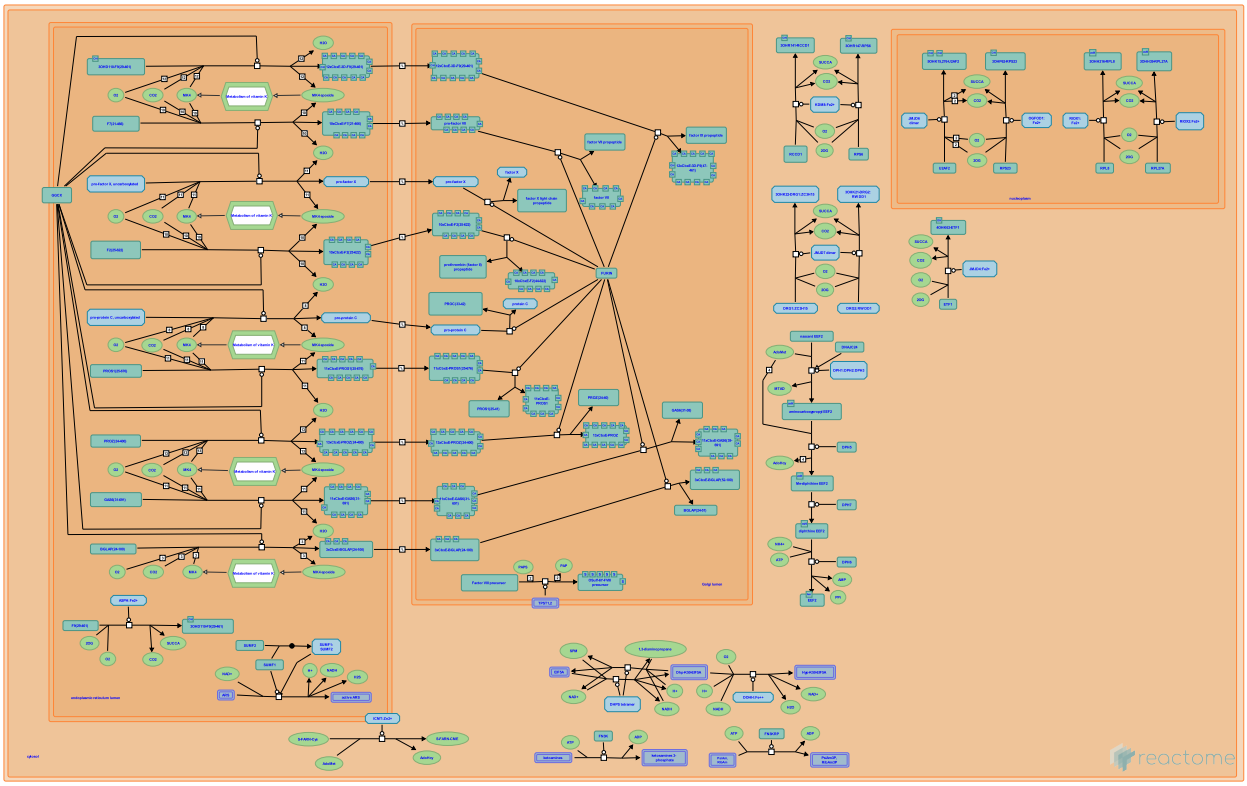
Gamma carboxylation, hypusinylation, hydroxylation, and arylsulfatase activation



D'Eustachio, P., Jassal, B., Johansson, HE., Liu, S., Orlean, P., Shamovsky, V., Stafford, DW., Zhang, B.

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

28/04/2024

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. ↗

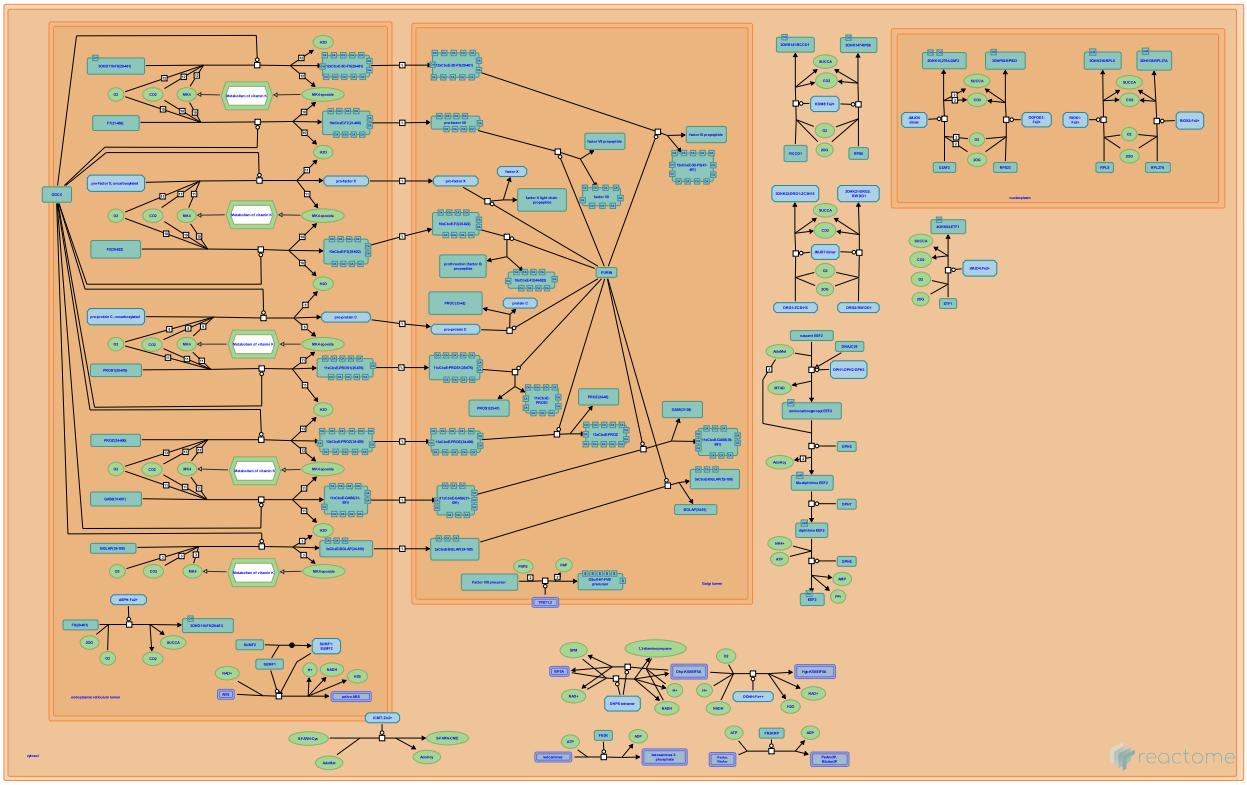
Fabregat, A., Korninger, F., Viteri, G., Sidiropoulos, K., Marin-Garcia, P., Ping, P. et al. (2018). Reactome graph database: Efficient access to complex pathway data. *PLoS computational biology, 14*, e1005968. ↗

Reactome database release: 88

This document contains 6 pathways and 4 reactions (see Table of Contents)

Gamma carboxylation, hypusinylation, hydroxylation, and arylsulfatase activation ↗

Stable identifier: R-HSA-163841



After translation, many newly formed proteins undergo further covalent modifications that alter their functional properties and that are essentially irreversible under physiological conditions in the body. These modifications include the vitamin K-dependent attachment of carboxyl groups to glutamate residues and the conversion of a lysine residue in eIF5A to hypusine, the conversion of a histidine residue in EEF to diphthamide, and the hydrxylation of various amino acid side chains.

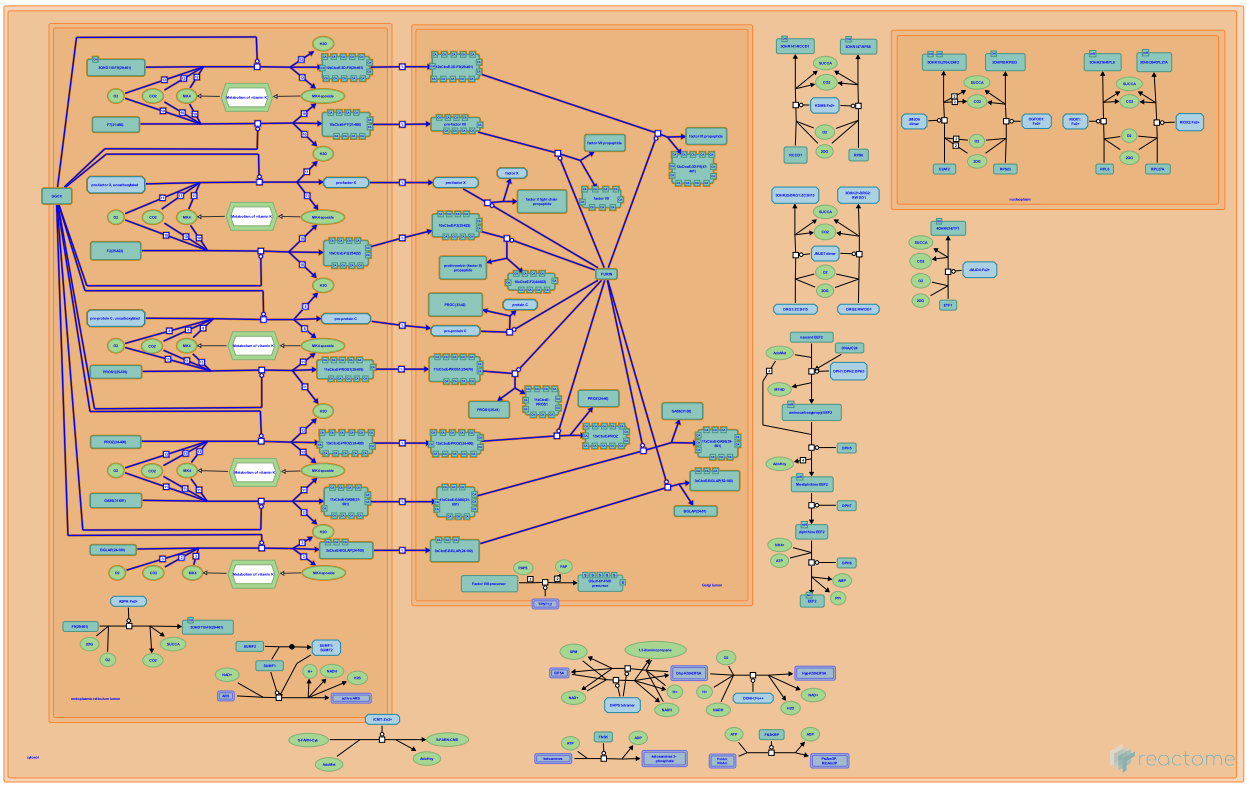
Editions

2005-05-08	Authored	D'Eustachio, P.
2024-03-06	Edited	D'Eustachio, P.
2024-03-06	Reviewed	Stafford, DW., Orlean, P.

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

Location: Gamma carboxylation, hypusinylation, hydroxylation, and arylsulfatase activation

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

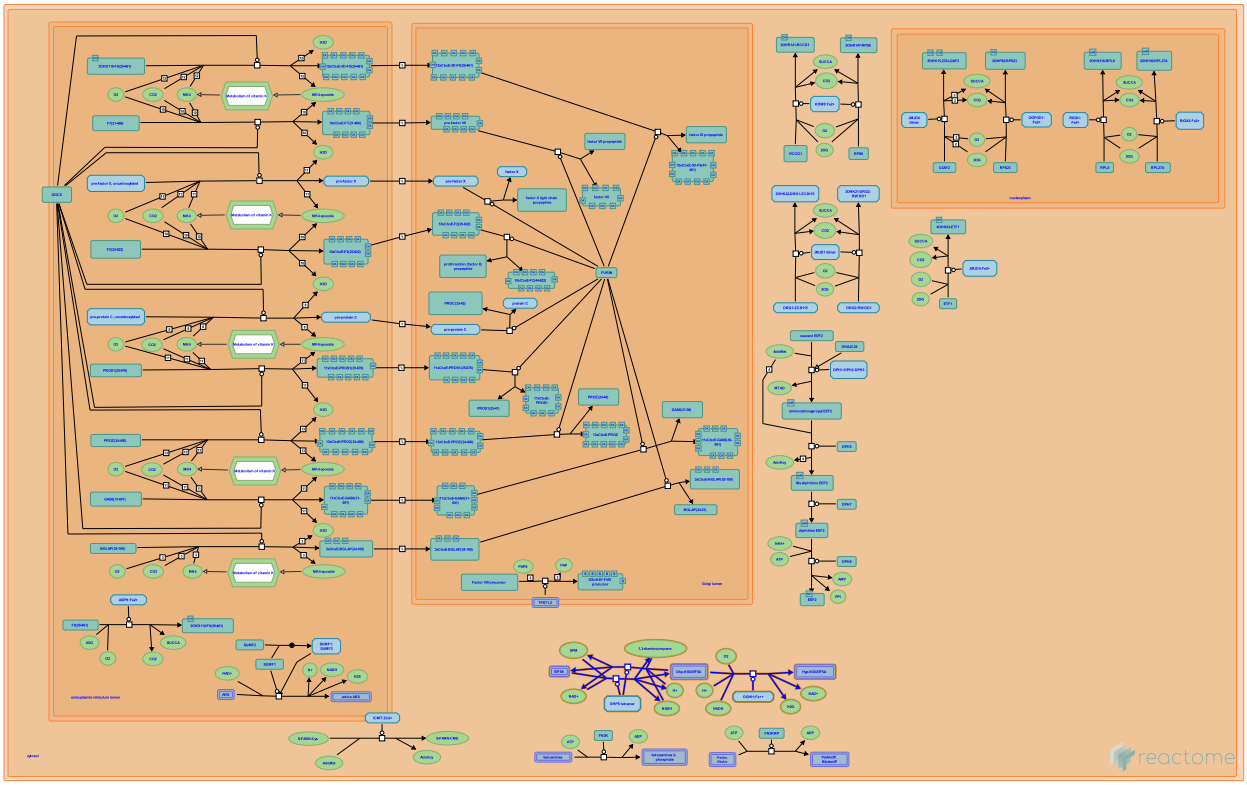
2005-03-17	Authored	D'Eustachio, P.
2024-03-06	Edited	D'Eustachio, P.
2024-03-06	Reviewed	Stafford, DW.

Hypusine synthesis from eIF5A-lysine ↗

Location: Gamma carboxylation, hypusinylation, hydroxylation, and arylsulfatase activation

Stable identifier: R-HSA-204626

Compartments: cytosol



Cytosolic eukaryotic translation initiation factor 5A (eIF5A) undergoes a unique two-step post-translational modification at Lys 50 via deoxyhypusine (Dhp) to hypusine (Hyp). In the first step deoxyhypusine synthase transfers the aminobutyl group of spermidine to the epsilon-amino group of lysine 50, using NAD+ as a cofactor. Hydroxylation of the C2 of the newly added moiety in the second step is catalyzed by deoxyhypusine hydroxylase/monooxygenase with molecular oxygen as the source. The molecular function of eIF5A is unknown, but the protein is required for viability in eukaryotic cells and its normal function requires hypusinylation. eIF5A is the only protein known to undergo hypusinylation (Park 2006).

Literature references

Park, MH. (2006). The post-translational synthesis of a polyamine-derived amino acid, hypusine, in the eukaryotic translation initiation factor 5A (eIF5A). *J Biochem (Tokyo), 139*, 161-9. ↗

Editions

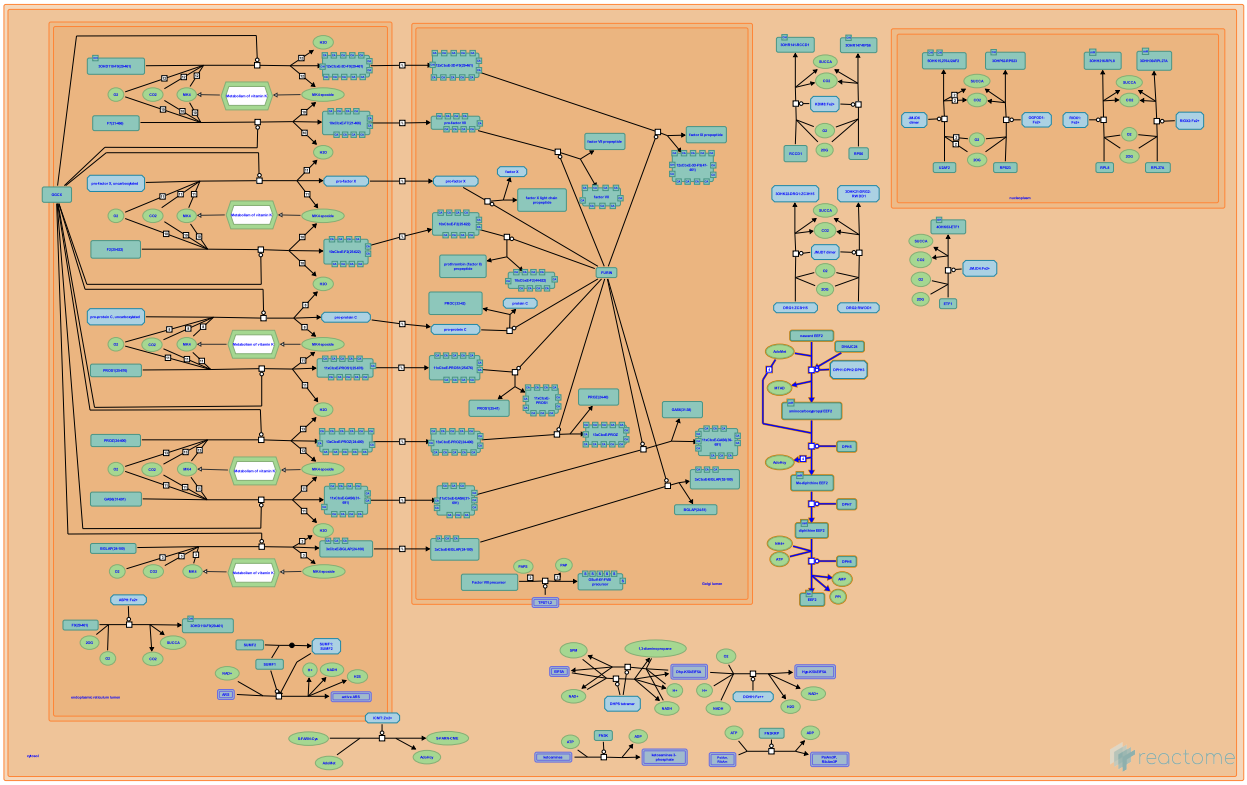
2007-11-29	Edited	D'Eustachio, P.
2007-11-29	Authored	Johansson, HE.
2008-01-28	Reviewed	Jassal, B.

Synthesis of diphthamide-EEF2 ↗

Location: Gamma carboxylation, hypusinylation, hydroxylation, and arylsulfatase activation

Stable identifier: R-HSA-5358493

Compartments: cytosol



Eukaryotic elongation factor 2 (EEF2) catalyzes the GTP dependent ribosomal translocation step during translation elongation. This function requires the presence of a posttranslational modification, the conversion of histidine residue 715 to diphthamide (2' [3 carboxamido 3 (trimethylammonio)propyl] L histidine) (Van Ness et al. 1978). No other protein is known to undergo this modification. The diphthamide residue is also the target of ADP ribosylation catalyzed by diphtheria toxin, which inactivates EEF2 and leads to cell death (Collier 1975; Pappenheim 1977).

Diphthamide synthesis proceeds in four steps: the transfer of 3 amino 3 carboxypropyl group from S adenosylmethionine to histidine 715 of EEF2, the addition of four methyl groups to the 3 amino 3 carboxypropyl moiety, the demethylation of the methylated carboxylate group to form diphthine, and the amidation of the diphthine carboxyl group (Liu et al. 2004; Lin et al. 2014; Schaffrath et al. 2014; Su et al. 2013; Uthman et al. 2013).

Literature references

Howard, JB., Bodley, JW., Van Ness, BG. (1978). Isolation and properties of the trypsin-derived ADP-ribosyl peptide from diphtheria toxin-modified yeast elongation factor 2. *J. Biol. Chem., 253*, 8687-90. ↗

Schaffrath, R., Stark, MJ., Klassen, R., Abdel-Fattah Mohamed, W. (2014). The Diphthamide Modification Pathway from Saccharomyces cerevisiae - Revisited. *Mol. Microbiol.*. ↗

Uthman, S., Schaffrath, R., Stark, MJ., Liu, S., ten Have, S., Scheidt, V. et al. (2013). The amidation step of diphthamide biosynthesis in yeast requires DPH6, a gene identified through mining the DPH1-DPH5 interaction network. *PLoS Genet., 9*, e1003334. ↗

Su, X., Lin, Z., Lin, H. (2013). The biosynthesis and biological function of diphthamide. *Crit. Rev. Biochem. Mol. Biol., 48*, 515-21. ↗

Chen, W., Ci, B., Zhang, S., Su, X., Lin, Z., Lin, H. (2014). Dph7 catalyzes a previously unknown demethylation step in diphthamide biosynthesis. *J. Am. Chem. Soc.*. ↗

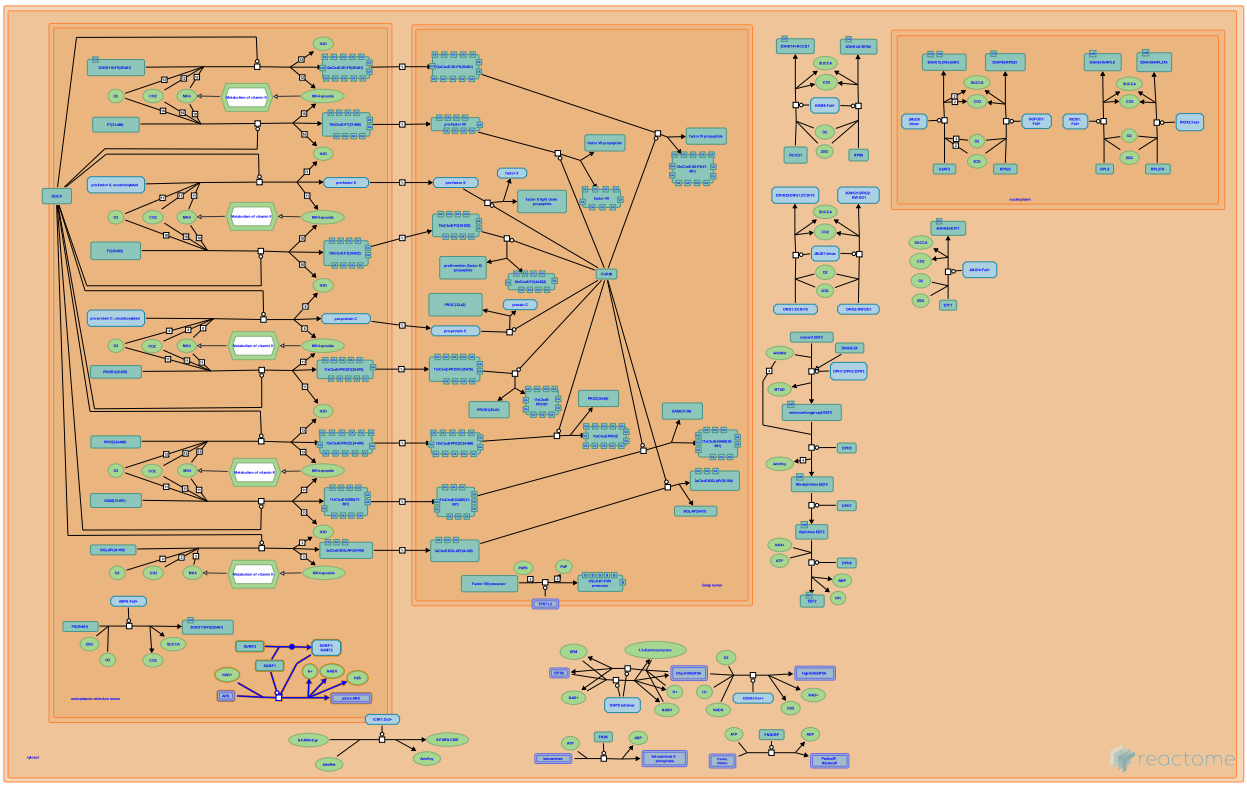
Editions

2014-03-29	Authored, Edited	D'Eustachio, P.
2014-11-18	Reviewed	Liu, S.

The activation of arylsulfatases ↗

Location: Gamma carboxylation, hypusinylation, hydroxylation, and arylsulfatase activation

Stable identifier: R-HSA-1663150



Sulfatase activity requires a unique posttranslational modification (PTM) of a catalytic cysteine residue into a formylglycine. This modification is impaired in patients with multiple sulfatase deficiency (MSD) due to defects in the SUMF1 (sulfatase-modifying factor 1) gene responsible for this PTM. SUMF2 can inhibit the activity of SUMF1 thereby providing a mechanism for the regulation of sulfatase activation (Ghosh 2007, Diez-Roux & Ballabio 2005).

Literature references

Ghosh, D. (2007). Human sulfatases: a structural perspective to catalysis. *Cell Mol Life Sci, 64*, 2013-22. ↗

Diez-Roux, G., Ballabio, A. (2005). Sulfatases and human disease. *Annu Rev Genomics Hum Genet, 6*, 355-79. ↗

Editions

2011-10-14	Authored, Edited	Jassal, B.
2012-05-14	Reviewed	D'Eustachio, P.

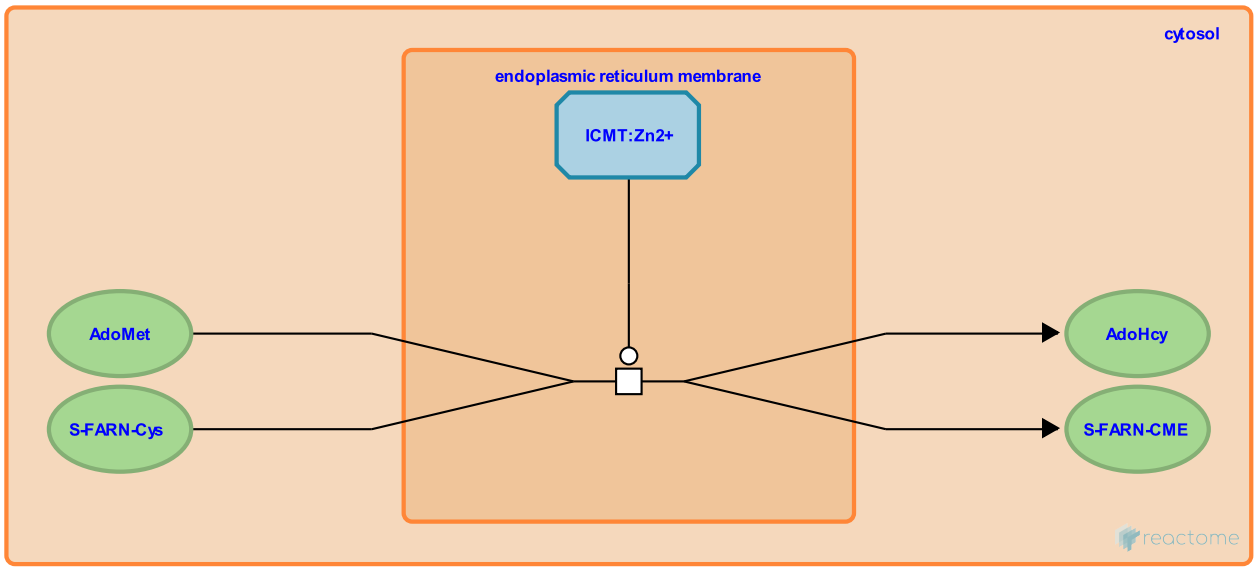
ICMT:Zn2+ transfers CH3 from AdoMet to isoprenylated proteins ↗

Location: Gamma carboxylation, hypusinylation, hydroxylation, and arylsulfatase activation

Stable identifier: R-HSA-6788650

Type: transition

Compartments: endoplasmic reticulum membrane, cytosol



Protein-S-isoprenylcysteine O-methyltransferase (ICMT) mediates the post-translational methyl esterification of C-terminal CAAX motifs in prenylated proteins such as the oncoprotein RAS and related GTPases, neutralising the negative charge of prenylcysteine species and thereby determining their subcellular localisation and correct biological function (Wright et al. 2009, Yang et al. 2011). ICMT may serve as a therapeutic target in cancer development (Lau et al. 2014, Diver et al. 2014).

Literature references

Zhang, Z., Yang, J., Kulkarni, K., Mas-Droux, C., Manolaridis, I., Barford, D. et al. (2011). Mechanism of isoprenylcysteine carboxyl methylation from the crystal structure of the integral membrane methyltransferase ICMT. *Mol. Cell, 44*, 997-1004. ↗

Guo, D., Yang, T., Wirawan, M., Casey, PJ., Lau, HY., Wang, M. et al. (2014). An improved isoprenylcysteine carboxylmethyltransferase inhibitor induces cancer cell death and attenuates tumor growth in vivo. *Cancer Biol. Ther., 15*, 1280-91. ↗

Court, H., Casey, PJ., Philips, MR., Wright, LP., Ahearn, IM., Mor, A. (2009). Topology of mammalian isoprenylcysteine carboxyl methyltransferase determined in live cells with a fluorescent probe. *Mol. Cell. Biol., 29*, 1826-33 . ↗

Long, SB., Diver, MM. (2014). Mutational analysis of the integral membrane methyltransferase isoprenylcysteine carboxyl methyltransferase (ICMT) reveals potential substrate binding sites. *J. Biol. Chem., 289*, 26007-20. ↗

Editions

2015-07-24	Authored, Edited	Jassal, B.
2015-09-14	Reviewed	D'Eustachio, P.

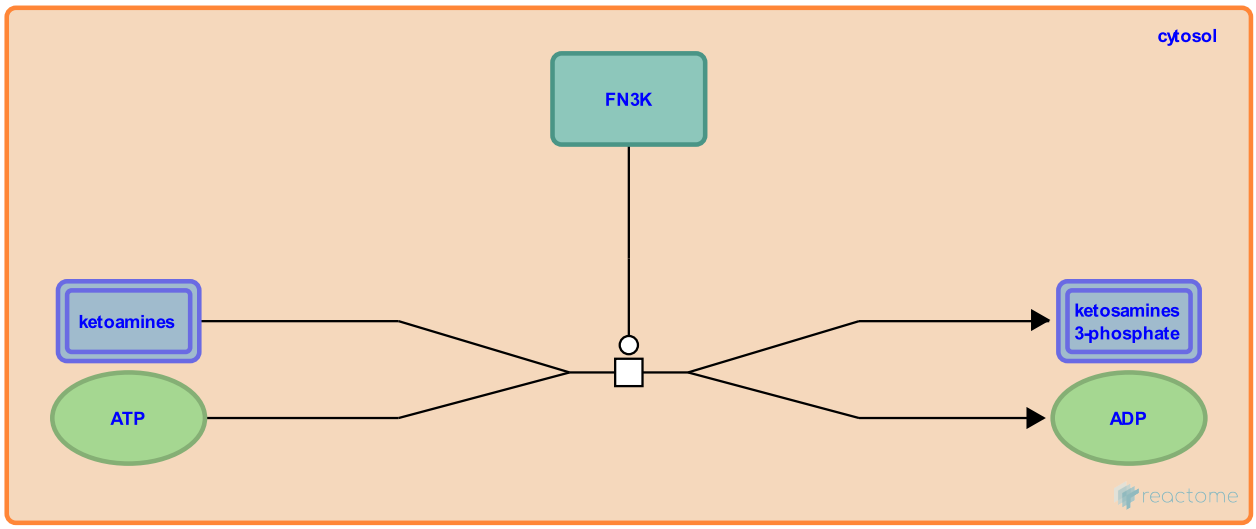
FN3K phosphorylates ketosamines ↗

Location: Gamma carboxylation, hypusinylation, hydroxylation, and arylsulfatase activation

Stable identifier: R-HSA-6788867

Type: transition

Compartments: cytosol



Proteins can undergo chemical modifications such as glycation, which occurs when glucose and other free aldoses spontaneously react with N-terminal and eta-amino groups of proteins to form Schiff bases, which slowly rearrange to ketosamines or, if the sugar is glucose, fructosamines. Fructosamines can further react slowly and become advanced glycation end products, which are thought to play a role in the pathophysiology of several disorders, especially diabetic complications. Ketosamine-3-kinase (FN3K) and ketosamine-3-kinase-related protein (FN3KRP) can phosphorylate protein-bound or free ketosamines on the third carbon of the sugar moiety and the resultant, unstable ketosamine 3-phosphates decompose under physiological conditions (a process called deglycation). Both enzymes can 3-phosphorylate psicosamines (PsiAm) and ribulosamines (RibAm), but only FN3K can 3-phosphorylate fructosamines (FruAm) as well (Delpierre et al. 2000, 2004).

Literature references

Delpierre, G., Vertommen, D., Van Schaftingen, E., Rider, MH., Communi, D. (2004). Identification of fructosamine residues deglycated by fructosamine-3-kinase in human hemoglobin. *J. Biol. Chem., 279*, 27613-20. ↗

Stroobant, V., Delpierre, G., Santos, H., Vanstapel, F., Van Schaftingen, E., Collard, F. et al. (2000). Identification, cloning, and heterologous expression of a mammalian fructosamine-3-kinase. *Diabetes, 49*, 1627-34. ↗

Editions

2015-07-27	Authored, Edited	Jassal, B.
2015-09-14	Reviewed	D'Eustachio, P.

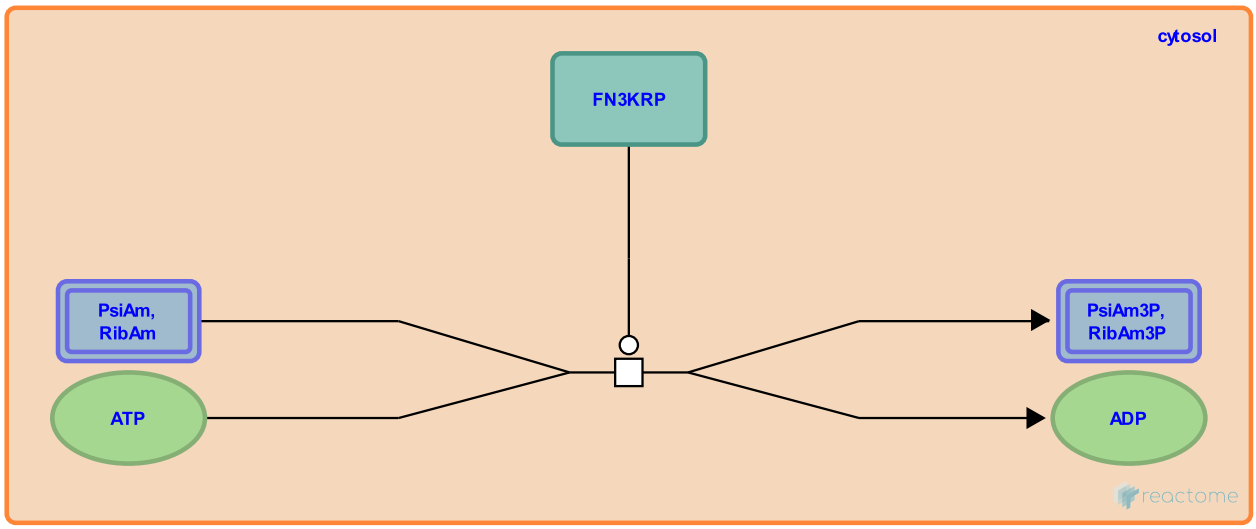
FN3KRP phosphorylates PsiAm, RibAm ↗

Location: Gamma carboxylation, hypusinylation, hydroxylation, and arylsulfatase activation

Stable identifier: R-HSA-6788855

Type: transition

Compartments: cytosol



Proteins can undergo chemical modifications such as glycation, which occurs when glucose and other free aldoses spontaneously react with N-terminal and eta-amino groups of proteins to form Schiff bases, which slowly rearrange to ketosamines or, if the sugar was glucose, fructosamines. Fructosamines can further react slowly and become advanced glycation end products, which are thought to play a role in the pathophysiology of several disorders, especially diabetic complications. Ketosamine-3-kinase (FN3K) and ketosamine-3-kinase-related protein (FN3KRP) can phosphorylate protein-bound or free ketosamines on the third carbon of the sugar moiety and the resultant, unstable ketosamine 3-phosphates decompose under physiological conditions (a process called deglycation). Both enzymes can 3-phosphorylate psicosamines (PsiAm) and ribulosamines (RibAm) (Collard et al. 2003, 2004), but only FN3K can 3-phosphorylate fructosamines (FruAm) as well.

Literature references

Matthijs, G., Stroobant, V., Delpierre, G., Van Schaftingen, E., Collard, F. (2003). A mammalian protein homologous to fructosamine-3-kinase is a ketosamine-3-kinase acting on psicosamines and ribulosamines but not on fructosamines. *Diabetes, 52*, 2888-95. ↗

Delpierre, G., Vanstapel, F., Wiame, E., Vertommen, D., Bergans, N., Van Schaftingen, E. et al. (2004). Fructosamine 3-kinase-related protein and deglycation in human erythrocytes. *Biochem. J., 382*, 137-43. ↗

Editions

2015-07-27	Authored, Edited	Jassal, B.
2015-09-14	Reviewed	D'Eustachio, P.

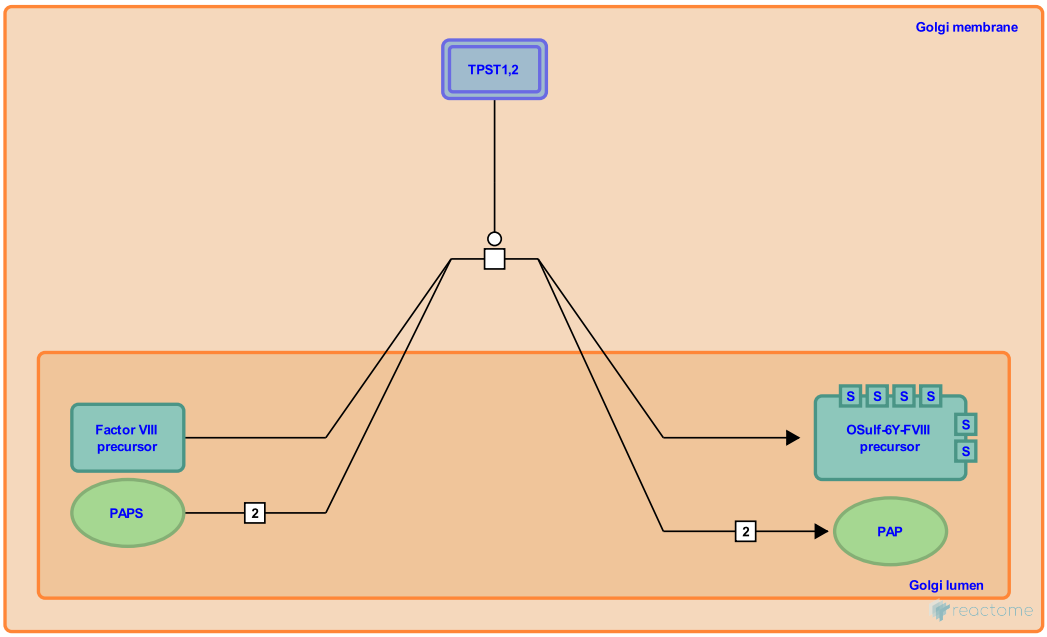
TPST1,2 transfer SO4(2-) from PAPS to FVIII ↗

Location: Gamma carboxylation, hypusinylation, hydroxylation, and arylsulfatase activation

Stable identifier: R-HSA-9668023

Type: transition

Compartments: Golgi membrane, Golgi lumen



Post-translational cellular processing of the factor VIII (FVIII or F8) precursor enables O-sulfation of tyrosine residues (Pittman DD et al. 1992; Michnick DA et al. 1994). Biochemical characterization demonstrated that recombinant human FVIII when metabolically labeled with [35S]-sulfate upon expression in Chinese hamster ovary (CHO) cells or monkey kidney tissue COS-1 cells contains six potential tyrosine sulfation sites, ie, four on the heavy chain (at amino acid residues 365, 737, 738, and 742) and two in the a3 subdomain of the light chain (residues 1683 and 1699) (Pittman DD et al. 1992; Michnick DA et al. 1994). The presence of six tyrosine sulfate residues in FVIII was further confirmed by a combination of liquid chromatography and electrospray ionization mass spectrometry (LC/ESI-MS) studies of the recombinant human FVIII protein derived from baby hamster kidney (BHK) cells (Severs JC et al. 1999) or CHO cells (Schmidbauer S et al. 2015). Site-directed mutagenesis of individual or multiple tyrosine residues showed that all the six sulfation sites are required to modulate FVIII activity (Pittman DD et al. 1992; Michnick DA et al. 1994). Further, treatment of CHO cells that express FVIII with sodium chlorate, an inhibitor of ATP sulphurylase involved in the synthesis of PAPS, did not affect FVIII secretion, but reduced the functional activity by 5-fold, indicating that sulfation was not required for FVIII secretion (Pittman DD et al. 1992). In addition, mutagenesis of Tyr1699 to Phe (Y1699F) demonstrated that sulfation at that residue was required for high affinity interaction of FVIII with von Willebrand factor (vWF) (Leyte A et al. 1991). In the absence of tyrosine sulfation at 1699 in FVIII, the affinity for vWF was reduced by 5-fold (Leyte A et al. 1991). The nuclear magnetic resonance (NMR) spectrum studies of the complex between FVIII and vWF showed significantly larger residue-specific chemical shift changes when Y1699 was sulfated further highlighting the importance of FVIII sulfation at Y1699 for the binding affinity to vWF (Dagil L et al. 2019). The significance of FVIII sulfation at Y1699 in vivo is made evident by the presence of a Y1699F mutation that causes a moderate hemophilia A, likely due to reduced interaction with vWF and decreased plasma half-life (Higuchi M et al. 1990; van den Biggelaar M et al. 2011). Sulfation at tyrosine residues 365 and 1683 increased FVIII activity by increasing the rate of thrombin cleavage at the adjacent thrombin cleavage sites 391 and 1708, respectively (Michnick DA et al. 1994). Mutation of tyrosine residues 737, 738, and 742 had no effect on the thromhin activation rate, even though the cleavage rate at Arg759 was slightly reduced (Michnick et al. 1994). Further. lower FXa-generation activity (86% of the wild-type activity) and lower clotting activity (51% of the wild-type activity) was observed for the FVIII triple point mutant at Tyr residues 737, 738, and 742 (Michnick et al. 1994). This result is in contrast to other study in which no functional differences were found between full-length FVIIl lacking sulfation at one or more of these three residues (Y737, Y738, and Y742) and the fully sulfated form of FVIII (Mikkelsen J et al. 1991).

Protein tyrosine O-sulfation is a common post-translational modification that is catalyzed by a tyrosyl protein sulfotransferase (TPST) (Moore KL 2003; Yang YS et al. 2015). In humans, two TPST isoforms, termed TPST1 and

TPST2, have been identified (Ouyang Yb et al. 1998; Mishiro E et al. 2006). The enzyme was shown to catalyze the transfer of sulfate from the universal sulfate donor adenosine 3′-phosphate 5′-phosphosulfate (PAPS) to the hydroxyl group of a peptidyltyrosine residue to form a tyrosine O4-sulfate ester and 3′,5′-ADP (Lee RW & Huttner WB 1983). Structural studies showed that human TPSTs share the same catalytic mechanism (Teramoto T et al. 2013; Tanaka S et al. 2017). In mammalian cells, tyrosine O-sulfation of membrane and secretory proteins was found to occur in the trans-Golgi network, and biochemical studies indicated that the enzyme was membrane-bound (Lee RW & Huttner WB 1985; Baeuerle PA & Huttner WB 1987).

Literature references

Adachi, R., Nakanishi, Y., Kurogi, K., Kawaguchi, Y., Kakuta, Y., Suiko, M. et al. (2013). Crystal structure of human tyrosylprotein sulfotransferase-2 reveals the mechanism of protein tyrosine sulfation reaction. *Nat Commun, 4*, 1572. ↗

Pittman, DD., Kaufman, RJ., Wang, JH. (1992). Identification and functional importance of tyrosine sulfate residues within recombinant factor VIII. *Biochemistry, 31*, 3315-25. ↗

Moore, KL., Danan, LM., Hoffhines, AJ., Leary, JA., Yu, Z. (2008). Mass spectrometric kinetic analysis of human tyrosylprotein sulfotransferase-1 and -2. *J. Am. Soc. Mass Spectrom., 19*, 1459-66. ↗

Lane, WS., Ouyang, Yb., Moore, KL. (1998). Tyrosylprotein sulfotransferase: purification and molecular cloning of an enzyme that catalyzes tyrosine O-sulfation, a common posttranslational modification of eukaryotic proteins. *Proc. Natl. Acad. Sci. U.S.A., 95*, 2896-901. ↗

Pittman, DD., Kaufman, RJ., Wise, RJ., Michnick, DA. (1994). Identification of individual tyrosine sulfation sites within factor VIII required for optimal activity and efficient thrombin cleavage. *J. Biol. Chem., 269*, 20095-102. ↗

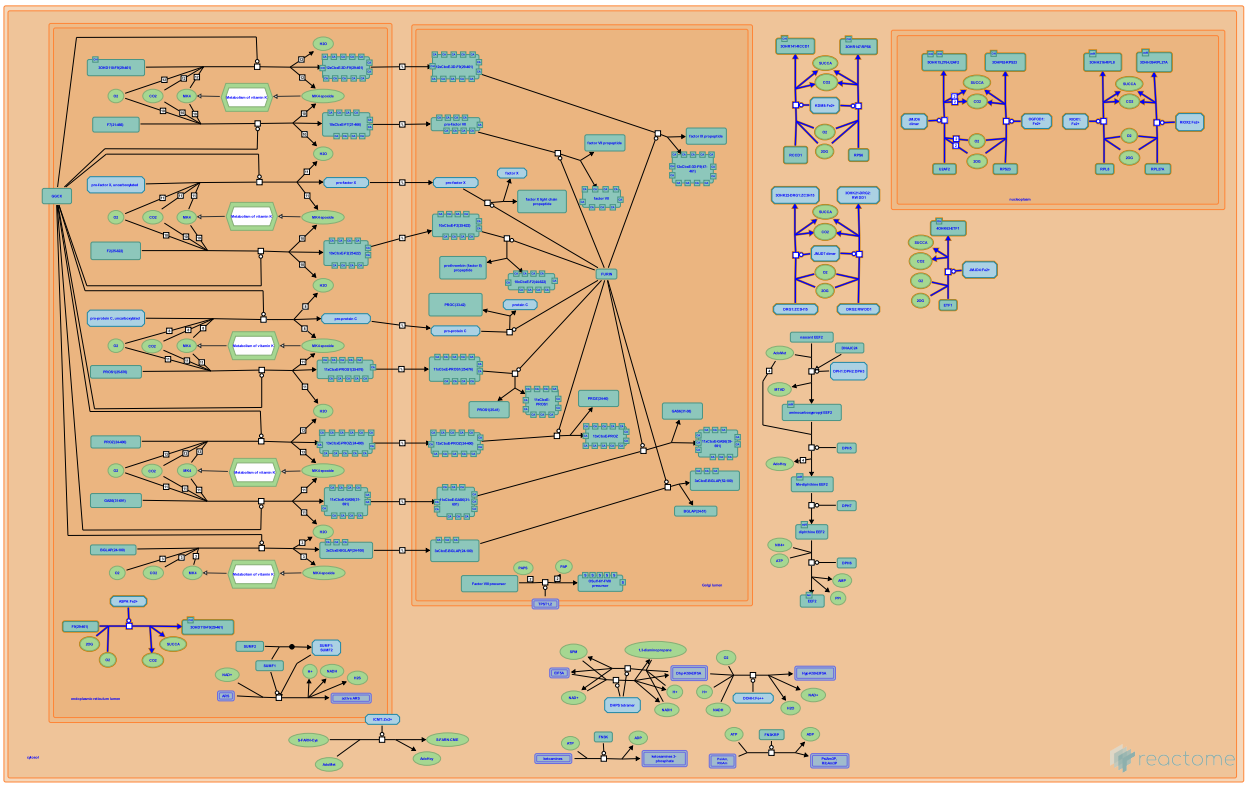
Editions

2019-11-19	Authored	Shamovsky, V.
2020-01-09	Reviewed	D'Eustachio, P.
2020-04-02	Reviewed	Zhang, B.
2020-05-26	Edited	Shamovsky, V.

Protein hydroxylation ↗

Location: Gamma carboxylation, hypusinylation, hydroxylation, and arylsulfatase activation

Stable identifier: R-HSA-9629569



This pathway groups reactions mediated by 2-OG (2-oxoglutarate)-dependent oxygenases that target proline, lysine, asparagine, arginine, aspartate, and histidine residues of diverse proteins, with effects that potentially modulate transcription and translation (Herr & Hausinger 2018; Markolovic et al. 2015; Stoehr et al. 2016; Zurlo et al. 2016).

The roles of members of this enzyme family in collagen assembly are annotated separately in pathway R-HSA-1650814, "Collagen biosynthesis and modifying enzymes".

Literature references

Murphy, E., Kloner, PH., Evangelista, AM., Lin, Y., Wang, G., Aponte, A. et al. (2016). Prolyl hydroxylation regulates protein degradation, synthesis, and splicing in human induced pluripotent stem cell-derived cardiomyocytes. *Cardiovasc. Res., 110*, 346-58. ↗

Hausinger, RP., Herr, CQ. (2018). Amazing Diversity in Biochemical Roles of Fe(II)/2-Oxoglutarate Oxygenases. *Trends Biochem. Sci., 43*, 517-532. ↗

Markolovic, S., Schofield, CJ., Wilkins, SE. (2015). Protein Hydroxylation Catalyzed by 2-Oxoglutarate-dependent Oxygenases. *J. Biol. Chem., 290*, 20712-22. ↗

Zurlo, G., Takada, M., Zhang, Q., Wei, W., Guo, J. (2016). New Insights into Protein Hydroxylation and Its Important Role in Human Diseases. *Biochim. Biophys. Acta, 1866*, 208-220. ↗

Editions

2018-11-24	Authored, Edited	D'Eustachio, P.

Table of Contents