D'Eustachio, P., Jassal, B., Sassa, S., Stephan, R.

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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.

12/11/2022

https://reactome.org
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


Reactome database release: 82

This document contains 1 pathway and 20 reactions (see Table of Contents)
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-aminolevulinate (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**


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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-aminolevulinate (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


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https://reactome.org
Mitochondrial dALA translocates to cytosol

Location: Heme biosynthesis

Stable identifier: R-HSA-189456

Type: transition

Compartments: mitochondrial outer membrane

5-aminolevulinate is transported from the mitochondrial matrix to the cytosol. The transporter that enables it to cross the inner mitochondrial membrane is unknown (Bayeva et al. 2013).

Preceded by: ALAS condenses SUCC-CoA and Gly to form dALA

Followed by: ALAD condenses 2 dALAs to form PBG

Literature references


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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**


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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-aminolevulinate dehydratase-deficient porphyria (e.g., Akagi et al. 2000).

**Preceded by:** Mitochondrial dALA translocates to cytosol

**Followed by:** 4 PBGs bind to form HMB

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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


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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


Hydroxymethybilane (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**


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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-Jiminez et al. 1996).

**Preceded by:** UROS transforms HMB to URO3

**Followed by:** Cytosolic COPRO3 translocates to mitochondrial intermembrane space

**Literature references**


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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


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https://reactome.org
Coproporpyrinogen 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**

CPO transforms COPRO3 to PPGEN9

**Location:** Heme biosynthesis

**Stable identifier:** R-HSA-189421

**Type:** transition

**Compartments:** mitochondrial intermembrane space

O2-dependent coproporpyrinogen oxidase (CPO) catalyzes the conversion of coproporphyrinogen III (COPRO3) to protoporphyrinogen IX (PPGEN9). 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 coproporphyria in vivo.

**Preceded by:** Cytosolic COPRO3 translocates to mitochondrial intermembrane space

**Followed by:** PPO oxidises PPGEN9 to PRIN9

**Literature references**


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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 protophorphyrinogen 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 non-covalently-bound FAD. The protein resides on the outer surface of the inner mitochondrial membrane. PPO deficiency is associated with variegate porphyria in vivo.

**Preceded by:** CPO transforms COPRO3 to PPGEN9

**Followed by:** Mitochondrial intermembrane PRIN9 translocates to mitochondrial matrix

**Literature references**


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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**


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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

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**


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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).

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**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.

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https://reactome.org
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 (Desuzinges-Mandon et al. 2010).

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COX10 transforms heme to heme O

**Location:** Heme biosynthesis

**Stable identifier:** R-HSA-2995330

**Type:** transition

**Compartments:** mitochondrial inner membrane, mitochondrial matrix

Heme O and heme A are specifically synthesised for the heme-copper respiratory oxidases. 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

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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 (Petruzzella et al. 1998, Antonicka et al. 2003). Defects in COX15 cause 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 O to heme A

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  - ALAS condenses SUCC-CoA and Gly to form dALA
  - Mitochondrial dALA translocates to cytosol
  - ALAD binds to Pb2+
  - ALAD condenses 2 dALAs to form PBG
  - 4 PBGs bind to form HMB
  - UROS transforms HMB to URO3
  - HMBL spontaneously transforms to URO1
  - UROD decarboxylates URO3 to COPRO3
  - UROD decarboxylates URO1 to COPRO1
  - Cytosolic COPRO3 translocates to mitochondrial intermembrane space
  - CPO transforms COPRO3 to PPGEN9
  - PPO oxidises PPGEN9 to PRIN9
  - Mitochondrial intermembrane PRIN9 translocates to mitochondrial matrix
  - FECH binds Fe2+ to PRIN9 to form heme
  - FLVCR1-2 transports heme from mitochondrial matrix to cytosol
  - ABCG2 tetramer transports heme from cytosol to extracellular region
  - FLVCR1-1 transports heme from cytosol to extracellular region
  - ALB binds extracellular heme
  - COX10 transforms heme to heme O
  - COX15 transforms heme O to heme A

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