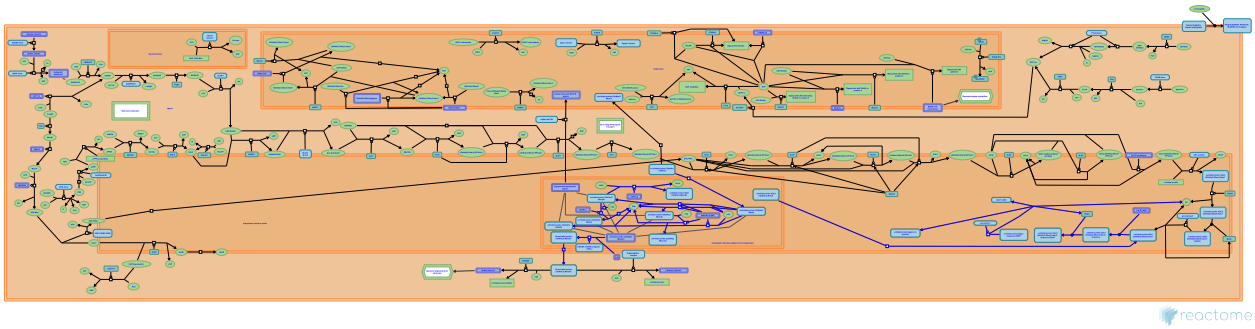
Calnexin/calreticulin cycle



Dall'Olio, GM., Gagneux, P., Jassal, B.

European Bioinformatics Institute, New York University Langone Medical Center, Ontario Institute for Cancer Research, Oregon Health and Science University.

The contents of this document may be freely copied and distributed in any media, provided the authors, plus the institutions, are credited, as stated under the terms of Creative Commons Attribution 4.0 International (CC BY 4.0) License. For more information see our license.

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. ↗

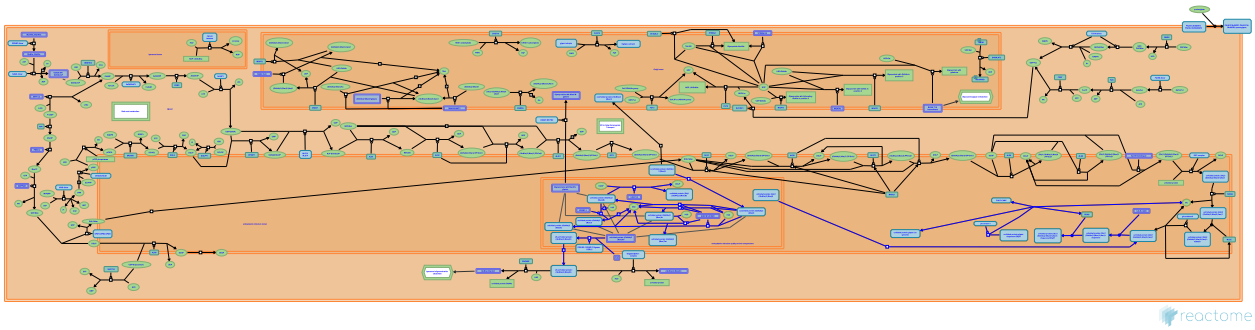
Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

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. ↗

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.

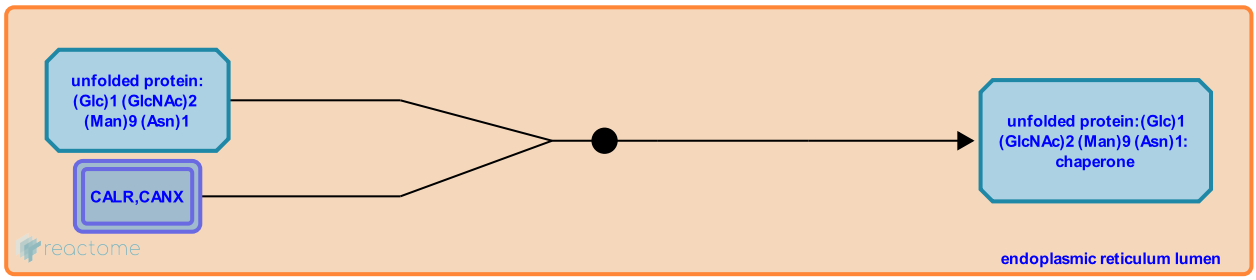
Binding of calnexin/calreticulin to the unfolded protein ↗

Location: Calnexin/calreticulin cycle

Stable identifier: R-HSA-535717

Type: binding

Compartments: endoplasmic reticulum lumen



Calnexin (membrane protein) and calreticulin (soluble in ER) are two lectins (proteins that can bind a glycan) which recognize the mono-glucosylated form of the N-glycan and mediate the folding of the glycoproteins to which they are attached to (Ou WJ et al, 1993; Nauseef Wm et al, 1995). Calmegin is another chaperone with the same role expressed only in testis (van Lith M et al, 2007). These lectins act as chaperons, providing a protected environment where the unfolded glycoprotein can fold without forming interactions with other proteins or components in the ER. The unfolded protein can loop between these two steps multiple time, therefore this process is called the 'calnexin/calreticulin cycle'. If the protein achieves correct folding, it is modified by Mannosidase I and then moved to the cis-Golgi where the glycan is further processed.

Followed by: Binding of ERp57

Literature references

Karala, AR., Gatehouse, JA., van Lith, M., Ruddock, LW., Saunders, PT., Bown, D. et al. (2007). A developmentally regulated chaperone complex for the endoplasmic reticulum of male haploid germ cells. *Mol Biol Cell, 18*, 2795-804. ↗

Cameron, PH., Thomas, DY., Bergeron, JJ., Ou, WJ. (1993). Association of folding intermediates of glycoproteins with calnexin during protein maturation. *Nature, 364*, 771-6. ↗

Clark, RA., McCormick, SJ., Nauseef, WM. (1995). Calreticulin functions as a molecular chaperone in the biosynthesis of myeloperoxidase. *J Biol Chem, 270*, 4741-7. ↗

Editions

2009-11-10	Authored	Dall'Olio, GM.
2010-03-05	Edited	Jassal, B.
2010-08-17	Reviewed	Gagneux, P.

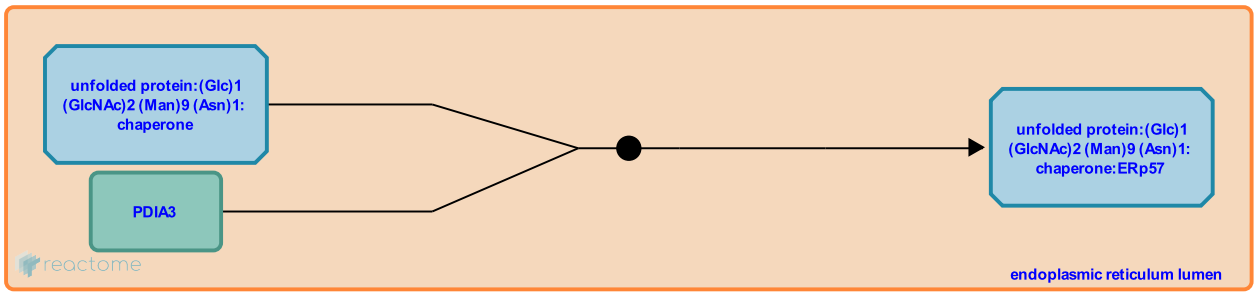
Binding of ERp57 ↗

Location: Calnexin/calreticulin cycle

Stable identifier: R-HSA-901047

Type: binding

Compartments: endoplasmic reticulum lumen



ERp57/ERp27 is a thiol-oxidoreductase that interacts with calnexin and mediates the formation of disulfide bonds in the unfolded glycoprotein (Alanen HI et al, 2006).

Preceded by: Binding of calnexin/calreticulin to the unfolded protein

Followed by: Removal of the third glucose by glucosidase II and release from the chaperone

Literature references

Kauppila, A., Ruddock, LW., Salo, KE., Alanen, HI., Kellokumpu, S., Williamson, RA. et al. (2006). ERp27, a new non-catalytic endoplasmic reticulum-located human protein disulfide isomerase family member, interacts with ERp57. *J Biol Chem, 281*, 33727-38. ↗

Editions

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

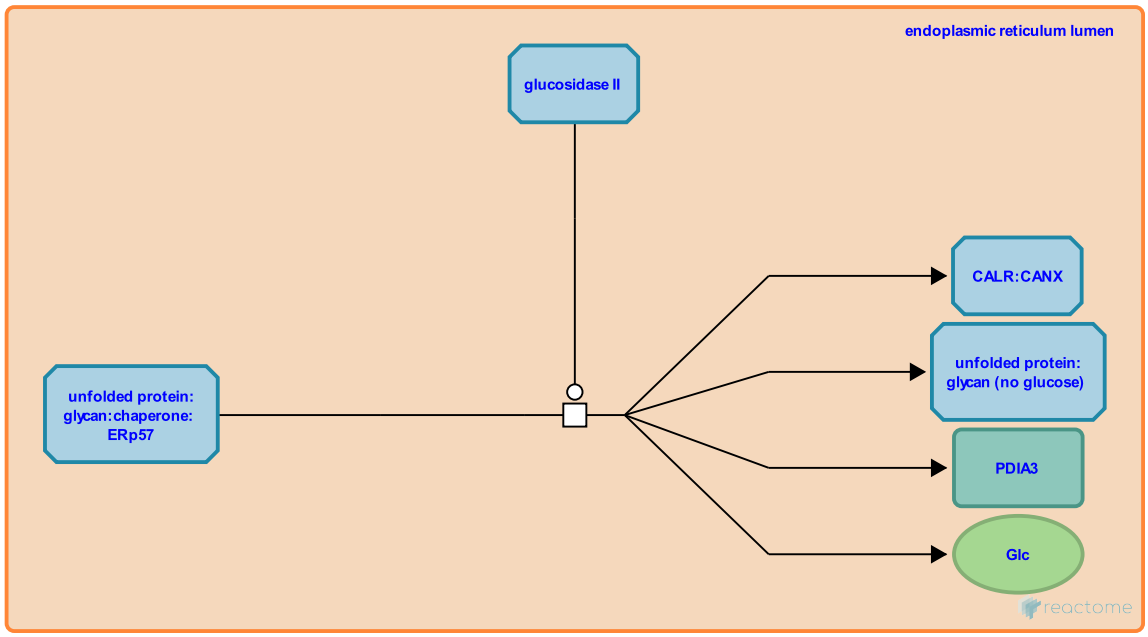
Removal of the third glucose by glucosidase II and release from the chaperone ↗

Location: Calnexin/calreticulin cycle

Stable identifier: R-HSA-548890

Type: transition

Compartments: endoplasmic reticulum lumen



While the protein is bound to the chaperone complex, the glycan is still accessible to glucosidase II, which eventually removes the last remaining glucose residue. This also results in breaking the interaction between the chaperone and the glycoprotein, independently of whether the latter has achieved proper folding (Pelletier MF et al, 2000). This has been interpreted as a 'timing mechanism', in which a protein has only a limited period of time to achieve correct folding when bound to the chaperone, to avoid the scenario where proteins that take too long to fold would block the availability of CNX or CRT. Proteins with folding defects get transported to the Endoplasmic Reticulum Quality Control Compartment, while proteins with correct folding are transported to the cis-Golgi where the glycan is further modified.

Preceded by: Binding of ERp57

Followed by: Incorrectly folded glycoproteins translocate to the ERQC

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.
2010-03-15	Edited	Jassal, B.
2010-08-17	Reviewed	Gagneux, P.

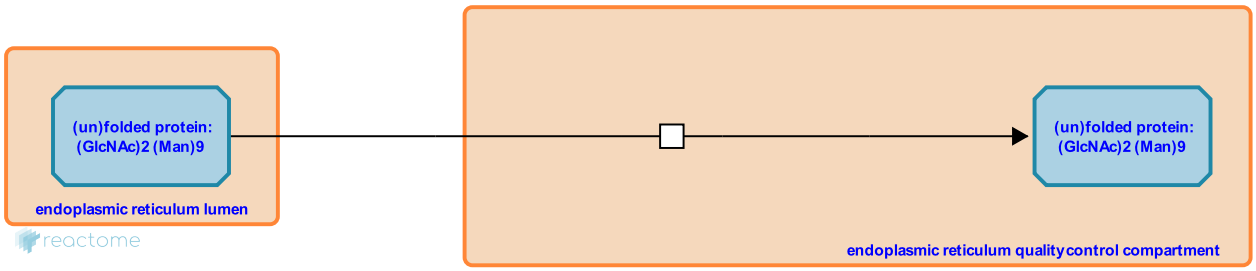
Incorrectly folded glycoproteins translocate to the ERQC ↗

Location: Calnexin/calreticulin cycle

Stable identifier: R-HSA-912291

Type: transition

Compartments: endoplasmic reticulum quality control compartment, endoplasmic reticulum lumen



Proteins with folding defects get transported to the Endoplasmic Reticulum Quality Control Compartment (Molinari, 2007).

Preceded by: Removal of the third glucose by glucosidase II and release from the chaperone

Literature references

Molinari, M. (2007). N-glycan structure dictates extension of protein folding or onset of disposal. *Nat Chem Biol, 3,* 313-20. ↗

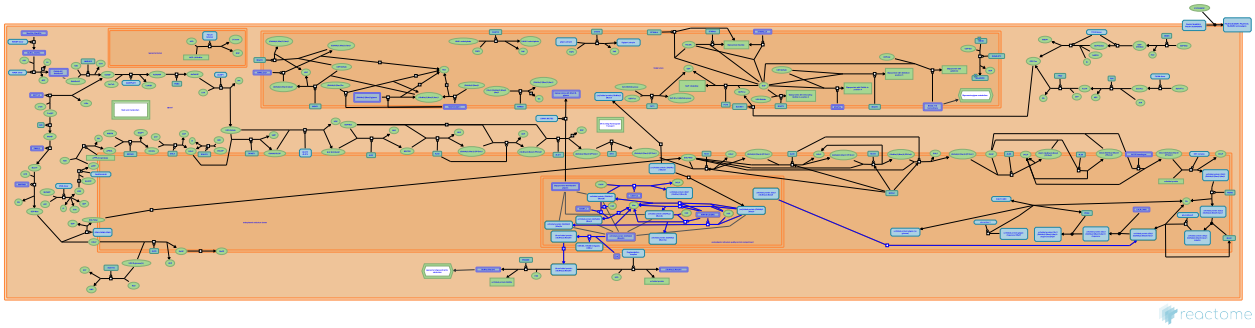
Editions

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

ER Quality Control Compartment (ERQC) ↗

Location: Calnexin/calreticulin cycle

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.

Table of Contents