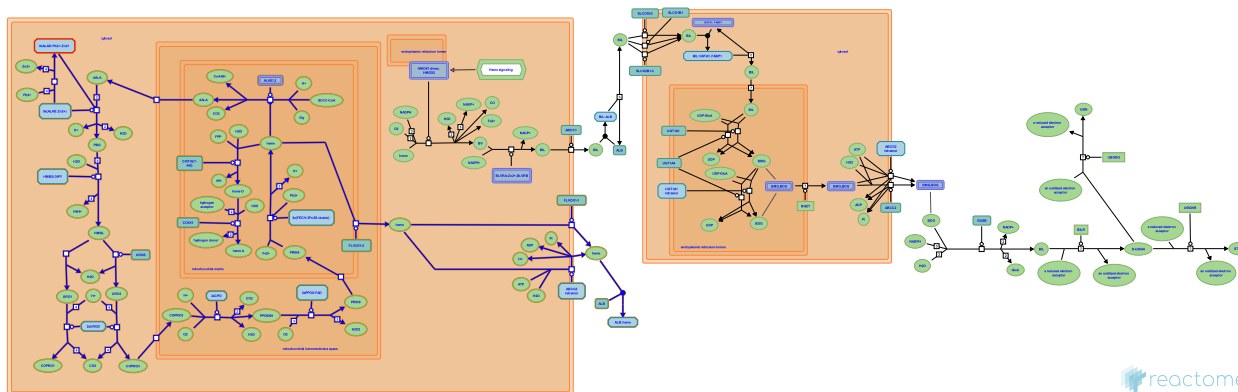


Heme biosynthesis



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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](https://reactome.org/textbook/).

25/04/2024

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).

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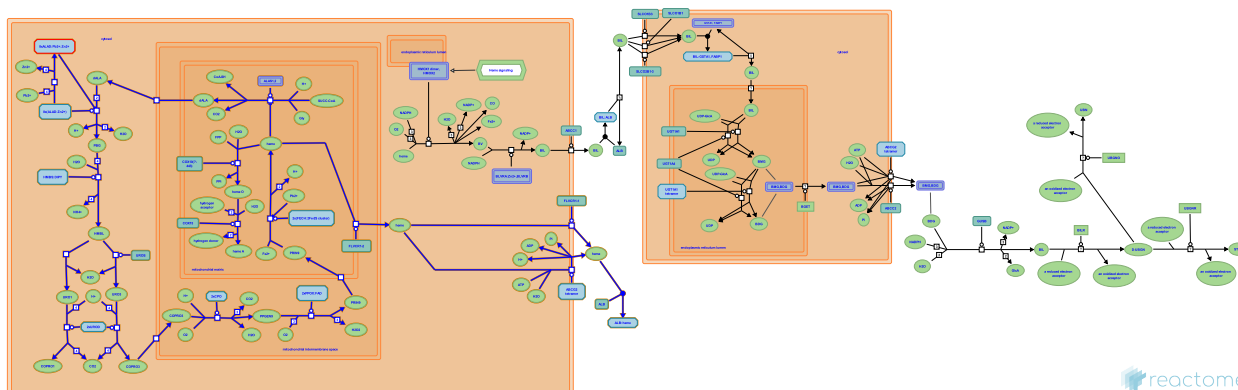
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Reactome database release: 88

This document contains 1 pathway and 20 reactions ([see Table of Contents](#))

Heme biosynthesis ↗

Stable identifier: R-HSA-189451



Although heme is synthesised in virtually all tissues, the principal sites of synthesis are erythroid cells (~85%) and hepatocytes (most of the remainder). Eight enzymes are involved in heme biosynthesis, four each in the mitochondria and the cytosol (Layer et al. 2010). The process starts in the mitochondria with the condensation of succinyl CoA (from the TCA cycle) and glycine to form 5-aminolevulinic acid (ALA). The next four steps take place in the cytosol. Two molecules of ALA are condensed to form the monopyrrole porphobilinogen (PBG). The next two steps convert four molecules of PBG into the cyclic tetrapyrrole uroporphyrinogen III, which is then decarboxylated into coproporphyrinogen III. The last three steps occur in the mitochondria and involve modifications to the tetrapyrrole side chains and finally, insertion of iron. In addition to these synthetic steps, a spontaneous cytosolic reaction allows the formation of uroporphyrinogen I which is then enzymatically decarboxylated to coproporphyrinogen I, which cannot be metabolized further in humans. Also, lead can inactivate ALAD, the enzyme that catalyzes PBG synthesis, and ferrochelatase, the enzyme that catalyzes heme synthesis (Ponka et al. 1999, Aijoka et al. 2006).

The porphyrias are disorders that arise from defects in the enzymes of heme biosynthesis. Defective pathway enzymes after ALA synthase result in accumulated substrates which can cause either skin problems, neurological complications, or both due to their toxicity in higher concentrations. They are broadly classified as hepatic porphyrias or erythropoietic porphyrias, based on the site of the overproduction of the substrate. Each defect is described together with the reaction it affects (Peoc'h et al. 2016).

Literature references

- Heinz, DW., Jahn, D., Layer, G., Reichelt, J. (2010). Structure and function of enzymes in heme biosynthesis. *Protein Sci.*, 19, 1137-61. ↗
- Phillips, JD., Ajioka, RS., Kushner, JP. (2006). Biosynthesis of heme in mammals. *Biochim Biophys Acta*, 1763, 723-36. ↗
- Deybach, JC., Puy, H., Peoc'h, K., Talbi, N., Gouya, L., Martin-Schmitt, C. (2016). [Porphyrias and haem related disorders]. *Rev Med Interne*, 37, 173-85. ↗
- Ponka, P. (1999). Cell biology of heme. *Am J Med Sci*, 318, 241-56. ↗

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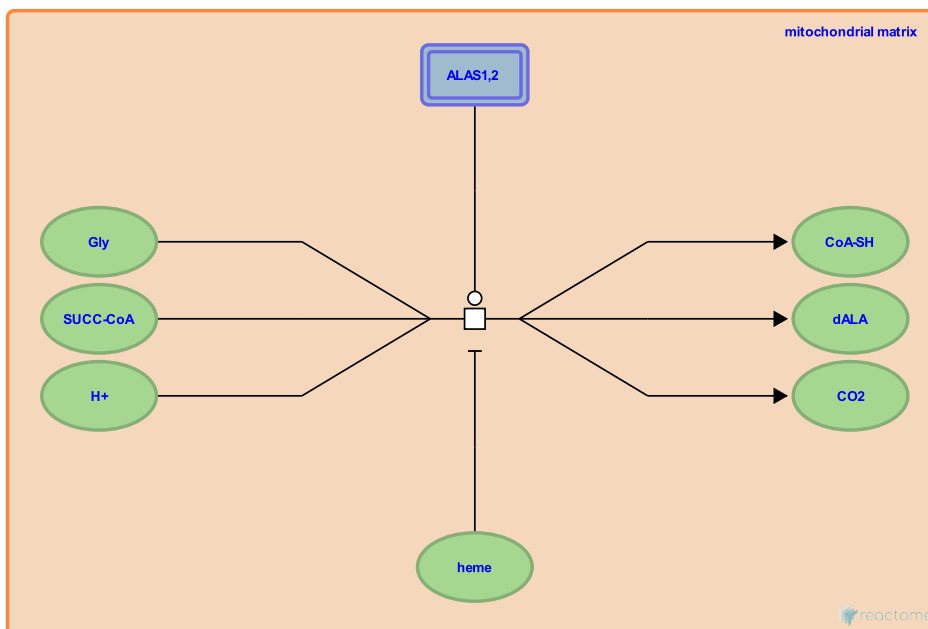
ALAS condenses SUCC-CoA and Gly to form dALA [↗](#)

Location: [Heme biosynthesis](#)

Stable identifier: R-HSA-189442

Type: transition

Compartments: mitochondrial matrix



The committed step for porphyrin synthesis is the formation of 5-aminolevulinic acid (ALA) by condensation of glycine (from the general amino acid pool) and succinyl-CoA (from the TCA cycle), in the mitochondrial matrix. The reaction is catalyzed by two different ALA synthases, one expressed ubiquitously (ALAS1) and the other only expressed in erythroid precursors (ALAS2). Both enzymes are expressed as homodimers and require pyridoxal 5-phosphate as a cofactor.

No disease-causing mutations of ALAS1 have been recognised in humans. Mutations in ALAS2 cause X-linked sideroblastic anaemia (XLSA), characterised by a microcytic hypochromic anaemia.

Followed by: [Mitochondrial dALA translocates to cytosol](#)

Literature references

Cox, TM., Smith, SJ., Gardner, LC. (1991). Biosynthesis of delta-aminolevulinic acid and the regulation of heme formation by immature erythroid cells in man. *J Biol Chem*, 266, 22010-8. [↗](#)

Heinz, DW., Jahn, D., Schubert, WD., van den Heuvel, J., Schulze, JO., Astner, I. (2005). Crystal structure of 5-aminolevulinic acid synthase, the first enzyme of heme biosynthesis, and its link to XLSA in humans. *EMBO J*, 24, 3166-77. [↗](#)

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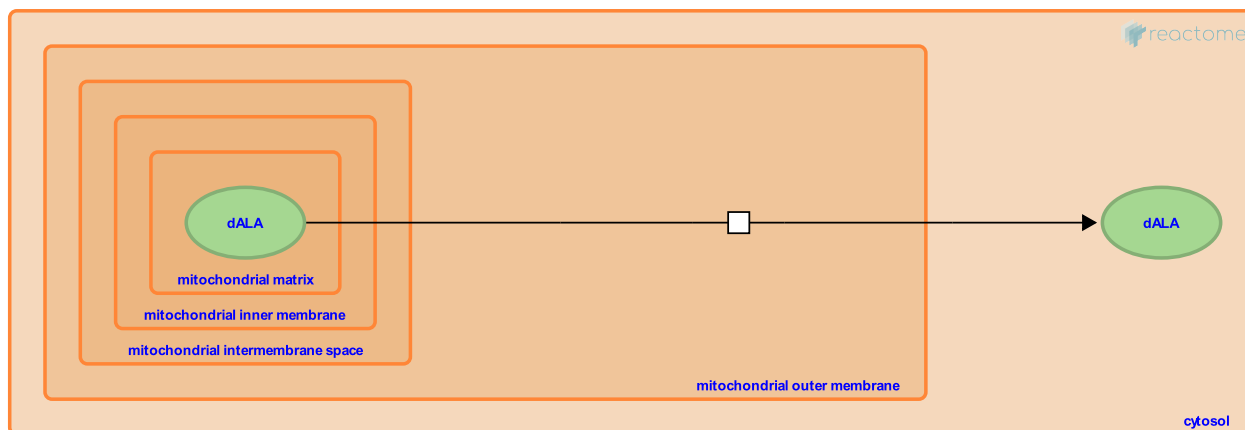
Mitochondrial dALA translocates to cytosol ↗

Location: [Heme biosynthesis](#)

Stable identifier: R-HSA-189456

Type: transition

Compartments: mitochondrial outer membrane



5-aminolevulinate (dALA) is transported from the mitochondrial matrix to the cytosol. While indirect studies suggest that activity of the ABCB10 transporter is correlated with dALA production (Bayeva et al. 2013), biochemical studies of the purified protein indicate that dALA is not a transported substrate (Qiu et al. 2015), leaving the transporter that mediates dALA export to the cytosol and the role of ABCB10 in heme biosynthesis unknown.

Preceded by: [ALAS condenses SUCC-CoA and Gly to form dALA](#)

Followed by: [ALAD condenses 2 dALAs to form PBG](#)

Literature references

Shirihai, OS., Qiu, W., Carpenter, EP., Liesa, M. (2015). ATP Binding and Hydrolysis Properties of ABCB10 and Their Regulation by Glutathione. *PLoS ONE*, 10, e0129772. ↗

Singh, N., Shirihai, OS., Paw, BH., Wu, R., Ardehali, H., Burke, MA. et al. (2013). ATP-binding cassette B10 regulates early steps of heme synthesis. *Circ. Res.*, 113, 279-87. ↗

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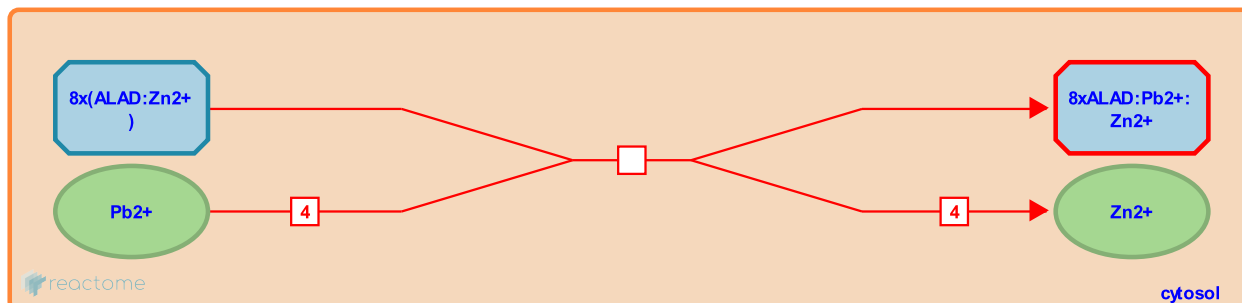
ALAD binds to Pb2+ ↗

Location: [Heme biosynthesis](#)

Stable identifier: R-HSA-190141

Type: transition

Compartments: cytosol



Lead binds to ALAD enzyme displacing half the zinc ions essential for its catalytic activity and inactivating it. Lead is a major environmental toxin and this enzyme is one of its principal molecular targets (Jaffe et al. 2001).

Literature references

Martins, J., Dunbrack RL, Jr., Kervinen, J., Li, J., Jaffe, EK. (2001). The molecular mechanism of lead inhibition of human porphobilinogen synthase. *J Biol Chem*, 276, 1531-7. ↗

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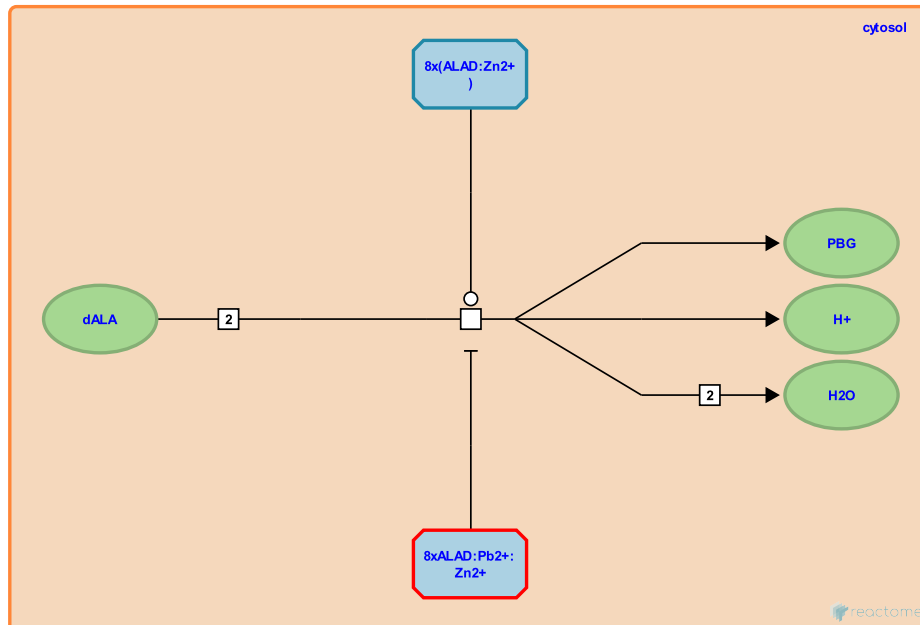
ALAD condenses 2 dALAs to form PBG ↗

Location: [Heme biosynthesis](#)

Stable identifier: R-HSA-189439

Type: transition

Compartments: cytosol



5-Aminolevulinic acid dehydratase (ALAD aka porphobilinogen synthase, PBGS), catalyzes the asymmetric condensation of two molecules of ALA to form porphobilinogen (PBG). The substrate that becomes the acetyl side chain-containing half of PBG is called A-side ALA; the half that becomes the propionyl side chains and the pyrrole nitrogen is called P-ALA (Jaffe 2004). PBG is the first pyrrole formed, the precursor to all tetrapyrrole pigments such as heme and chlorophyll. There are at least eight bonds that are made or broken during this reaction. The active form of the ALAD enzyme is an octamer complexed with eight Zn²⁺ ions, four that are strongly bound and four that are weakly bound. The four weakly bound ones are dispensible for enzyme activity in vitro (Bevan et al. 1980; Mitchell et al. 2001).

Deficiencies of ALAD enzyme in vivo are associated with 5-aminolevulinic acid dehydratase-deficient porphyria (e.g., Akagi et al. 2000).

Preceded by: [Mitochondrial dALA translocates to cytosol](#)

Followed by: [4 PBGs bind to form HMB](#)

Literature references

Martins, J., Mitchell, LW., Volin, M., Jaffe, EK. (2001). Mechanistic implications of mutations to the active site lysine of porphobilinogen synthase. *J Biol Chem*, 276, 1538-44. ↗

Akagi, R., Sassa, S., Doss, MO., Furuyama, K., Shimizu, R. (2000). Novel molecular defects of the delta-aminolevulinic acid dehydratase gene in a patient with inherited acute hepatic porphyria. *Hepatology*, 31, 704-8. ↗

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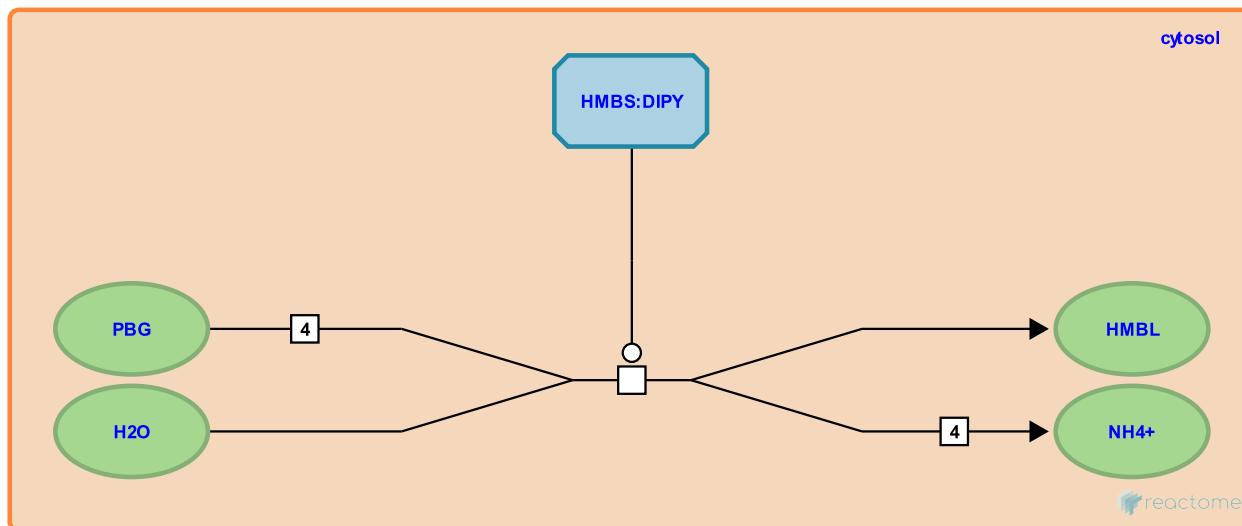
4 PBGs bind to form HMB ↗

Location: [Heme biosynthesis](#)

Stable identifier: R-HSA-189406

Type: transition

Compartments: cytosol



Cytosolic porphobilinogen deaminase catalyzes the polymerization of four molecules of porphobilinogen (PBG) to generate hydroxymethylbilane (HMB), an unstable tetrapyrrole. This reaction is the first step in the formation of the tetrapyrrole macrocycle. Two isoforms of porphobilinogen deaminase are generated by alternative splicing, one expressed in erythroid tissues and one ubiquitously expressed in the body. Deficiencies of both forms of PBG deaminase are associated with acute intermittent porphyria.

Preceded by: [ALAD condenses 2 dALAs to form PBG](#)

Followed by: [UROS transforms HMB to URO3](#), [HMBL spontaneously transforms to URO1](#)

Literature references

Anderson, PM., Desnick, RJ. (1980). Purification and properties of uroporphyrinogen I synthase from human erythrocytes. Identification of stable enzyme-substrate intermediates. *J Biol Chem*, 255, 1993-9. ↗

Sarwar, M., Shoolingin-Jordan, PM., Butler, D., McNeill, LA., Al-Dbass, A. (2003). Human porphobilinogen deaminase mutations in the investigation of the mechanism of dipyrromethane cofactor assembly and tetrapyrrole formation. *Biochem Soc Trans*, 31, 731-5. ↗

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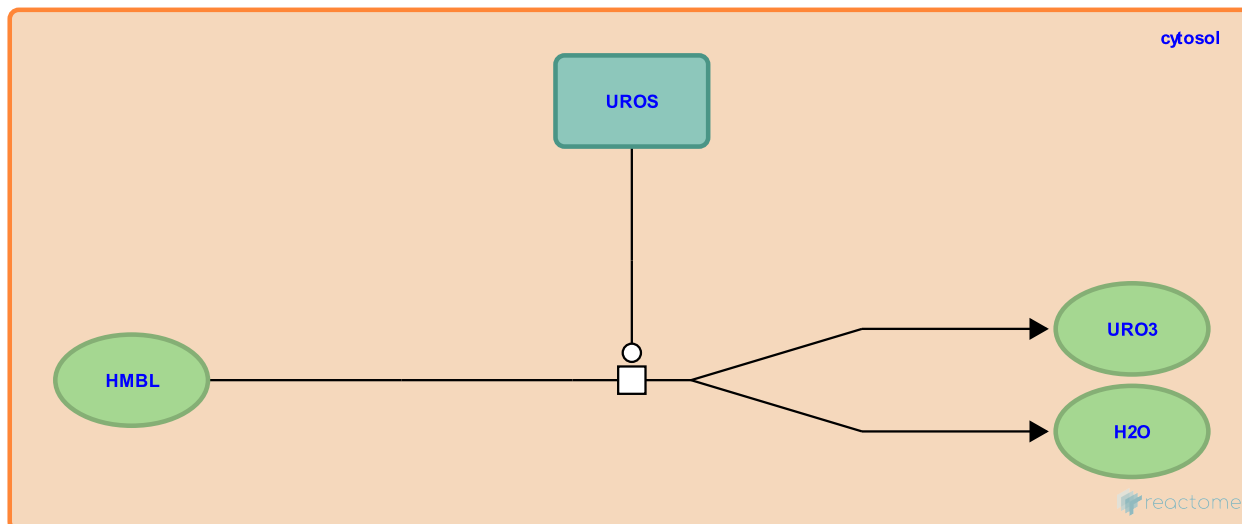
UROS transforms HMB to URO3 [↗](#)

Location: [Heme biosynthesis](#)

Stable identifier: R-HSA-189488

Type: transition

Compartments: cytosol



Cytosolic uroporphyrinogen III synthase (URO3S) catalyzes the conversion of HMB (hydroxymethylbilane) to uroporphyrinogen III, a reaction involving ring closure and intramolecular rearrangement. Uroporphyrinogen III represents a branch point for the pathways leading to formation of heme, chlorophyll and corrins. HMB is rapidly converted from a linear tetrapyrrole to the cyclic form. Deficiencies of URO3S in vivo are associated with congenital erythropoietic porphyria.

Preceded by: [4 PBGs bind to form HMB](#)

Followed by: [UROD decarboxylates URO3 to COPRO3](#)

Literature references

Tsai, SF., Bishop, DF., Desnick, RJ. (1987). Purification and properties of uroporphyrinogen III synthase from human erythrocytes. *J Biol Chem*, 262, 1268-73. [↗](#)

Shoolingin-Jordan, PM. (1995). Porphobilinogen deaminase and uroporphyrinogen III synthase: structure, molecular biology, and mechanism. *J Bioenerg Biomembr*, 27, 181-95. [↗](#)

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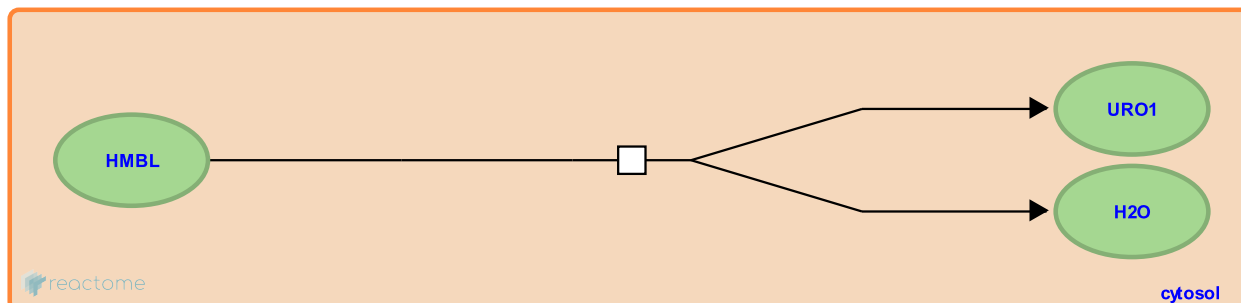
HMBL spontaneously transforms to URO1 [↗](#)

Location: [Heme biosynthesis](#)

Stable identifier: R-HSA-190168

Type: transition

Compartments: cytosol



Hydroxymethylbilane (HMBL) can spontaneously cyclize and rearrange to form uroporphyrinogen I (URO1).

Preceded by: [4 PBGs bind to form HMB](#)

Followed by: [UROD decarboxylates URO1 to COPRO1](#)

Literature references

Tsai, SF., Bishop, DF., Desnick, RJ. (1987). Purification and properties of uroporphyrinogen III synthase from human erythrocytes. *J Biol Chem*, 262, 1268-73. [↗](#)

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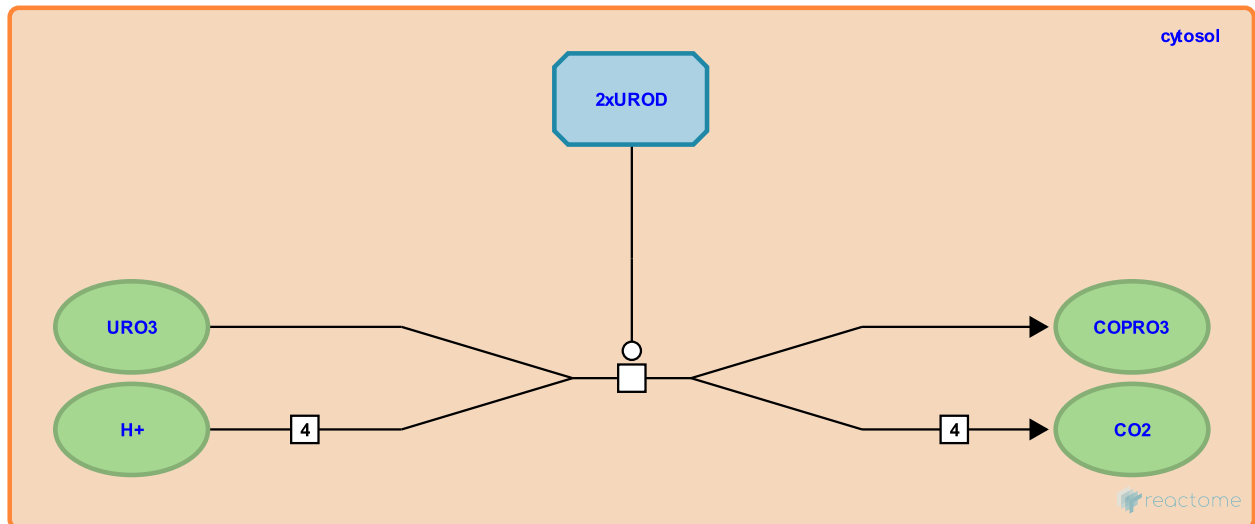
UROD decarboxylates URO3 to COPRO3 ↗

Location: [Heme biosynthesis](#)

Stable identifier: R-HSA-189425

Type: transition

Compartments: cytosol



Cytosolic uroporphyrinogen decarboxylase (UROD) catalyzes the sequential removal of four carboxylic groups from the acetic acid side chains of uroporphyrinogen III (URO3) to form coproporphyrinogen III (COPRO3) (de Verneuil et al. 1983). Human UROD is a dimer (Whitby et al. 1998). Heterogenous and homogenous deficiencies of UROD are associated with porphyria cutanea tarda and hepatoerythropoietic porphyria respectively in vivo (Moran-Jimenez et al. 1996).

Preceded by: [UROS transforms HMB to URO3](#)

Followed by: [Cytosolic COPRO3 translocates to mitochondrial intermembrane space](#)

Literature references

Romana, M., Taieb, A., Topi, G., Moran-Jimenez, MJ., Ged, C., D'Alessandro, L. et al. (1996). Uroporphyrinogen decarboxylase: complete human gene sequence and molecular study of three families with hepatoerythropoietic porphyria. *Am J Hum Genet*, 58, 712-21. ↗

Sassa, S., de Verneuil, H., Kappas, A. (1983). Purification and properties of uroporphyrinogen decarboxylase from human erythrocytes. A single enzyme catalyzing the four sequential decarboxylations of uroporphyrinogens I and III. *J Biol Chem*, 258, 2454-60. ↗

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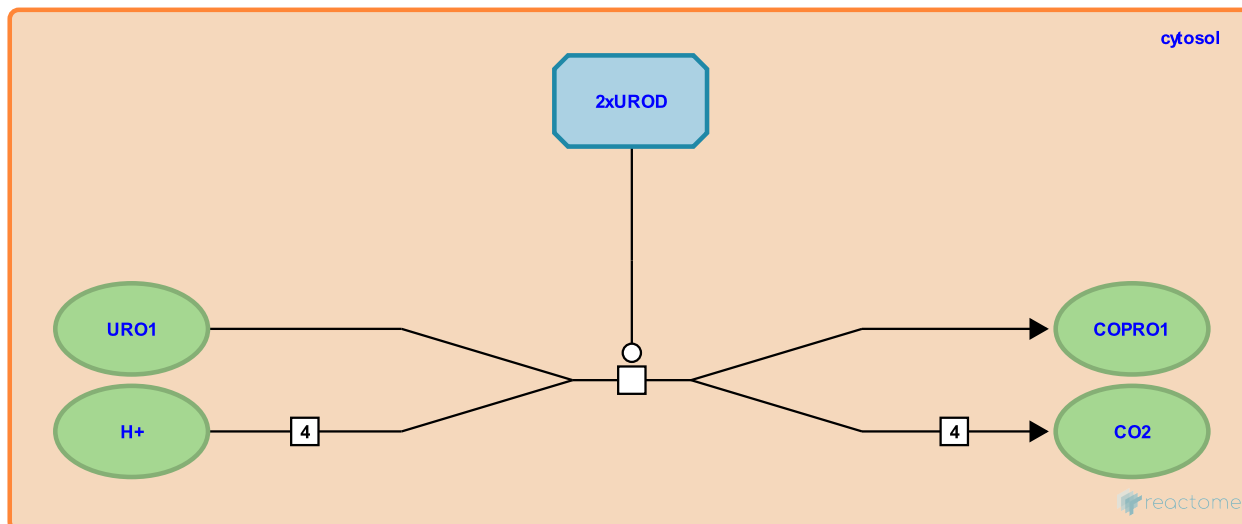
UROD decarboxylates URO1 to COPRO1 ↗

Location: [Heme biosynthesis](#)

Stable identifier: R-HSA-190182

Type: transition

Compartments: cytosol



Cytosolic uroporphyrinogen decarboxylase (UROD) catalyzes the sequential removal of four carboxylic groups from the acetic acid side chains of uroporphyrinogen I (URO1) to form coproporphyrinogen I (COPRO1). UROD catalyzes this reaction less efficiently than the decarboxylation of uroporphyrinogen III (de Verneuil et al. 1983).

Preceded by: [HMBL spontaneously transforms to URO1](#)

Literature references

Romana, M., Taieb, A., Topi, G., Moran-Jimenez, MJ., Ged, C., D'Alessandro, L. et al. (1996). Uroporphyrinogen decarboxylase: complete human gene sequence and molecular study of three families with hepatoerythropoietic porphyria. *Am J Hum Genet*, 58, 712-21. ↗

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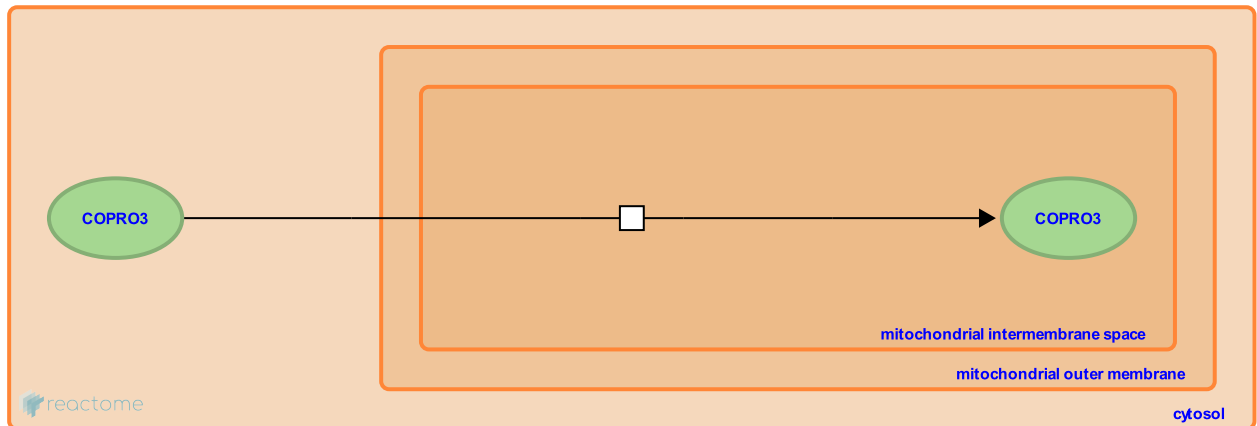
Cytosolic COPRO3 translocates to mitochondrial intermembrane space ↗

Location: [Heme biosynthesis](#)

Stable identifier: R-HSA-189467

Type: transition

Compartments: mitochondrial intermembrane space, cytosol



Coproporphyrinogen III (COPRO3) enters the mitochondrial intermembrane space from the cytosol. It is not known whether this process is facilitated by a transporter (Grandchamp et al. 1978).

Preceded by: [UROD decarboxylates URO3 to COPRO3](#)

Followed by: [CPO transforms COPRO3 to PPGEN9](#)

Literature references

Grandchamp, B., Phung, N., Nordmann, Y. (1978). The mitochondrial localization of coproporphyrinogen III oxidase . *Biochem. J.*, 176, 97-102. ↗

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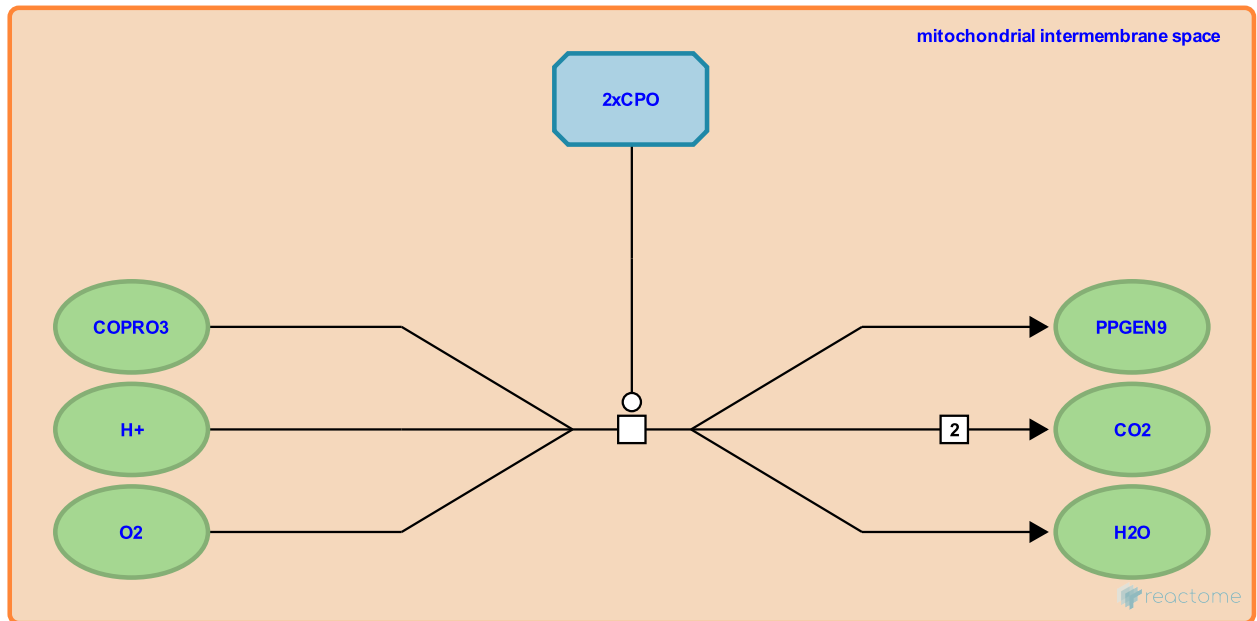
CPO transforms COPRO3 to PPGEN9 ↗

Location: [Heme biosynthesis](#)

Stable identifier: R-HSA-189421

Type: transition

Compartments: mitochondrial intermembrane space



O₂-dependent coproporphyrinogen oxidase (CPO) catalyzes the conversion of coproporphyrinogen III (COPRO3) to protoporphyrinogen IX (PPGEN9) (Martasek et al. 1994). The localization of the human enzyme to the mitochondrial intermembrane space is inferred from studies of the homologous rat enzyme (Elder and Evans 1978). The human enzyme functions as a homodimer (Lee et al. 2005). Enzyme deficiency is associated with hereditary coproporphyrinuria in vivo.

Preceded by: [Cytosolic COPRO3 translocates to mitochondrial intermembrane space](#)

Followed by: [PPO oxidises PPGEN9 to PRIN9](#)

Literature references

Grandchamp, B., Labbe, P., Dumas, JB., de Verneuil, H., Delfau-Larue, MH., Montagne, JJ. et al. (1994). Molecular cloning, sequencing, and functional expression of a cDNA encoding human coproporphyrinogen oxidase. *Proc Natl Acad Sci U S A*, 91, 3024-8. ↗

Evans, JO., Elder, GH. (1978). Evidence that the coproporphyrinogen oxidase activity of rat liver is situated in the intermembrane space of mitochondria. *Biochem J*, 172, 345-7. ↗

Cooper, CL., Jones, MA., Lash, TD. (2005). Kinetic evaluation of human cloned coproporphyrinogen oxidase using a ring isomer of the natural substrate. *Med Sci Monit*, 11, BR420-5. ↗

Lee, DS., Martasek, P., Flachsova, E., Demeler, B., Bodnarova, M., Raman, CS. (2005). Structural basis of hereditary coproporphyrinuria. *Proc Natl Acad Sci U S A*, 102, 14232-7. ↗

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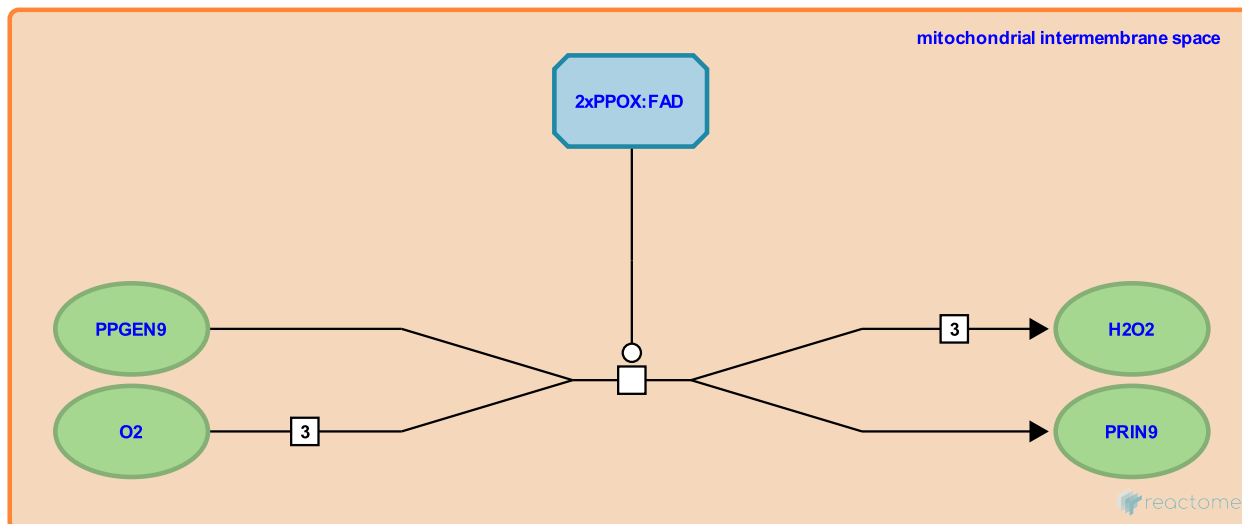
PPO oxidises PPGEN9 to PRIN9 ↗

Location: [Heme biosynthesis](#)

Stable identifier: R-HSA-189423

Type: transition

Compartments: mitochondrial intermembrane space



Six electrons are oxidized in protoporphyrinogen IX (PPGEN9) to form the planar macrocycle protoporphyrin IX (PRIN9). This reaction is performed by the enzyme protoporphyrinogen oxidase (PPO). PPO functions as a homodimer containing one noncovalently-bound FAD. The protein resides on the outer surface of the inner mitochondrial membrane. PPO deficiency is associated with variegate porphyria in vivo (Dailey & Dailey 1996; Wang et al. 2013).

Preceded by: [CPO transforms COPRO3 to PPGEN9](#)

Followed by: [Mitochondrial intermembrane PRIN9 translocates to mitochondrial matrix](#)

Literature references

Tan, Y., Wen, X., Wang, B., Qin, X., Shen, Y., Wang, Z. et al. (2013). Quantitative structural insight into human variegate porphyria disease. *J Biol Chem*, 288, 11731-40. ↗

Dailey, TA., Dailey, HA. (1996). Human protoporphyrinogen oxidase: expression, purification, and characterization of the cloned enzyme. *Protein Sci*, 5, 98-105. ↗

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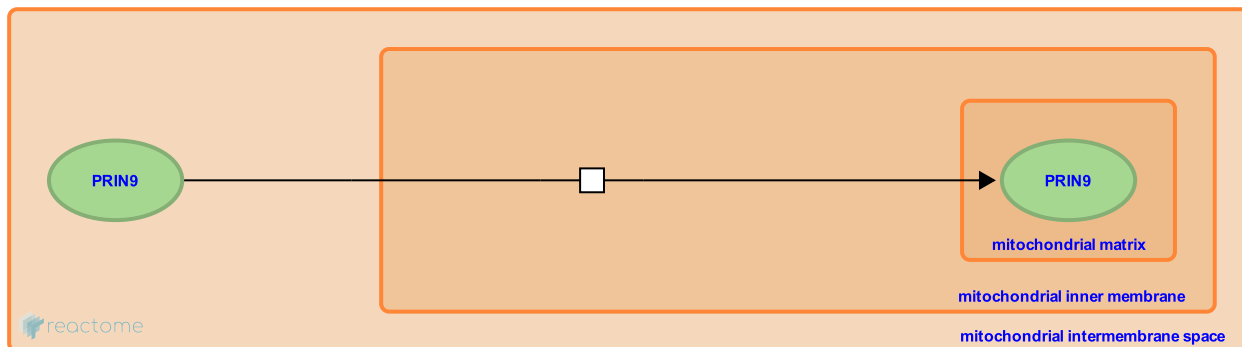
Mitochondrial intermembrane PRIN9 translocates to mitochondrial matrix [↗](#)

Location: [Heme biosynthesis](#)

Stable identifier: R-HSA-189457

Type: transition

Compartments: mitochondrial inner membrane



Protoporphyrin IX (PRIN9) is transported into the mitochondrial matrix where it becomes available for the last step in the heme biosynthetic pathway. The transporter that mediates this event is unknown (Krishnamurthy et al. 2006).

Preceded by: [PPO oxidises PPGEN9 to PRIN9](#)

Followed by: [FECH binds Fe²⁺ to PRIN9 to form heme](#)

Literature references

Sosa-Pineda, B., Sampath, J., Fukuda, Y., Sun, D., Murti, KG., Krishnamurthy, PC. et al. (2006). Identification of a mammalian mitochondrial porphyrin transporter. *Nature*, 443, 586-9. [↗](#)

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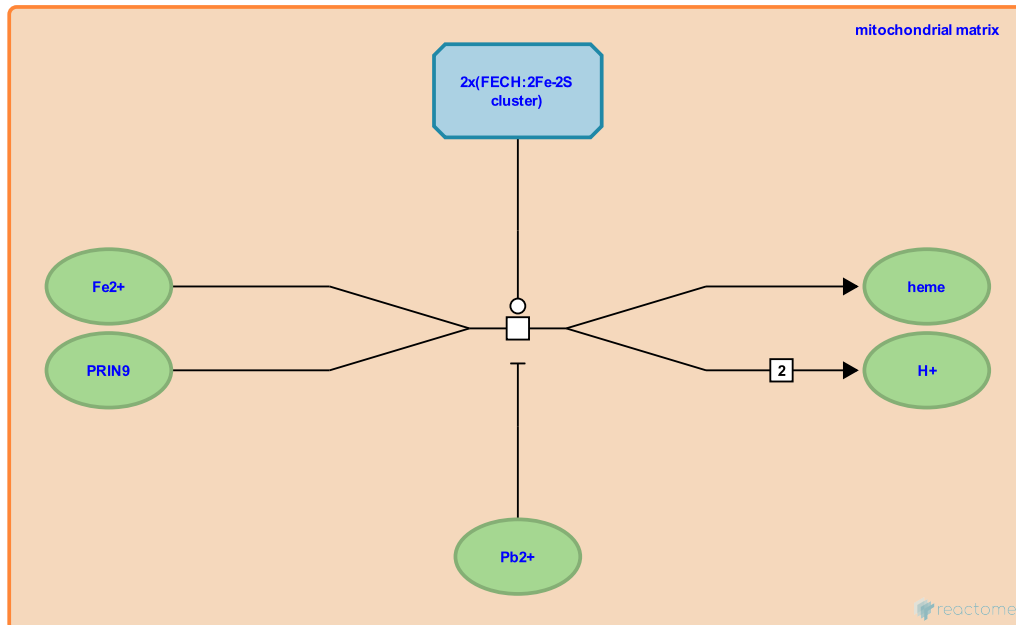
FECH binds Fe²⁺ to PRIN9 to form heme ↗

Location: [Heme biosynthesis](#)

Stable identifier: R-HSA-189465

Type: transition

Compartments: mitochondrial matrix



Ferrochelatase (FECH) catalyzes the insertion of ferrous iron into protoporphyrin IX (PRIN9) to form heme. FECH is localized on the matrix surface of the inner mitochondrial membrane and this reaction takes place within the mitochondrial matrix. The enzyme functions as a homodimer with each monomer containing a nitric oxide-sensitive 2Fe-2S cluster. Enzyme deficiency is associated with erythropoietic protoporphyria in vivo, and inhibition of ferrochelatase activity is a clinically important consequence of lead poisoning (Piomelli et al. 1987).

Preceded by: [Mitochondrial intermembrane PRIN9 translocates to mitochondrial matrix](#)

Followed by: [COX10 transforms heme to heme O](#)

Literature references

Wu, CK., Sellers, VM., Rose, JP., Burden, A., Wang, BC., Dailey, HA. (2001). The 2.0 Å structure of human ferrochelatase, the terminal enzyme of heme biosynthesis. *Nat Struct Biol*, 8, 156-60. ↗

Editions

2007-01-24	Authored, Edited	Jassal, B., D'Eustachio, P.
2007-01-24	Reviewed	Sassa, S.
2009-05-19	Revised	D'Eustachio, P.
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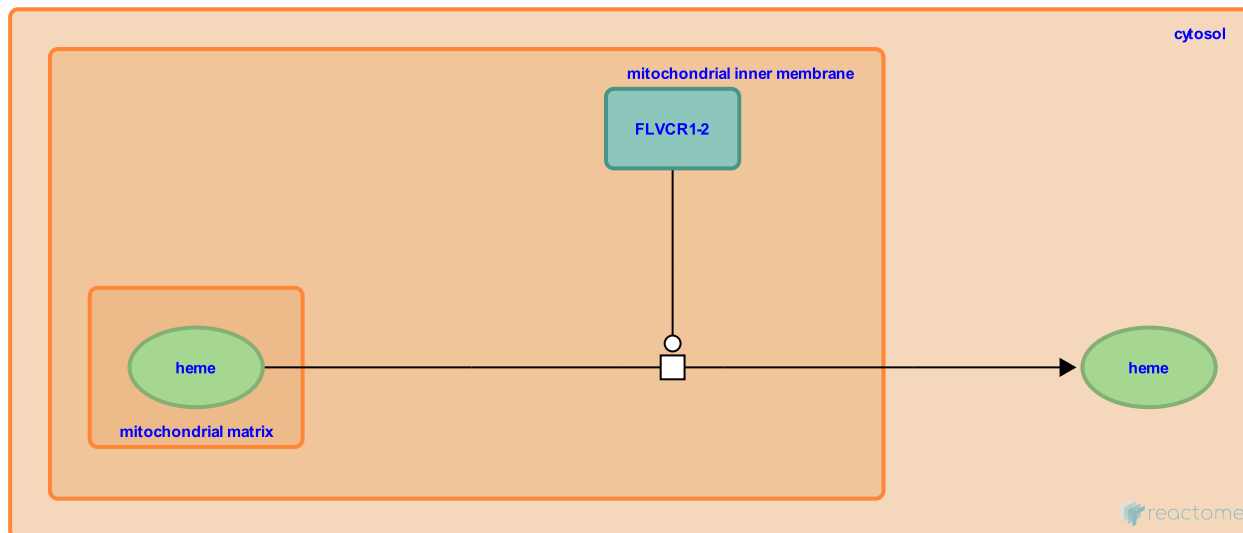
FLVCR1-2 transports heme from mitochondrial matrix to cytosol [↗](#)

Location: [Heme biosynthesis](#)

Stable identifier: R-HSA-9661408

Type: transition

Compartments: mitochondrial inner membrane, mitochondrial matrix, cytosol



Feline leukemia virus subgroup C receptor-related protein 1 isoform 2 (FLVCR1-2), located on the mitochondrial membrane of all hematopoietic tissues, is a heme transporter that mediates heme efflux from the mitochondrion to the cytosol (Chiabrando et al. 2012). Silencing of FLVCR1-2 causes mitochondrial heme accumulation and termination of erythroid differentiation.

Literature references

Pinton, P., Mercurio, S., Altruda, F., Tolosano, E., Vinchi, F., Fagoonee, S. et al. (2012). The mitochondrial heme exporter FLVCR1b mediates erythroid differentiation. *J. Clin. Invest.*, 122, 4569-79. [↗](#)

Editions

2019-09-16	Authored, Edited	Jassal, B.
2019-10-03	Reviewed	D'Eustachio, P.
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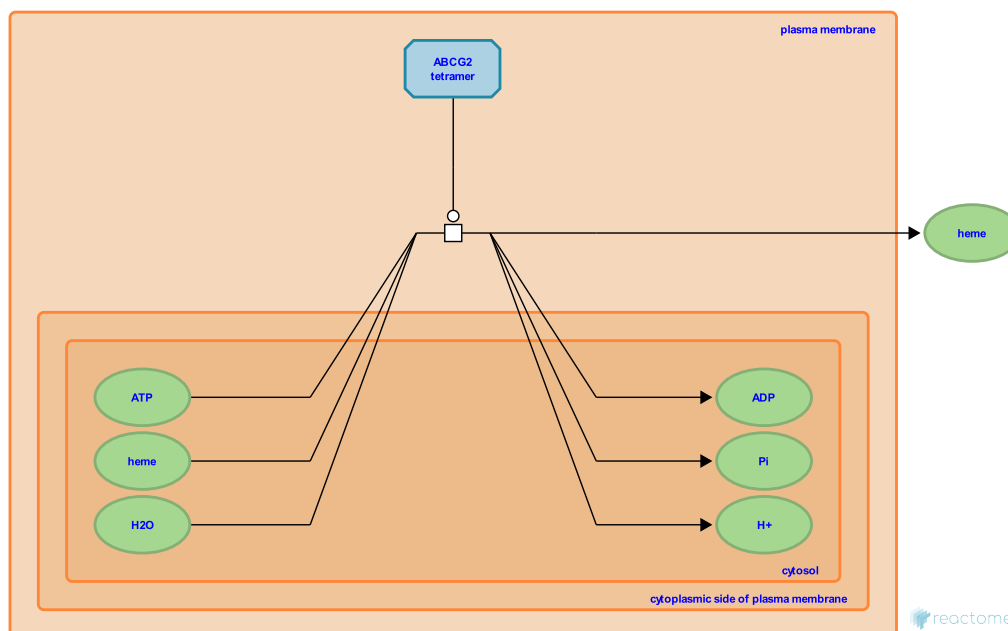
ABCG2 tetramer transports heme from cytosol to extracellular region ↗

Location: [Heme biosynthesis](#)

Stable identifier: R-HSA-917979

Type: transition

Compartments: plasma membrane



Heme is utilised as a prosthetic group in the production of hemoproteins inside cells. However, when intracellular heme accumulation occurs, heme is able to exert its pro-oxidant and cytotoxic action. The amount of free heme must be tightly controlled to maintain cellular homeostasis and avoid pathological conditions (Chiabrando et al. 2014). The tetrameric efflux pump ATP-binding cassette sub-family G member 2 (ABCG2) (Xu et al. 2004) can relieve cells from toxic heme concentrations even against a concentration gradient. It is expressed in placenta, liver, and small intestine (Krishnamurthy et al. 2004, Doyle & Ross 2003, Zhang et al. 2003).

Literature references

- Liu, Y., Xu, J., Bates, S., Zhang, JT., Yang, Y. (2004). Characterization of oligomeric human half-ABC transporter ATP-binding cassette G2. *J. Biol. Chem.*, 279, 19781-9. ↗
- Stanimirovic, DB., Zhang, H., Mojsilovic-Petrovic, J., Andrade, MF., Ball, M., Zhang, W. (2003). The expression and functional characterization of ABCG2 in brain endothelial cells and vessels. *FASEB J*, 17, 2085-7. ↗
- Zhou, S., Sarkadi, B., Ross, DD., Sorrentino, BP., Nakanishi, T., Bailey-Dell, K. et al. (2004). The stem cell marker Bcrp/ABCG2 enhances hypoxic cell survival through interactions with heme. *J Biol Chem*, 279, 24218-25. ↗
- Ross, DD., Doyle, LA. (2003). Multidrug resistance mediated by the breast cancer resistance protein BCRP (ABCG2). *Oncogene*, 22, 7340-58. ↗

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2010-07-07	Authored	Stephan, R.
2010-07-30	Edited	Jassal, B.
2010-11-05	Reviewed	D'Eustachio, P.
2019-09-18	Revised	Jassal, B.
2023-11-22	Revised	D'Eustachio, P.
2024-02-16	Reviewed	Hill, DP.

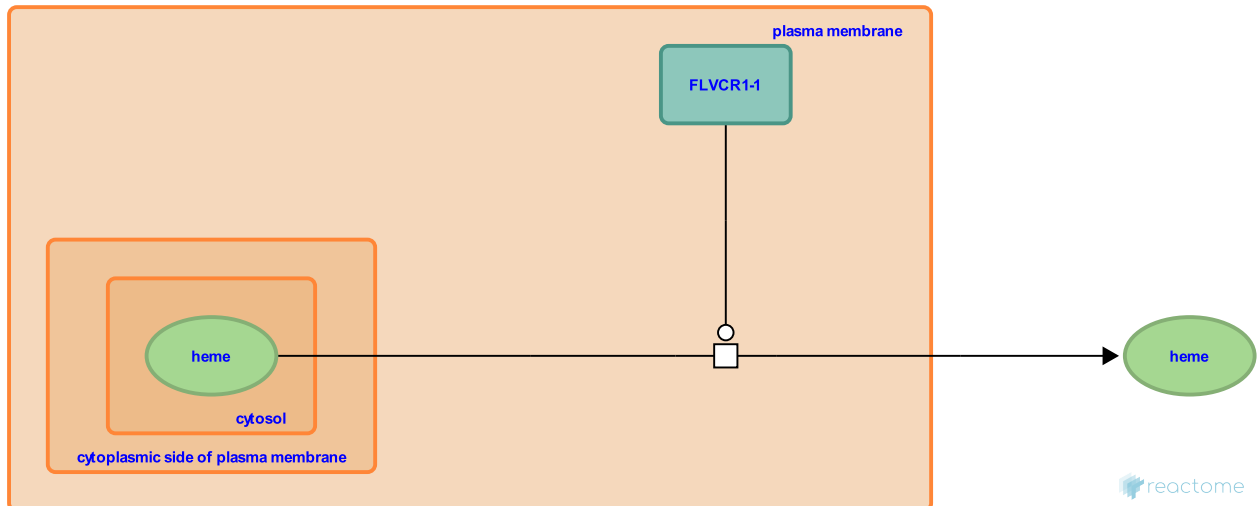
FLVCR1-1 transports heme from cytosol to extracellular region ↗

Location: [Heme biosynthesis](#)

Stable identifier: R-HSA-917892

Type: transition

Compartments: plasma membrane



Heme is utilised as a prosthetic group in the production of hemoproteins inside cells. However, when intracellular heme accumulation occurs, heme is able to exert its pro-oxidant and cytotoxic action. The amount of free heme must be tightly controlled to maintain cellular homeostasis and avoid pathological conditions (Chiabrando et al. 2014). The heme transporter FLVCR is expressed in intestine and liver tissue, but also in developing erythroid cells where it is required to protect them from heme toxicity (Quigley et al, 2004; Rey et al, 2008). Two different isoforms have been described. FLVCR1-1 (FLVCR1a) resides in the plasma membrane and is responsible for heme detoxification in several cell types, such as erythroid progenitors, endothelial cells, hepatocytes, lymphocytes and intestinal cells.

Literature references

Quigley, JG., Sassa, S., Sabo, KM., Berg, CL., Phillips, JD., Sabath, DE. et al. (2004). Identification of a human heme exporter that is essential for erythropoiesis. *Cell*, 118, 757-66. ↗

Dick, JE., Kennedy, JA., Brown, JK., Tailor, CS., Rey, MA., Duffy, SP. et al. (2008). Enhanced alternative splicing of the FLVCR1 gene in Diamond Blackfan anemia disrupts FLVCR1 expression and function that are critical for erythropoiesis. *Haematologica*, 93, 1617-26. ↗

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2010-07-06	Authored	Stephan, R.
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2023-11-22	Revised	D'Eustachio, P.

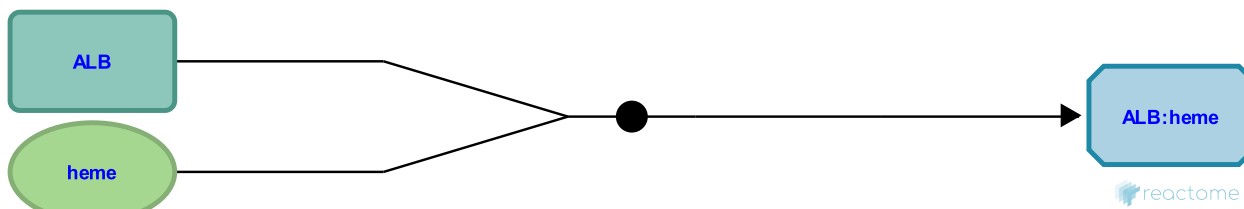
ALB binds extracellular heme [↗](#)

Location: [Heme biosynthesis](#)

Stable identifier: R-HSA-9661419

Type: binding

Compartments: extracellular region



Circulating free heme is cytotoxic. Binding of albumin (ALB) to heme protects cells from this potential toxicity. Heme transported out of cells by ABCG2 may be directly transferred from the transport protein onto HSA (human serum albumin) (Desuzinges-Mandon et al. 2010), while heme transported by FLVCR1-1 may initially associated with lipoproteins before transfer to HSA (De Simone et al. 2023).

Literature references

Ruberto, TF., Ascenzi, P., De Simone, G., Varricchio, R., di Masi, A. (2023). Heme Scavenging and Delivery: The Role of Human Serum Albumin. *Biomolecules*, 13. [↗](#)

Huché, F., Martinez, L., Di Pietro, A., Arnaud, O., Falson, P., Desuzinges-Mandon, E. (2010). ABCG2 transports and transfers heme to albumin through its large extracellular loop. *J. Biol. Chem.*, 285, 33123-33. [↗](#)

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2019-10-03	Reviewed	D'Eustachio, P.
2023-11-22	Revised	D'Eustachio, P.

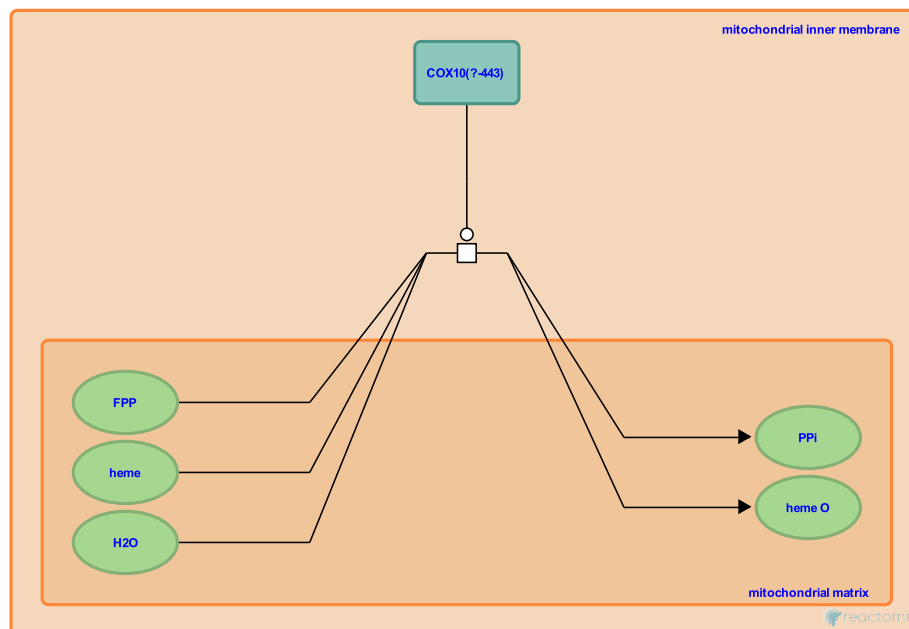
COX10 transforms heme to heme O [↗](#)

Location: [Heme biosynthesis](#)

Stable identifier: R-HSA-2995330

Type: transition

Compartments: mitochondrial inner membrane, mitochondrial matrix



Heme A and less frequently heme O function as prosthetic groups of heme-copper respiratory oxidases (Rivett et al. 2021). Mitochondrial protoheme IX farnesyltransferase (COX10) mediates the transformation of protoheme IX (heme) and farnesyl diphosphate (FAPP) to heme O (Glerum & Tzagoloff 1994). COX10 is highly expressed in muscle, heart and brain (Murakami et al. 1997).

Preceded by: [FECH binds Fe²⁺ to PRIN9 to form heme](#)

Followed by: [COX15 transforms heme O to heme A](#)

Literature references

Reiter, LT., Murakami, T., Lupski, JR. (1997). Genomic structure and expression of the human heme A:farnesyltransferase (COX10) gene. *Genomics*, 42, 161-4. [↗](#)

Feig, M., Rivett, ED., Heo, L., Hegg, EL. (2021). Biosynthesis and trafficking of heme *o* and heme *a*: new structural insights and their implications for reaction mechanisms and prenylated heme transfer. *Crit Rev Biochem Mol Biol*, 56, 640-668. [↗](#)

Tzagoloff, A., Glerum, DM. (1994). Isolation of a human cDNA for heme A:farnesyltransferase by functional complementation of a yeast *cox10* mutant. *Proc. Natl. Acad. Sci. U.S.A.*, 91, 8452-6. [↗](#)

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2013-01-22	Authored, Edited	Jassal, B.
2013-04-15	Reviewed	D'Eustachio, P.
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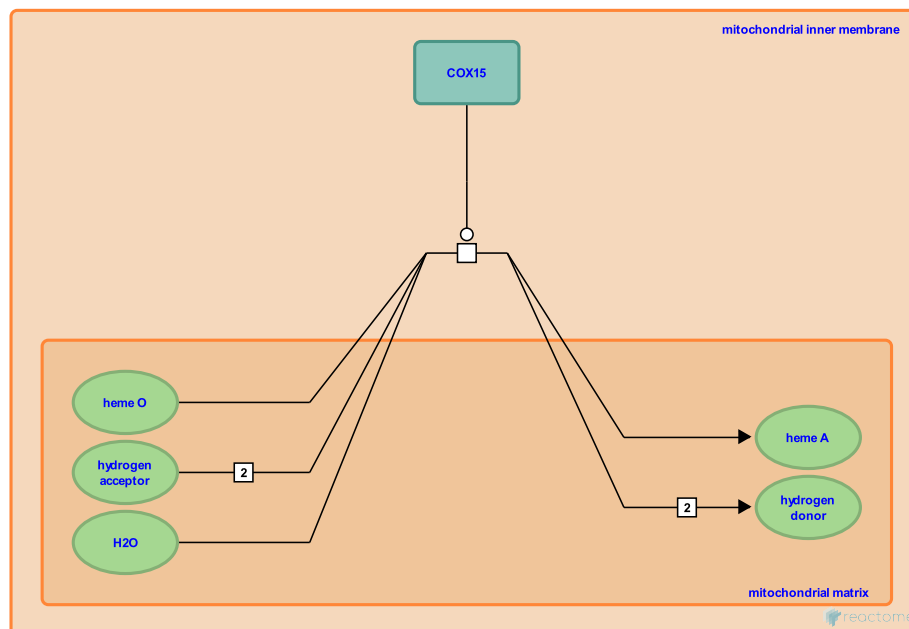
COX15 transforms heme O to heme A [↗](#)

Location: [Heme biosynthesis](#)

Stable identifier: R-HSA-2995334

Type: transition

Compartments: mitochondrial inner membrane, mitochondrial matrix



Heme A is the prosthetic group of cytochrome c oxidase, the terminal enzyme in the respiratory chain. It is formed by the action of cytochrome c oxidase assembly protein COX15 homolog (COX15) on heme O, coupled to the conversion of an unknown hydrogen acceptor molecule to its cognate hydrogen donor (Petruzzella et al. 1998, Antonicka et al. 2003, Rivett et al. 2021). Defects in COX15 cause of mitochondrial complex IV deficiency (MT-C4D; MIM:220110), also called cytochrome c oxidase deficiency resulting in a disorder of the mitochondrial respiratory chain seen as heterogeneous clinical manifestations, ranging from isolated myopathy to severe multisystem disease affecting several tissues and organs (Antonicka et al. 2003). Defects in COX15 also cause Leigh syndrome (LS; MIM:256000), an early-onset progressive neurodegenerative disorder characterised by the presence of focal, bilateral lesions in one or more areas of the central nervous system (Oquendo et al. 2004, Bugiani et al. 2005).

Preceded by: [COX10 transforms heme to heme O](#)

Literature references

- Petruzzella, V., Ianna, P., Zeviani, M., Carrozzo, R., Fernandez, P., Tiranti, V. (1998). Identification and characterization of human cDNAs specific to BCS1, PET112, SCO1, COX15, and COX11, five genes involved in the formation and function of the mitochondrial respiratory chain. *Genomics*, 54, 494-504. [↗](#)
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- Brown, GK., Shoubridge, EA., Oquendo, CE., Reardon, W., Antonicka, H. (2004). Functional and genetic studies demonstrate that mutation in the COX15 gene can cause Leigh syndrome. *J. Med. Genet.*, 41, 540-4. [↗](#)
- Zeviani, M., Uziel, G., Bugiani, M., Tiranti, V., Farina, L. (2005). Novel mutations in COX15 in a long surviving Leigh syndrome patient with cytochrome c oxidase deficiency. *J. Med. Genet.*, 42, e28. [↗](#)
- Kennaway, NG., Carlson, CG., Antonicka, H., Hoffbuhr, KC., Mattman, A., Shoubridge, EA. et al. (2003). Mutations in COX15 produce a defect in the mitochondrial heme biosynthetic pathway, causing early-onset fatal hypertrophic cardiomyopathy. *Am. J. Hum. Genet.*, 72, 101-14. [↗](#)

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2013-01-22	Authored, Edited	Jassal, B.
2013-04-15	Reviewed	D'Eustachio, P.
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