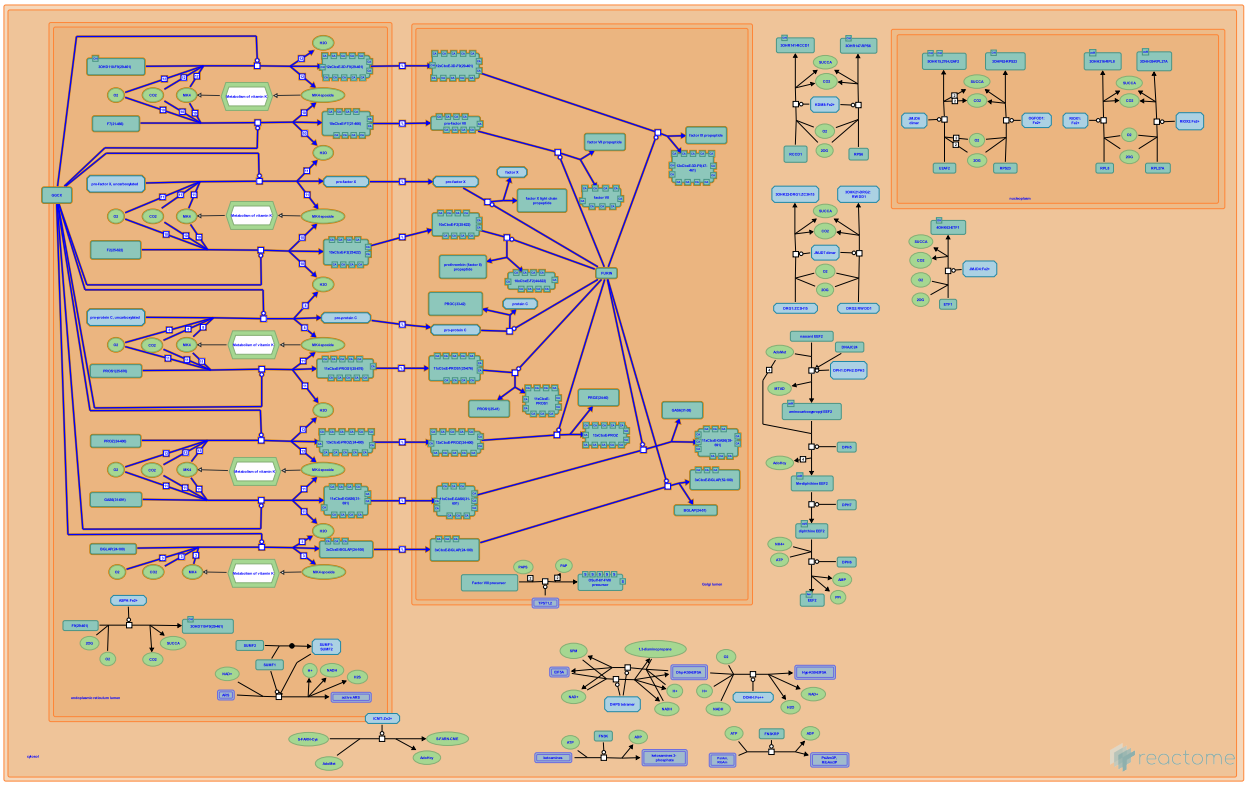
Gamma-carboxylation, transport, and amino-terminal cleavage of proteins



D'Eustachio, P., Stafford, DW.

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

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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. ↗

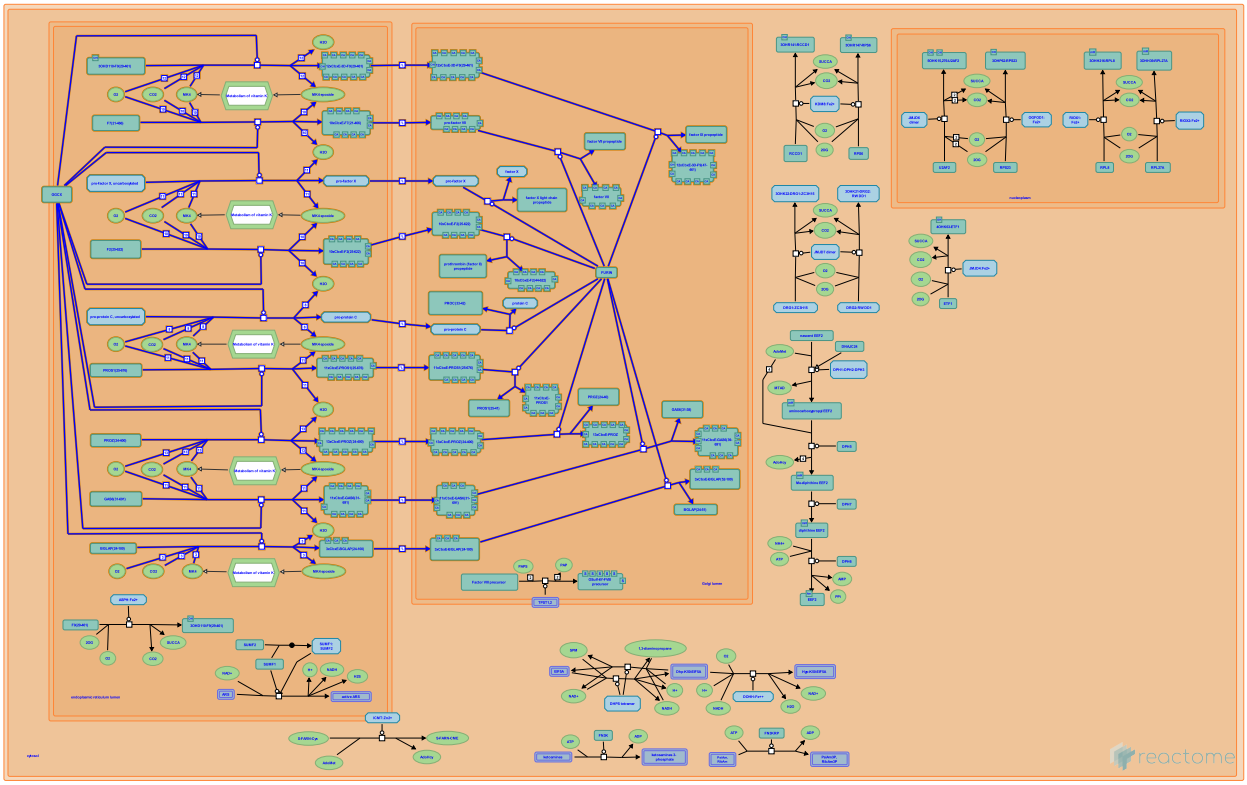
Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

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. ↗

Gamma-carboxylation, transport, and amino-terminal cleavage of proteins ↗

Stable identifier: R-HSA-159854



A number of proteins, including eight required for normal blood clot formation and its regulation (Prothrombin (factor II), factor VII, factor IX, factor X, protein C, protein S, protein Z, and Gas6) share a sequence motif rich in glutamate residues near their amino termini. Carboxylation of the glutamate residues within this motif followed by removal of an aminoterminal propeptide is required for each of these proteins to function. These modifications occur as the proteins move through the endoplasmic reticulum and Golgi apparatus.

Editions

2005-03-17	Authored	D'Eustachio, P.
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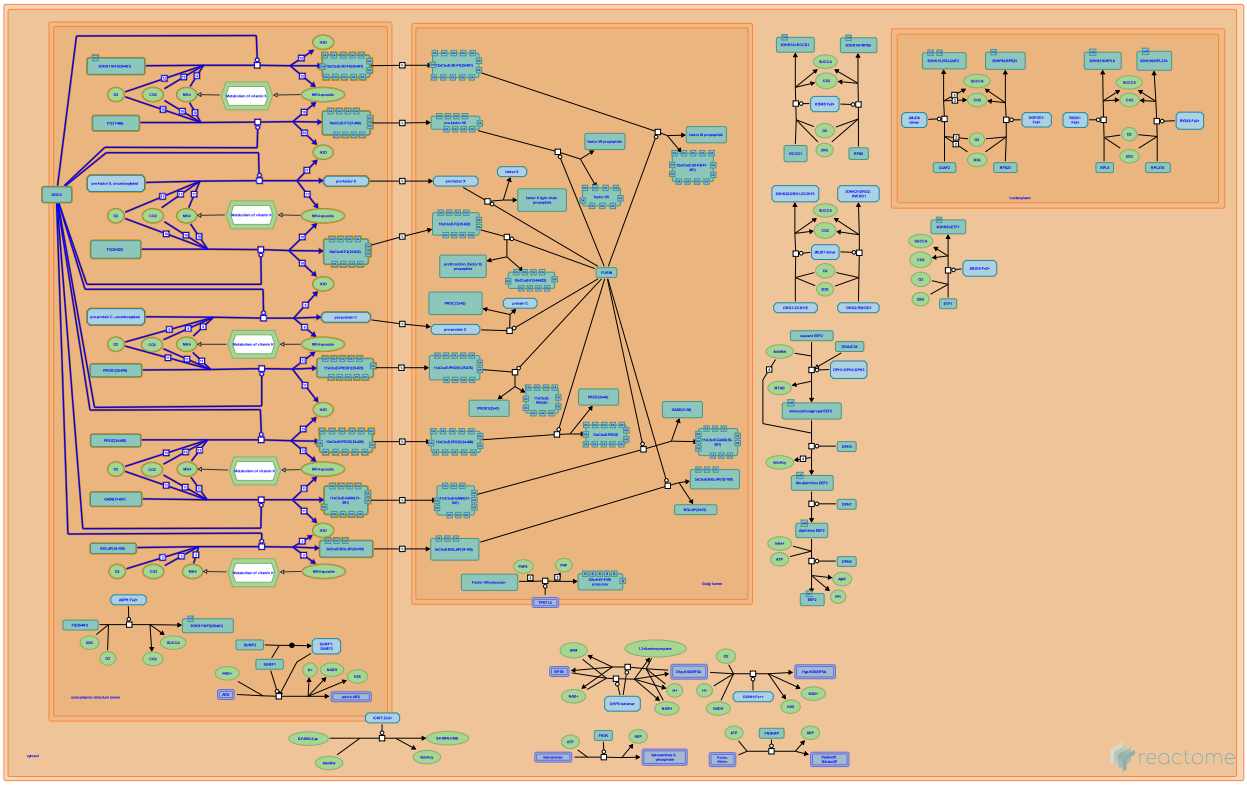
Gamma-carboxylation of protein precursors ↗

Location: Gamma-carboxylation, transport, and amino-terminal cleavage of proteins

Stable identifier: R-HSA-159740

Compartments: endoplasmic reticulum membrane



Gamma-carboxylation of a cluster of glutamate residues near the amino termini of thrombin, factor VII, factor IX, factor X, protein C, protein S, protein Z, and Gas 6 is required for these proteins to bind Ca++ and function efficiently in blood clotting. A single enzyme, vitamin K-dependent gamma-carboxylase, catalyzes the gamma-carboxylation of all eight proteins involved in clotting (Morris et al. 1995; Brenner et al. 1998; Spronk et al. 2000). In the carboxylation reaction, the enzyme binds its substrate protein via a sequence motif on the amino terminal side of the glutamate residues to be carboxylated (Furie et al. 1999), then processively carboxylates all glutamates in the cluster before releasing the substrate (Morris et al. 1995; Berkner 2000; Stenina et al. 2001). The reaction occurs in the endoplasmic reticulum (Bristol et al. 1996).

Literature references

Furie, B., Bouchard, BA., Furie, BC. (1999). Vitamin K-dependent biosynthesis of gamma-carboxyglutamic acid. *Blood, 93*, 1798-808. ↗

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Stenina, O., Pudota, BN., Berkner, KL., McNally, BA., Hommema, EL. (2001). Tethered processivity of the vitamin K-dependent carboxylase: factor IX is efficiently modified in a mechanism which distinguishes Gla's from Glu's and which accounts for comprehensive carboxylation in vivo. *Biochemistry, 40*, 10301-9. ↗

Editions

2005-03-17	Authored	D'Eustachio, P.
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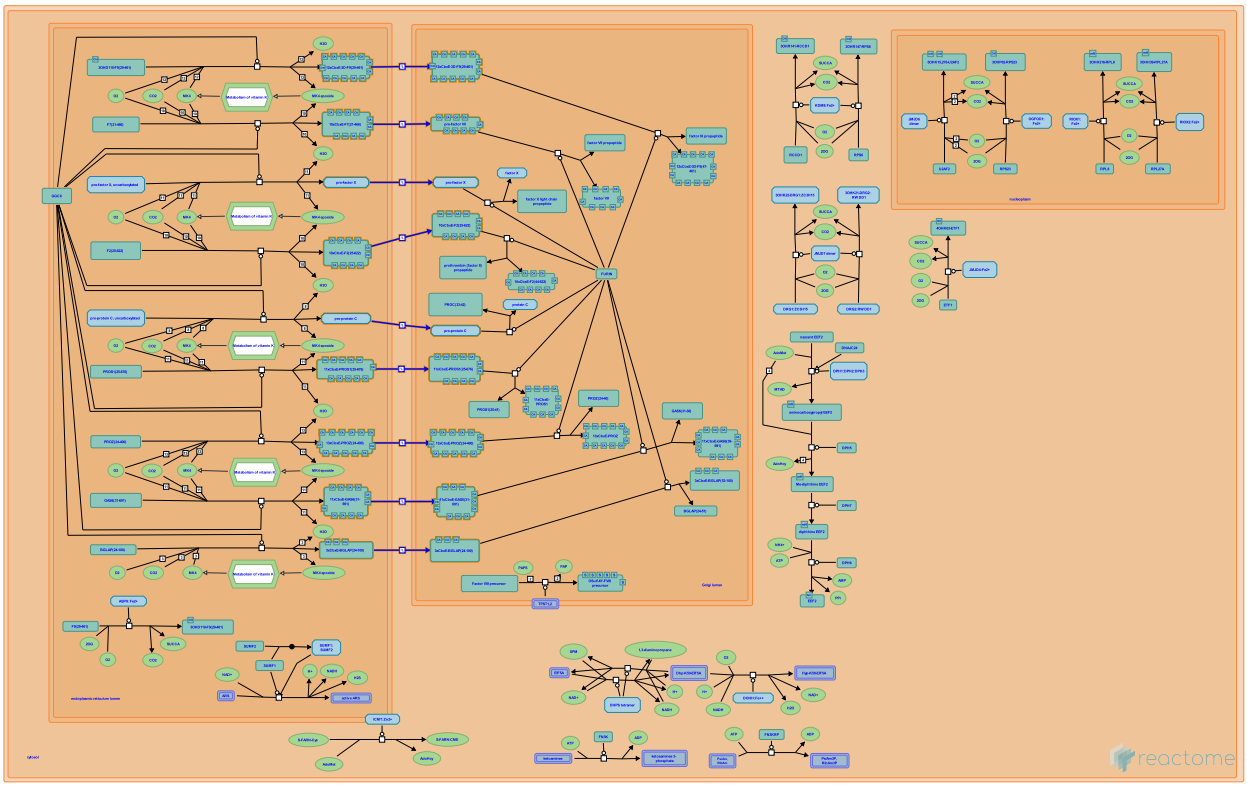
Transport of gamma-carboxylated protein precursors from the endoplasmic reticulum to the Golgi apparatus ↗

Location: Gamma-carboxylation, transport, and amino-terminal cleavage of proteins

Stable identifier: R-HSA-159763

Compartments: COPII-coated ER to Golgi transport vesicle



Gamma-carboxylated proteins are moved by anterograde transport from the endoplasmic reticulum to the Golgi apparatus (Kirchhausen 2000).

Literature references

Kirchhausen, Tomas. (2000). Three ways to make a vesicle. *Nat Rev Mol Cell Biol, 1*, 187-98. ↗

Editions

2005-03-17	Authored	D'Eustachio, P.
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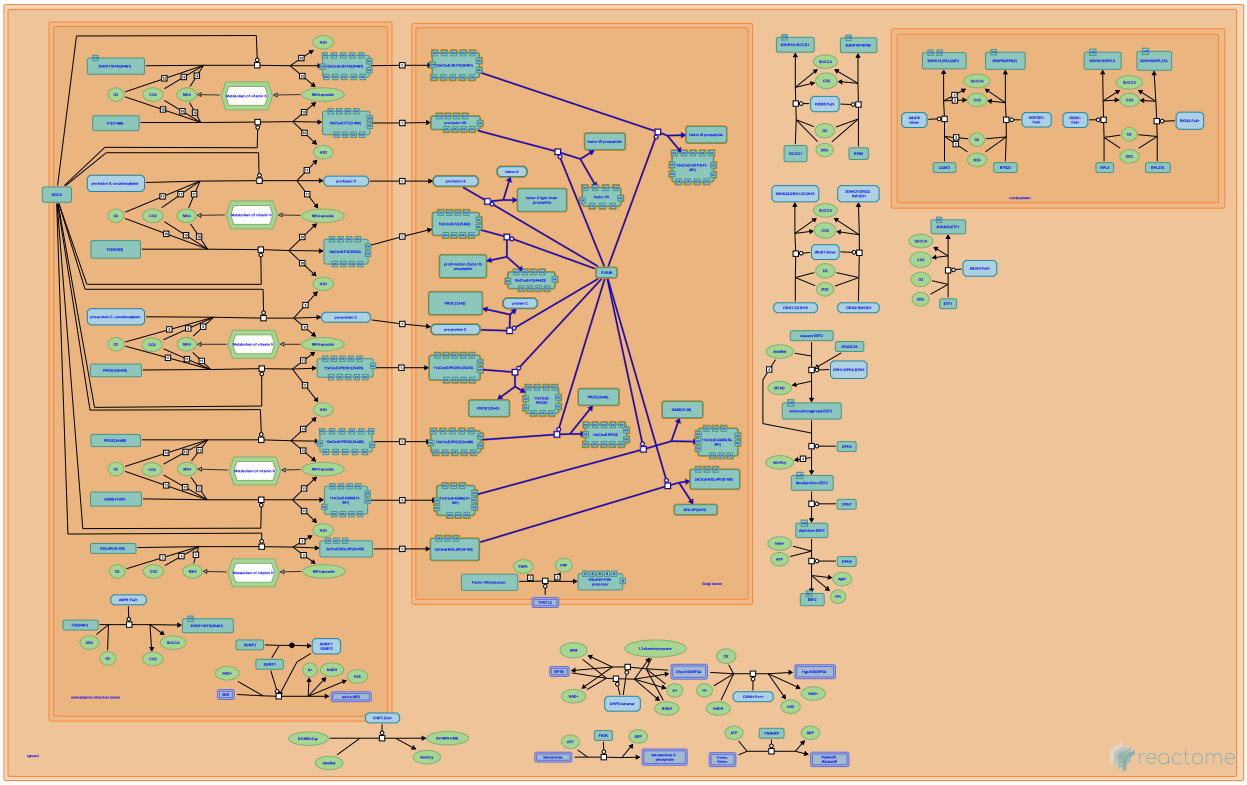
Removal of aminoterminal propeptides from gamma-carboxylated proteins ↗

Location: Gamma-carboxylation, transport, and amino-terminal cleavage of proteins

Stable identifier: R-HSA-159782

Compartments: Golgi lumen



Furin is an endopeptidase localized to the Golgi membrane that cleaves many proteins on the carboxyterminal side of the sequence motif Arg-[any residue]-(Lys or Arg)-Arg (Jones et al. 1995; Leduc et al. 1992). In the case of gamma-carboxylated proteins, if this cleavage does not occur, the proteins are still secreted but do not function properly (Bristol et al. 1993; Lind et al. 1997; Wasley et al. 1993). The aminoterminal fragments, "propeptides", generated in this reaction have no known function; the carboxylated, cleaved proteins are delivered to the cell membrane or secreted from the cell.

Literature references

Furie, B., Bristol, JA., Furie, BC. (1993). Propeptide processing during factor IX biosynthesis. Effect of point mutations adjacent to the propeptide cleavage site. *J Biol Chem, 268*, 7577-84. ↗

Leduc, R., Molloy, S S., Thorne, BA., Thomas, G. (1992). Activation of human furin precursor processing endoprotease occurs by an intramolecular autoproteolytic cleavage. *J Biol Chem, 267*, 14304-8. ↗

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Editions

2005-03-17	Authored	D'Eustachio, P.
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