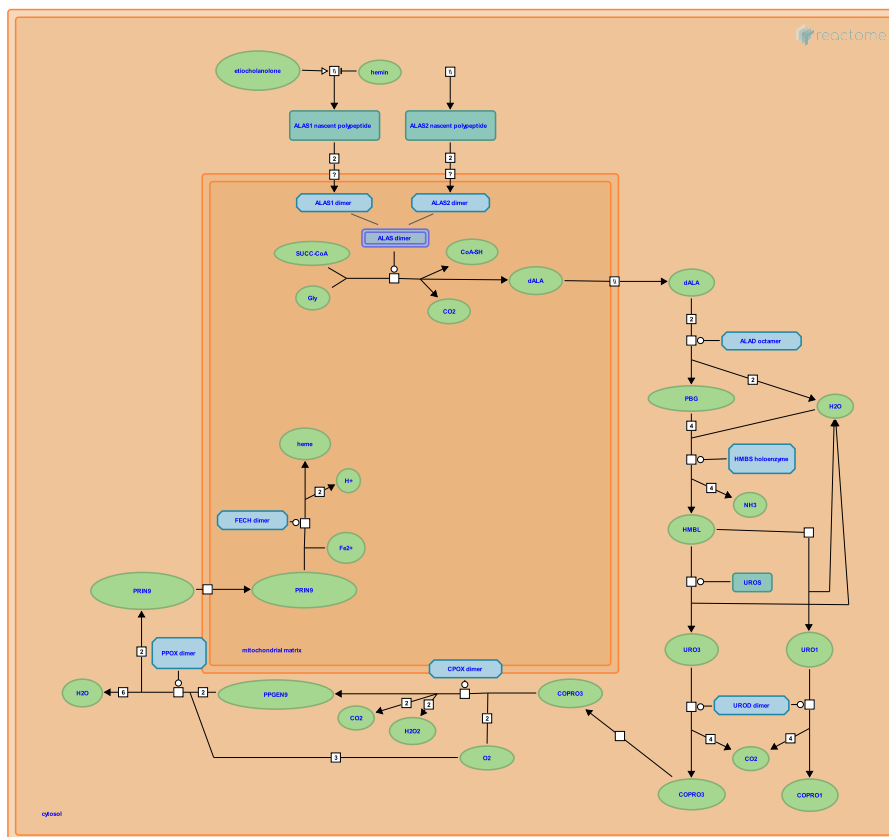


Heme synthesis



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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/).

24/04/2024

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 1 pathway and 17 reactions ([see Table of Contents](#))

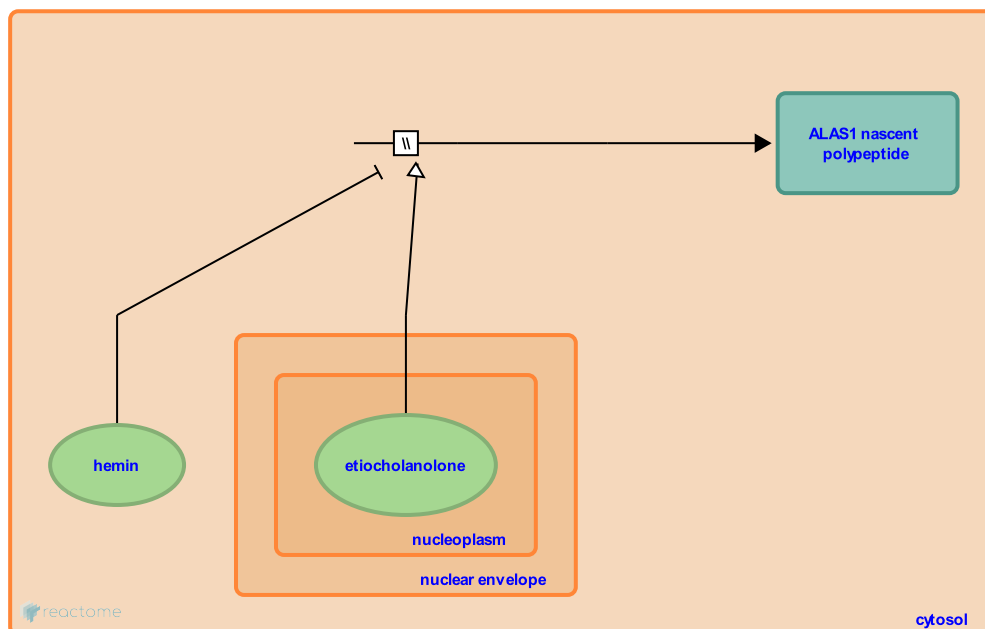
Synthesis of ALAS1 nascent polypeptide ↗

Location: [Heme synthesis](#)

Stable identifier: R-GGA-421508

Type: omitted

Compartments: cytosol



Expression of ALAS1, the ubiquitous form of delta-aminolevulinate synthase, is positively regulated at the transcriptional level by steroids such as etiocholanolone and negatively regulated at the level of translation by hemin (Sassa and Granick 1970).

Followed by: [Mitochondrial uptake and processing of ALAS1](#)

Literature references

Sassa, S., Granick, S. (1970). Induction of delta-aminolevulinic acid synthetase in chick embryo liver cells in culture. *Proc Natl Acad Sci U S A*, 67, 517-22. ↗

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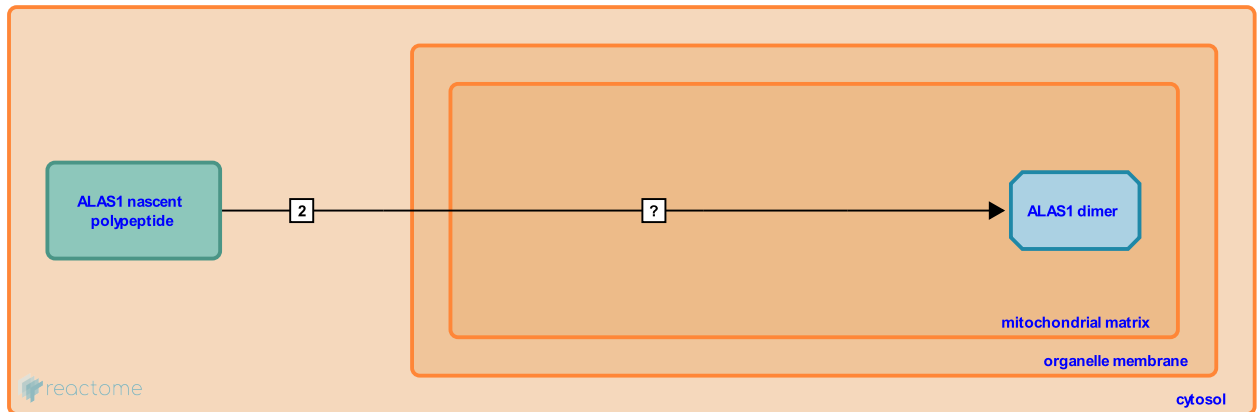
Mitochondrial uptake and processing of ALAS1 ↗

Location: [Heme synthesis](#)

Stable identifier: R-GGA-421453

Type: uncertain

Compartments: mitochondrial matrix



Comparison of ALAS1 protein translated in vitro with that recovered from mitochondria has shown that in the course of becoming localized to the mitochondrion, the nascent ALAS1 polypeptide is shortened (Watanabe et al. 1983), though the annotated loss of 56 aminoterminal residues is an inference from analysis of the predicted ALAS1 amino acid sequence. By analogy to a bacterial ALAS protein whose three-dimensional structure is known (Astner et al. 2005), the active form of chicken ALAS1 is inferred to be a complex of two ALAS1 protein molecules, each bound to a molecule of pyridoxal phosphate. The order of proteolytic processing, cofactor binding, and protein-protein binding to form the active enzyme complex is unknown.

Preceded by: [Synthesis of ALAS1 nascent polypeptide](#)

Followed by: [succinyl-CoA + glycine => delta-aminolevulinate + CoA SH + CO2](#)

Literature references

Kikuchi, G., Hayashi, N., Watanabe, N. (1983). delta-Aminolevulinate synthase isozymes in the liver and erythroid cells of chicken. *Biochem Biophys Res Commun*, 113, 377-83. ↗

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

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Synthesis of ALAS2 nascent polypeptide [↗](#)

Location: [Heme synthesis](#)

Stable identifier: R-GGA-421495

Type: omitted

Compartments: cytosol



ALAS2 protein is synthesized at high levels in erythroid precursor cells to meet these cells' need for heme synthesis (Watanabe et al. 1983).

Followed by: [Mitochondrial uptake and processing of ALAS2](#)

Literature references

Kikuchi, G., Hayashi, N., Watanabe, N. (1983). delta-Aminolevulinate synthase isozymes in the liver and erythroid cells of chicken. *Biochem Biophys Res Commun*, 113, 377-83. [↗](#)

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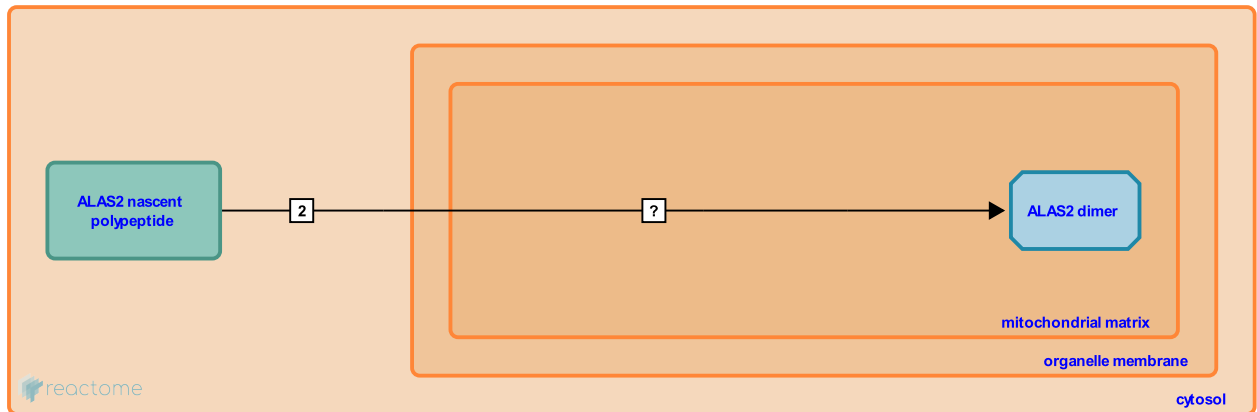
Mitochondrial uptake and processing of ALAS2 [↗](#)

Location: [Heme synthesis](#)

Stable identifier: R-GGA-421457

Type: uncertain

Compartments: mitochondrial matrix



Comparison of ALAS2 protein translated in vitro with that recovered from mitochondria has shown that in the course of becoming localized to the mitochondrion, the nascent ALAS2 polypeptide is shortened (Watanabe et al. 1983), though the annotated loss of 18 aminoterminal residues is an inference from analysis of the predicted ALAS2 amino acid sequence. By analogy to a bacterial ALAS protein whose three-dimensional structure is known (Astner et al. 2005), the active form of chicken ALAS2 is inferred to be a complex of two ALAS1 protein molecules, each bound to a molecule of pyridoxal phosphate. The order of proteolytic processing, cofactor binding, and protein-protein binding to form the active enzyme complex is unknown.

Preceded by: [Synthesis of ALAS2 nascent polypeptide](#)

Followed by: [succinyl-CoA + glycine => delta-aminolevulinate + CoA SH + CO2](#)

Literature references

Kikuchi, G., Hayashi, N., Watanabe, N. (1983). delta-Aminolevulinate synthase isozymes in the liver and erythroid cells of chicken. *Biochem Biophys Res Commun*, 113, 377-83. [↗](#)

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

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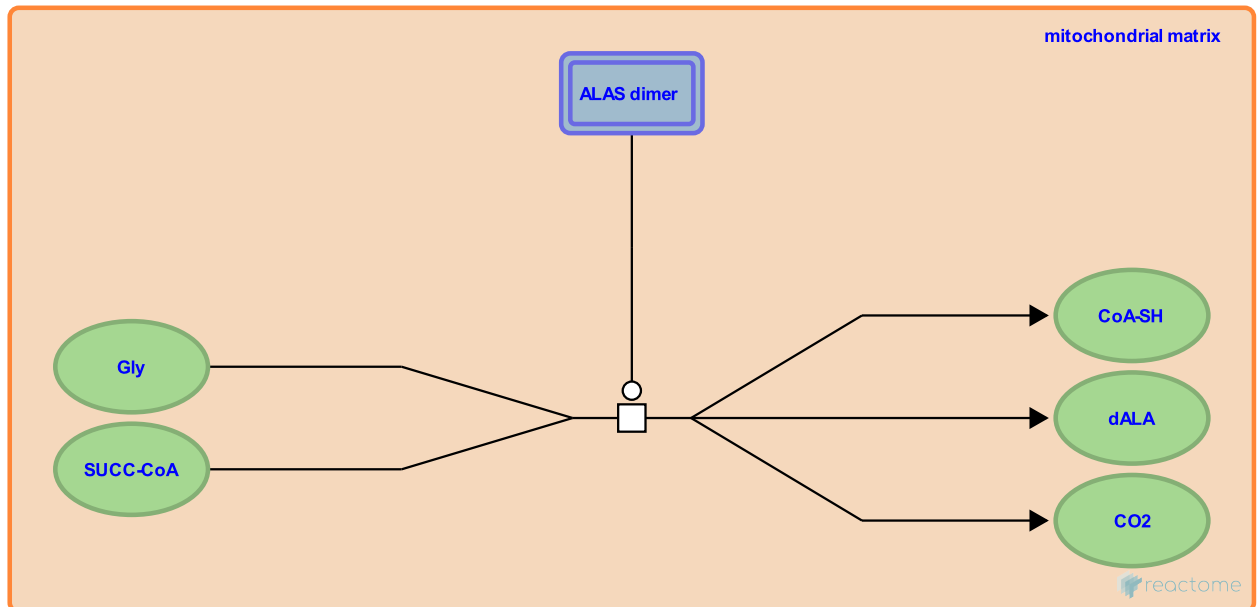
succinyl-CoA + glycine => delta-aminolevulinate + CoA SH + CO2 ↗

Location: [Heme synthesis](#)

Stable identifier: R-GGA-421493

Type: transition

Compartments: mitochondrial matrix



Mitochondrial ALAS (delta-aminolevulinate synthase) catalyzes the reaction of succinyl-CoA and glycine to form delta-aminolevulinate, CoA SH and CO₂. ALAS occurs in two isoforms. ALAS1 is widely expressed in the body though particularly abundant in liver. Its expression can be induced by steroids and other substrates of cytochrome P450-mediated reactions, and repressed by hemin. ALAS2 is expressed at high levels in erythroid precursor cells. Both ALAS1 and ALAS2 are active as dimers, with each subunit polypeptide bound to a molecule of pyridoxal phosphate. The two proteins are encoded by separate genes; cDNAs corresponding to both have been cloned (Riddle et al. 1989).

Preceded by: [Mitochondrial uptake and processing of ALAS1](#), [Mitochondrial uptake and processing of ALAS2](#)

Followed by: [Transport of delta-aminolevulinate from the mitochondrial matrix to the cytosol](#)

Literature references

Yamamoto, M., Engel, JD., Riddle, RD. (1989). Expression of delta-aminolevulinate synthase in avian cells: separate genes encode erythroid-specific and nonspecific isozymes. *Proc Natl Acad Sci U S A*, 86, 792-6. ↗

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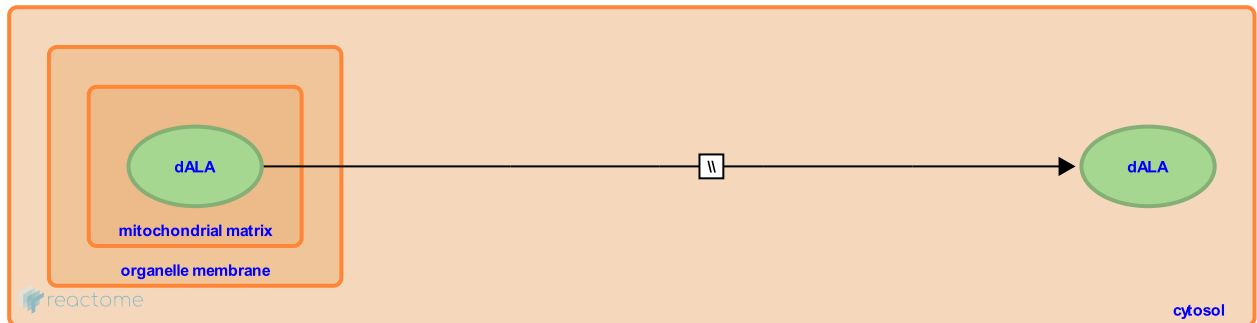
Transport of delta-aminolevulinate from the mitochondrial matrix to the cytosol ↗

Location: [Heme synthesis](#)

Stable identifier: R-GGA-421517

Type: omitted

Compartments: cytosol, mitochondrial matrix



Delta-aminolevulinate is transported from the mitochondrial matrix to the cytosol. The transporter that enables it to cross the inner mitochondrial membrane is unknown (Rebeiz et al. 1996). This is a black box event, since we know the 5ALA translocates from cytosol to the mitochondria but more detailed evidences should be provided.

Preceded by: [succinyl-CoA + glycine => delta-aminolevulinate + CoA SH + CO2](#)

Followed by: [2 delta-aminolevulinate => porphobilinogen + 2 H2O](#)

Literature references

Quigley, JG., Khan, AA. (2011). Control of intracellular heme levels: heme transporters and heme oxygenases. *Biochim. Biophys. Acta*, 1813, 668-82. ↗

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2 delta-aminolevulinate => porphobilinogen + 2 H2O ↗

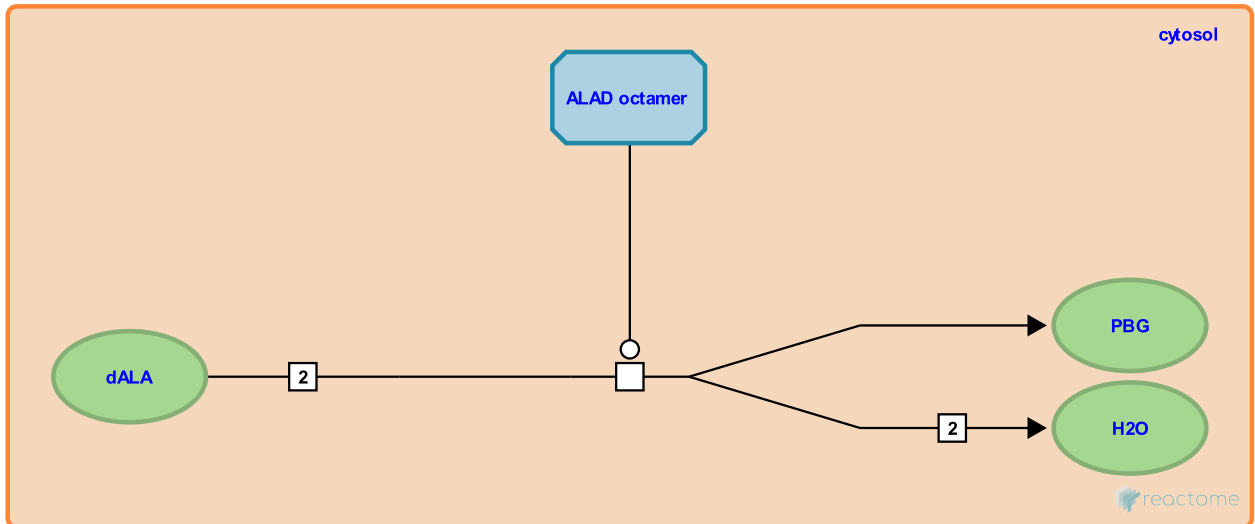
Location: [Heme synthesis](#)

Stable identifier: R-GGA-421472

Type: transition

Compartments: cytosol

Inferred from: [ALAD condenses 2 dALAs to form PBG \(Homo sapiens\)](#)



Cytosolic ALAD (delta-aminolevulinate dehydratase) catalyzes the reaction of two molecules of delta-aminolevulinate to form porphobilinogen plus two molecules of water. Chicken ALAD is known only as the inferred product of a gene discovered by analysis of the chicken genomic DNA sequence. Its formation of an octamer with eight zinc ions and its catalytic activity are inferred from the properties of its better-studied human counterpart.

Preceded by: [Transport of delta-aminolevulinate from the mitochondrial matrix to the cytosol](#)

Followed by: [4 porphobilinogen + H2O => hydroxymethylbilane + 4 NH3](#)

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4 porphobilinogen + H₂O => hydroxymethylbilane + 4 NH₃ ↗

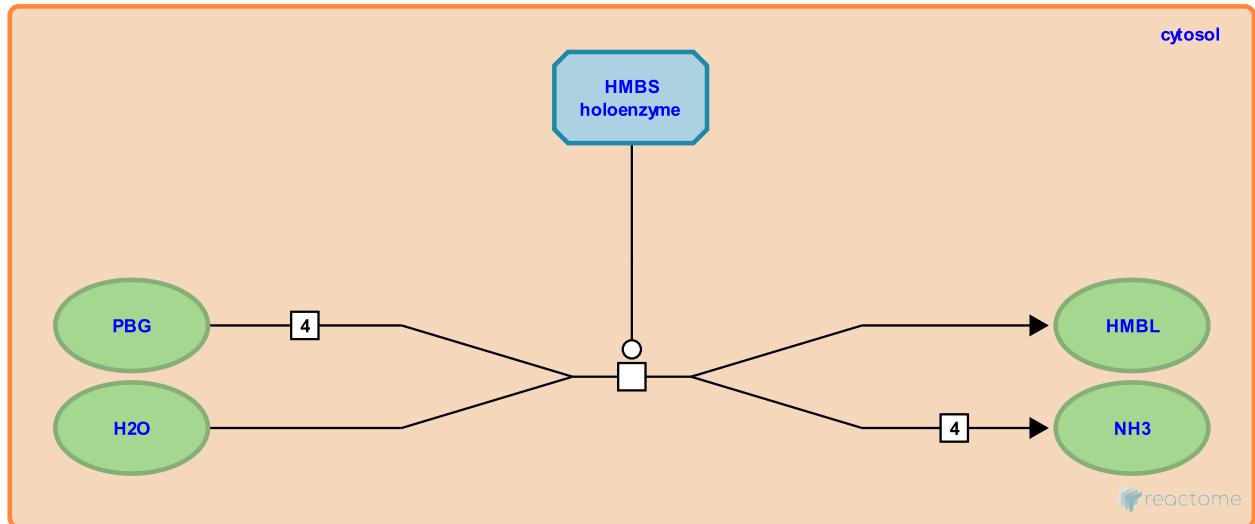
Location: [Heme synthesis](#)

Stable identifier: R-GGA-421439

Type: transition

Compartments: cytosol

Inferred from: [4 PBGs bind to form HMB \(Homo sapiens\)](#)



Cytosolic HMBS (hydroxymethylbilane synthase) catalyzes the reaction of four molecules of porphobilinogen and one of H₂O to form hydroxymethylbilane and four molecules of NH₃. Chicken HMBS is known only as the inferred product of a gene discovered by analysis of the chicken genomic DNA sequence. Its requirement for dipyrromethane as a cofactor and its catalytic activity are inferred from the properties of its better-studied human counterpart.

Preceded by: [2 delta-aminolevulinate => porphobilinogen + 2 H₂O](#)

Followed by: [hydroxymethylbilane => uroporphyrinogen I + H₂O](#), [hydroxymethylbilane => uroporphyrinogen III + H₂O](#)

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hydroxymethylbilane => uroporphyrinogen III + H2O ↗

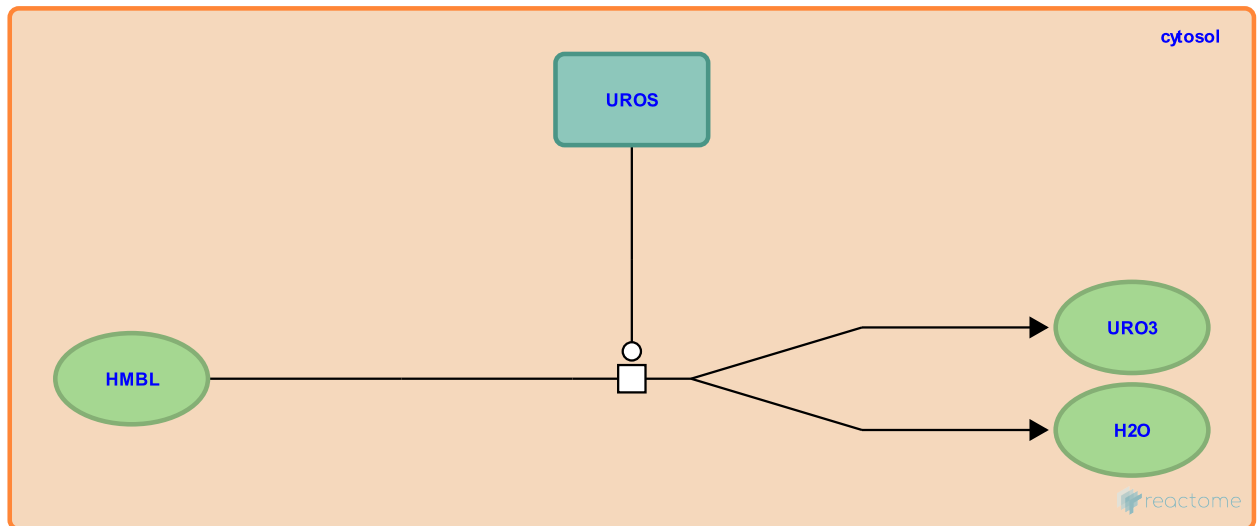
Location: [Heme synthesis](#)

Stable identifier: R-GGA-421482

Type: transition

Compartments: cytosol

Inferred from: [UROS transforms HMB to URO3 \(Homo sapiens\)](#)



Cytosolic UROS (uroporphyrinogen III synthase) catalyzes the reaction of hydroxymethylbilane to form uroporphyrinogen III and H₂O. Chicken UROS is known only as the inferred product of a gene discovered by analysis of the chicken genomic DNA sequence. Its catalytic activity is inferred from the properties of its better-studied human counterpart.

Preceded by: [4 porphobilinogen + H2O => hydroxymethylbilane + 4 NH3](#)

Followed by: [uroporphyrinogen III => coproporphyrinogen III + 4 CO2](#)

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hydroxymethylbilane => uroporphyrinogen I + H2O ↗

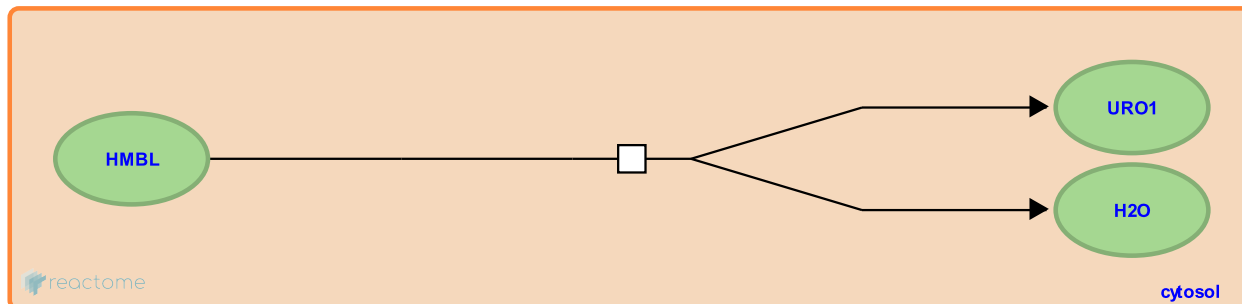
Location: [Heme synthesis](#)

Stable identifier: R-GGA-421471

Type: transition

Compartments: cytosol

Inferred from: [HMBL spontaneously transforms to URO1 \(Homo sapiens\)](#)



Cytosolic hydroxymethylbilane reacts spontaneously to form uroporphyrinogen I and H₂O. The existence of this reaction in chickens is inferred from studies of heme biosynthesis in humans.

Preceded by: [4 porphobilinogen + H₂O => hydroxymethylbilane + 4 NH₃](#)

Followed by: [uroporphyrinogen I => coproporphyrinogen I + 4 CO₂](#)

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uroporphyrinogen III => coproporphyrinogen III + 4 CO2 ↗

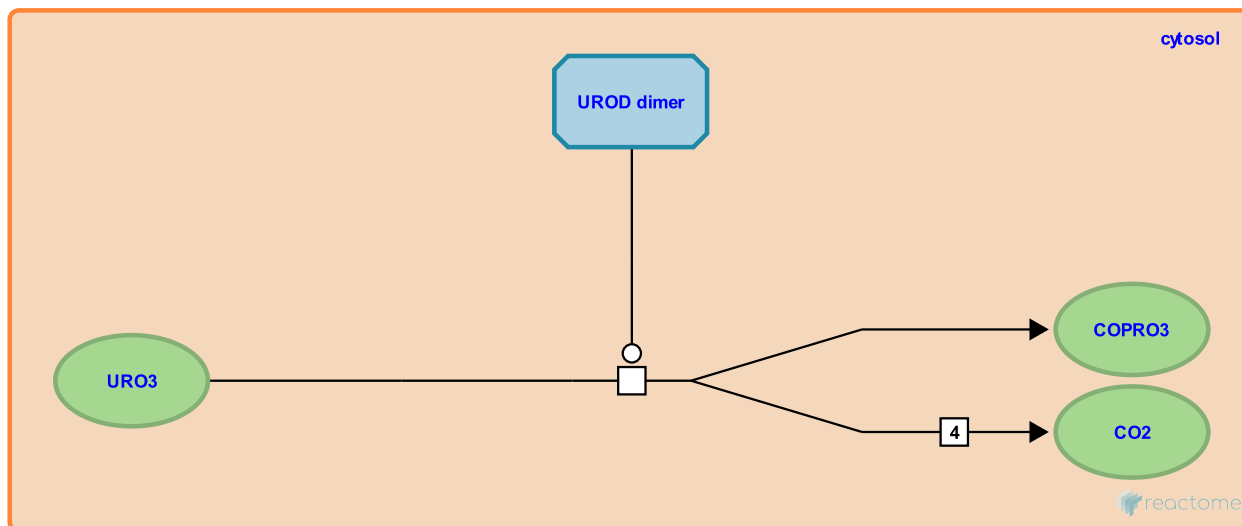
Location: [Heme synthesis](#)

Stable identifier: R-GGA-421515

Type: transition

Compartments: cytosol

Inferred from: [UROD decarboxylates URO3 to COPRO3 \(Homo sapiens\)](#)



Cytosolic UROD (uroporphyrinogen decarboxylase) catalyzes the reaction of uroporphyrinogen III to form coproporphyrinogen III and four molecules of CO₂. Chicken UROD is known only as the inferred product of a gene discovered by analysis of the chicken genomic DNA sequence. Its dimerization to form an active enzyme and its catalytic activity are inferred from the properties of its better-studied human counterpart.

Preceded by: [hydroxymethylbilane => uroporphyrinogen III + H₂O](#)

Followed by: [Translocation of coproporphyrinogen III from the cytosol to the mitochondrial intermembrane space](#), [coproporphyrinogen III + 2 O₂ => protoporphyrinogen IX + 2 H₂O₂ + 2 CO₂](#)

Literature references

Kushner, JP., Phillips, JD., Reilly, CA., Bergonia, HA., Franklin, MR. (2007). A porphomethene inhibitor of uroporphyrinogen decarboxylase causes porphyria cutanea tarda. *Proc. Natl. Acad. Sci. U.S.A.*, 104, 5079-84. ↗

Valle, D. (2001). *The Metabolic and Molecular Bases of Inherited Diseases*. McGraw Hill, 6338.

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uroporphyrinogen I => coproporphyrinogen I + 4 CO2 ↗

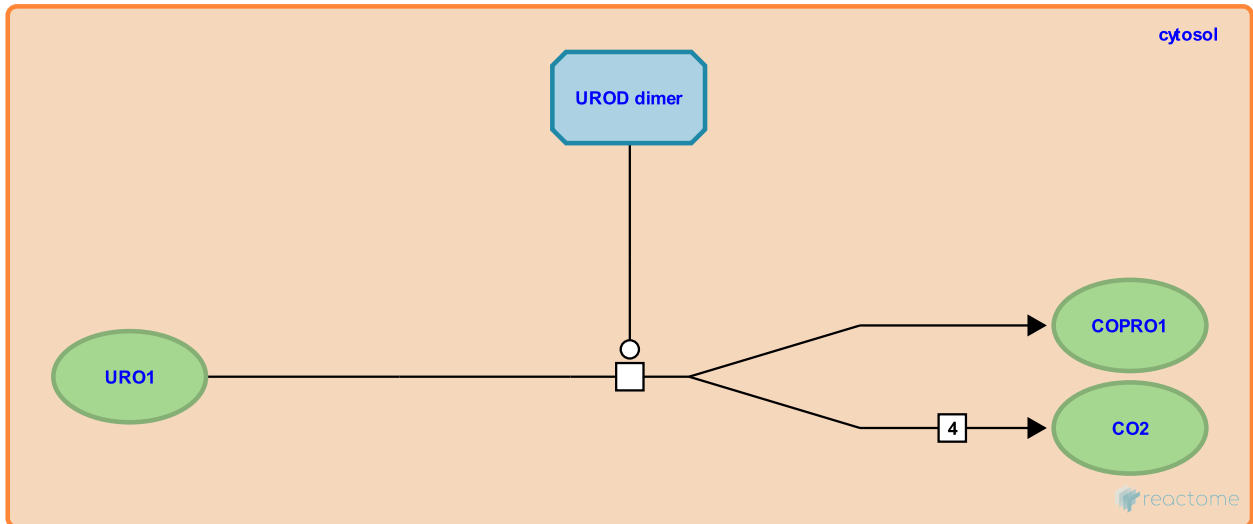
Location: [Heme synthesis](#)

Stable identifier: R-GGA-421459

Type: transition

Compartments: cytosol

Inferred from: [UROD decarboxylates URO1 to COPRO1 \(Homo sapiens\)](#)



Cytosolic UROD (uroporphyrinogen decarboxylase) catalyzes the reaction of uroporphyrinogen I to form coproporphyrinogen I and four molecules of CO₂. Chicken UROD is known only as the inferred product of a gene discovered by analysis of the chicken genomic DNA sequence. Its dimerization to form an active enzyme and its catalytic activity are inferred from the properties of its better-studied human counterpart.

Preceded by: [hydroxymethylbilane => uroporphyrinogen I + H₂O](#)

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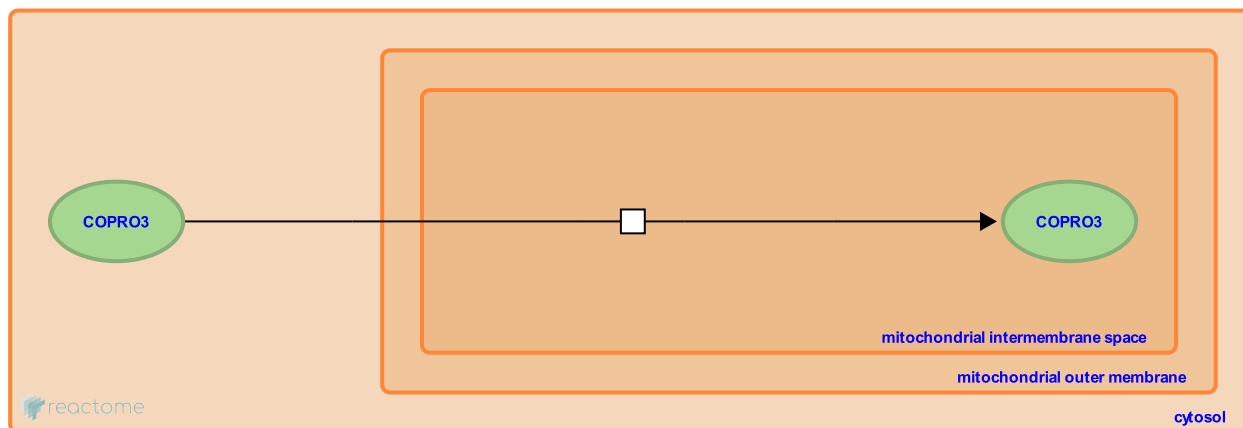
Translocation of coproporphyrinogen III from the cytosol to the mitochondrial intermembrane space ↗

Location: [Heme synthesis](#)

Stable identifier: R-GGA-421485

Type: transition

Compartments: mitochondrial intermembrane space, cytosol



Coproporphyrinogen III enters the mitochondrial intermembrane space from the cytosol. It is not known whether this process is facilitated by a transporter (Anderson et al.2001, Philips et al.2007).

Preceded by: [uroporphyrinogen III => coproporphyrinogen III + 4 CO2](#)

Literature references

Kushner, JP., Phillips, JD., Reilly, CA., Bergonia, HA., Franklin, MR. (2007). A porphomethene inhibitor of uroporphyrinogen decarboxylase causes porphyria cutanea tarda. *Proc. Natl. Acad. Sci. U.S.A.*, 104, 5079-84. ↗

Valle, D. (2001). *The Metabolic and Molecular Bases of Inherited Diseases*. McGraw Hill, 6338.

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coproporphyrinogen III + 2 O₂ => protoporphyrinogen IX + 2 H₂O₂ + 2 CO₂ ↗

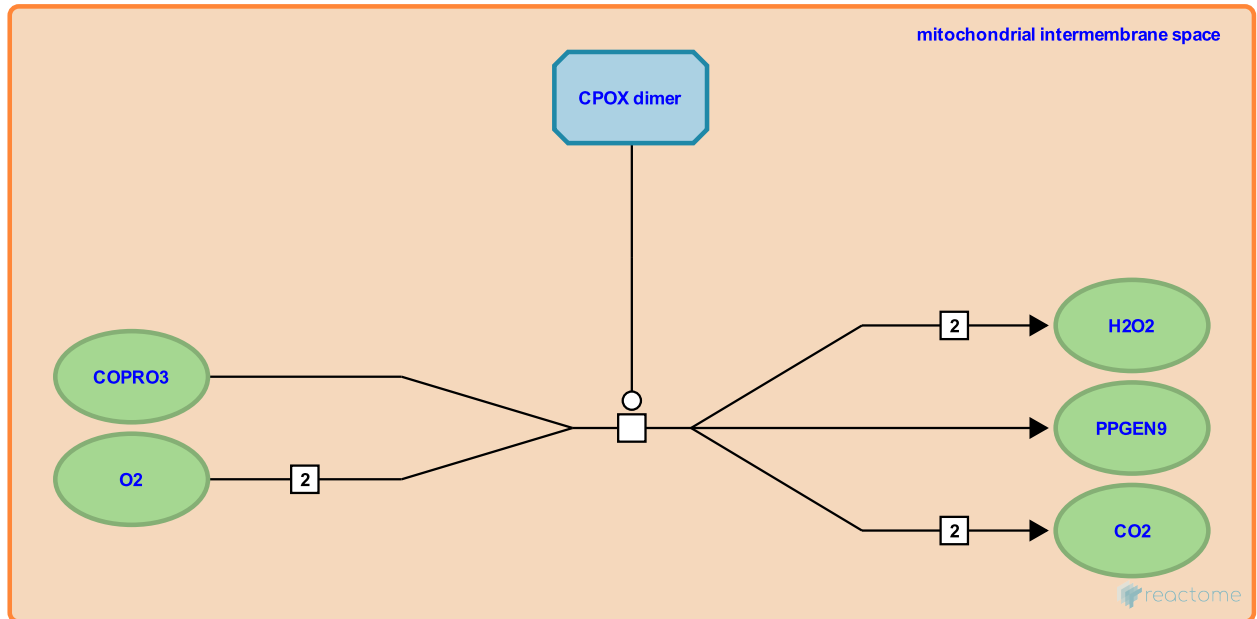
Location: [Heme synthesis](#)

Stable identifier: R-GGA-421478

Type: transition

Compartments: mitochondrial intermembrane space

Inferred from: [CPO transforms COPRO3 to PPGEN9 \(Homo sapiens\)](#)



CPOX (coproporphyrinogen III oxidase) localized in the mitochondrial intermembrane space catalyzes the reaction of coproporphyrinogen III with two molecules of O₂ to form protoporphyrinogen IX, two molecules of H₂O₂, and two molecules of CO₂. Chicken CPOX is known only as the inferred product of a gene discovered by analysis of the chicken genomic DNA sequence. Its subcellular location, dimerization to form an active enzyme, and catalytic activity are inferred from the properties of its better-studied human counterpart.

Preceded by: [uroporphyrinogen III => coproporphyrinogen III + 4 CO₂](#)

Followed by: [2 protoporphyrinogen IX + 3 O₂ => 2 protoporphyrin IX + 6 H₂O](#)

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2 protoporphyrinogen IX + 3 O₂ => 2 protoporphyrin IX + 6 H₂O ↗

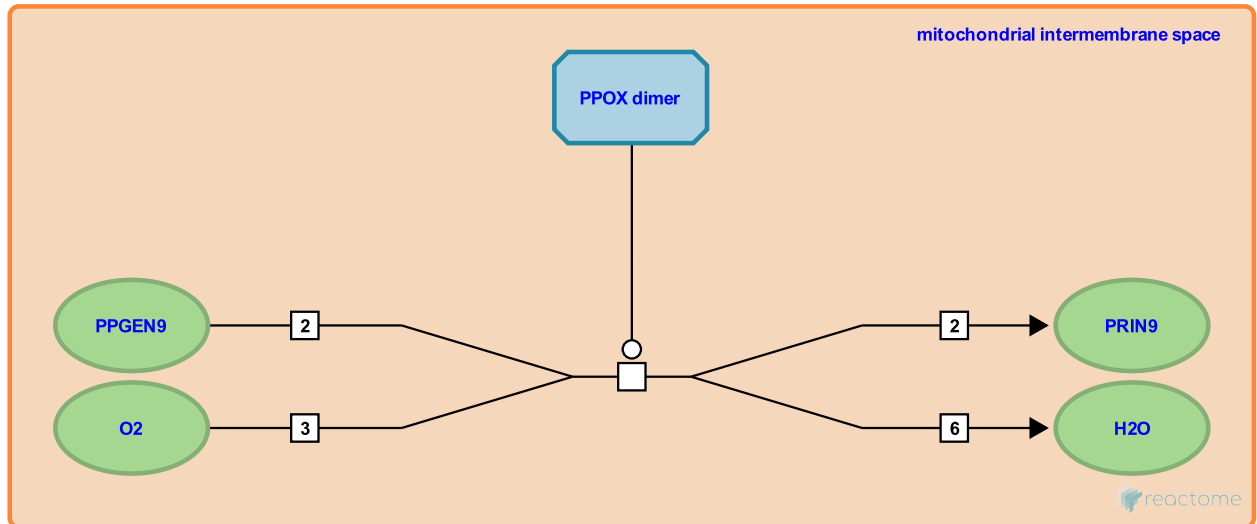
Location: [Heme synthesis](#)

Stable identifier: R-GGA-421452

Type: transition

Compartments: mitochondrial intermembrane space

Inferred from: [PPO oxidises PPGEN9 to PRIN9 \(Homo sapiens\)](#)



PPOX dimer in the mitochondrial intermembrane space catalyzes the reaction of two molecules of protoporphyrinogen IX and three of oxygen to form two molecules of protoporphyrin IX and six of water. While the process of heme biosynthesis, including this reaction, is believed to be well conserved among vertebrates, no chicken gene capable of encoding a PPOX homologue has yet been discovered, and this reaction and all of the properties of chicken PPOX enzyme are inferred from those of their better-studied human counterparts.

Preceded by: [coproporphyrinogen III + 2 O₂ => protoporphyrinogen IX + 2 H₂O₂ + 2 CO₂](#)

Followed by: [Transport of protoporphyrin IX from the mitochondrial intermembrane space into the mitochondrial matrix](#)

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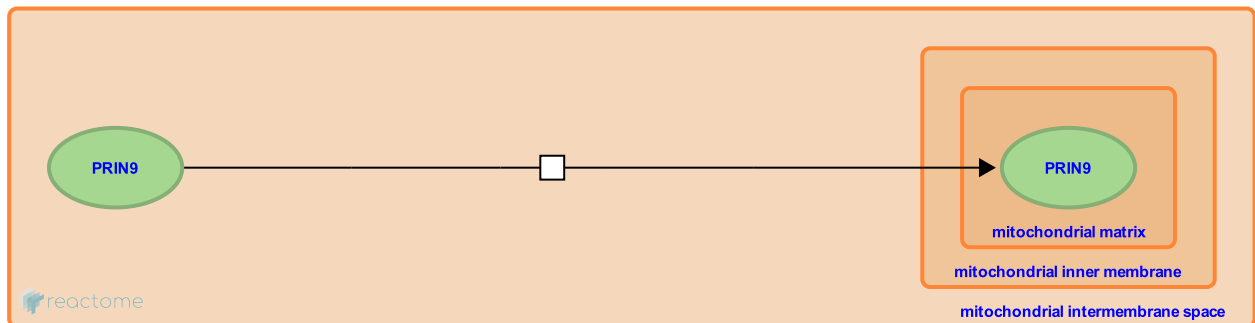
Transport of protoporphyrin IX from the mitochondrial intermembrane space into the mitochondrial matrix ↗

Location: [Heme synthesis](#)

Stable identifier: R-GGA-421454

Type: transition

Compartments: mitochondrial intermembrane space, mitochondrial matrix



Protoporphyrin IX is transported from the mitochondrial intermembrane space into the mitochondrial matrix. The transporter that enables it to cross the inner mitochondrial membrane is unknown (Lin et al.2013).

Preceded by: [2 protoporphyrinogen IX + 3 O₂ => 2 protoporphyrin IX + 6 H₂O](#)

Followed by: [protoporphyrin IX + Fe⁺⁺ => heme + 2 H⁺](#)

Literature references

Lee, HS., Mao, WY., Lin, CC., Liu, CL., Shen, CR., Lin, YH. et al. (2013). Protoporphyrin IX accumulation disrupts mitochondrial dynamics and function in ABCG2-deficient hepatocytes. *FEBS Lett.*, 587, 3202-9. ↗

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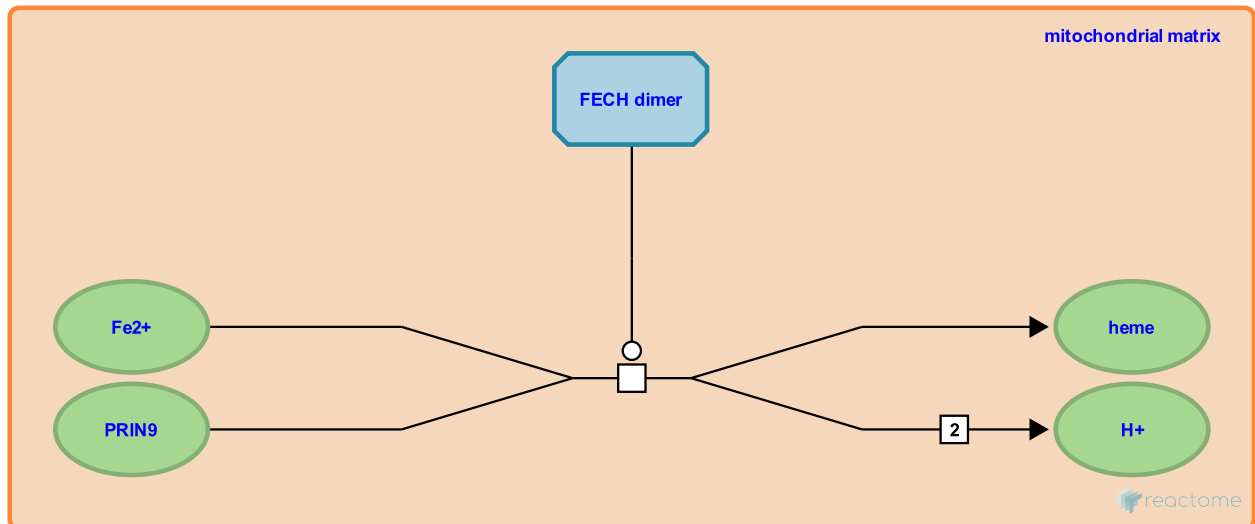
protoporphyrin IX + Fe⁺⁺ => heme + 2 H⁺ ↗

Location: [Heme synthesis](#)

Stable identifier: R-GGA-421447

Type: transition

Compartments: mitochondrial matrix



FECH (ferrochelatase) in the mitochondrial matrix catalyzes the reaction of protoporphyrin IX and ferrous iron to form heme, releasing two H⁺. The active form of FECH is a dimer with one iron-sulfur cluster bound per monomer (Day et al. 1998).

Preceded by: [Transport of protoporphyrin IX from the mitochondrial intermembrane space into the mitochondrial matrix](#)

Literature references

Day, AL., Parsons, BM., Dailey, HA. (1998). Cloning and characterization of Gallus and Xenopus ferrochelatases: presence of the [2Fe-2S] cluster in nonmammalian ferrochelatase. *Arch Biochem Biophys*, 359, 160-9. ↗

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