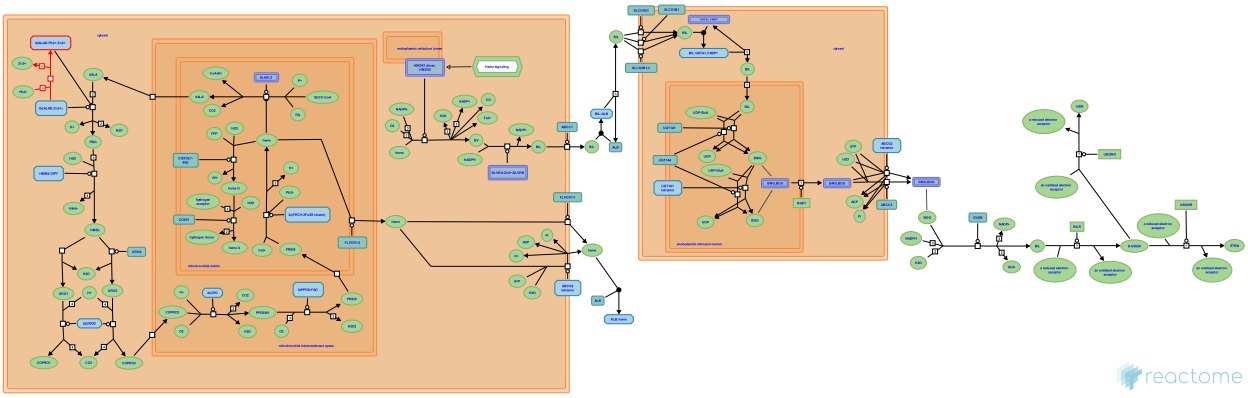
Metabolism of porphyrins



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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.

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Introduction

Reactome is open-source, open access, manually curated and peer-reviewed pathway database. Pathway annotations are authored by expert biologists, in collaboration with Reactome editorial staff and cross-referenced to many bioinformatics databases. A system of evidence tracking ensures that all assertions are backed up by the primary literature. Reactome is used by clinicians, geneticists, genomics researchers, and molecular biologists to interpret the results of high-throughput experimental studies, by bioinformaticians seeking to develop novel algorithms for mining knowledge from genomic studies, and by systems biologists building predictive models of normal and disease variant pathways.
The development of Reactome is supported by grants from the US National Institutes of Health (P41 HG003751), University of Toronto (CFREF Medicine by Design), European Union (EU STRP, EMI-CD), and the European Molecular Biology Laboratory (EBI Industry program).

Literature references

Fabregat, A., Sidiropoulos, K., Viteri, G., Forner, O., Marin-Garcia, P., Arnau, V. et al. (2017). Reactome pathway analysis: a high-performance in-memory approach. *BMC bioinformatics, 18*, 142. ↗

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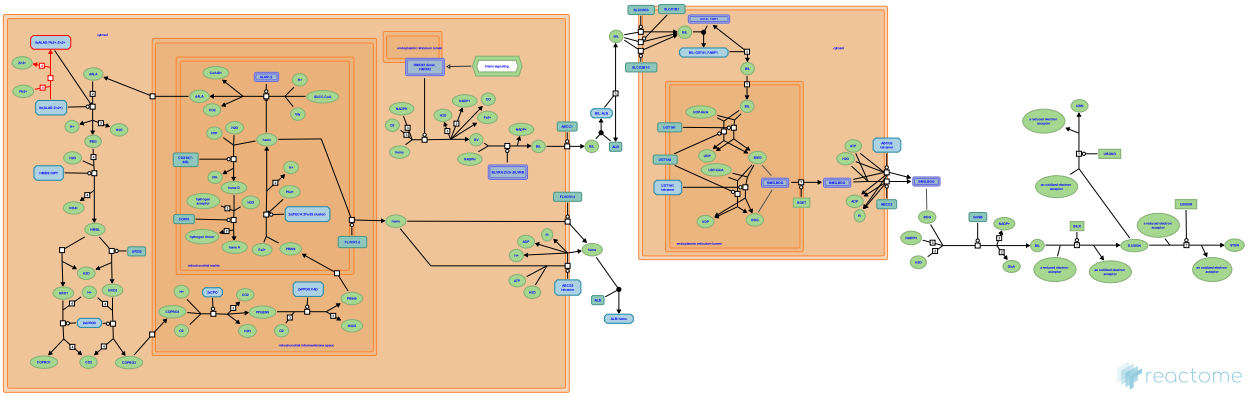
Fabregat, A., Korninger, F., Viteri, G., Sidiropoulos, K., Marin-Garcia, P., Ping, P. et al. (2018). Reactome graph database: Efficient access to complex pathway data. *PLoS computational biology, 14*, e1005968. ↗

Reactome database release: 88

This document contains 3 pathways (see Table of Contents)

Metabolism of porphyrins ↗

Stable identifier: R-HSA-189445



Porphyrins are heterocyclic macrocycles, consisting of four pyrrole subunits (tetrapyrrole) linked by four methine (=CH-) bridges. The extensive conjugated porphyrin macrocycle is chromatic and the name itself, **porphyrin**, is derived from the Greek word for *purple*. The aromatic character of porphyrins can be seen by NMR spectroscopy.
Porphyrins readily combine with metals by coordinating them in the central cavity. Iron (heme) and magnesium (chlorophyll) are two well known examples although zinc, copper, nickel and cobalt form other known metal-containing phorphyrins. A porphyrin which has no metal in the cavity is called a *free base*.
Some iron-containing porphyrins are called hemes (heme-containing proteins or hemoproteins) and these are found extensively in nature ie. hemoglobin. Hemoglobin is quantitatively the most important hemoprotein. The hemoglobin iron is the transfer site of oxygen and carries it in the blood all round the body for cell respiration. Other examples are cytochromes present in mitochondria and endoplasmic reticulum which takes part in electron transfer events, catalase and peroxidase whic protect the body against the oxidant hydrogen peroxide and tryptophan oxygenase which is present in intermediary metabolism. Hemoproteins are synthesized in all mammalian cells and the major sites are erythropoietic tissue and the liver.

The processes by which heme is synthesized, transported, and metabolized are a critical part of human iron metabolism (Severance and Hamze 2009); here the core processes of heme biosynthesis and catabolism have been annotated.

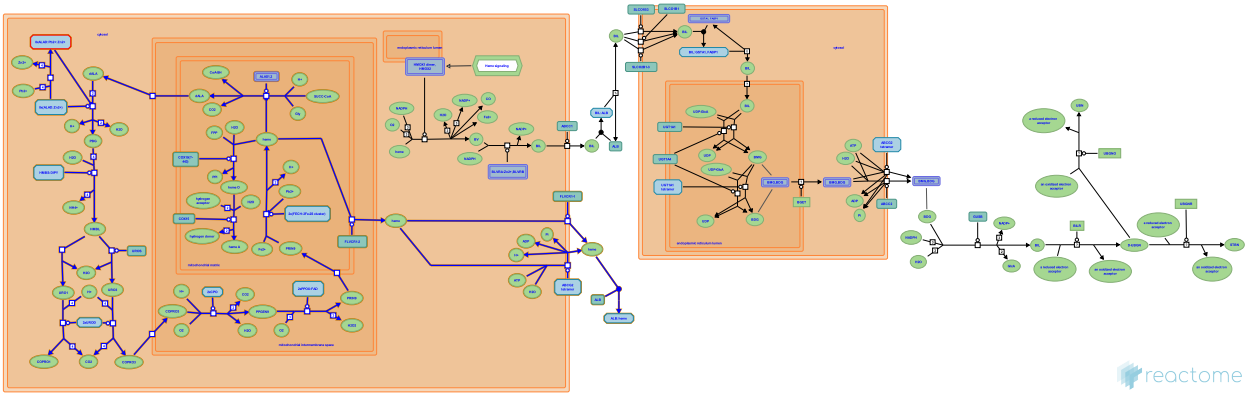
Editions

2007-01-24	Reviewed	Sassa, S.
2009-05-19	Revised	D'Eustachio, P.

Heme biosynthesis ↗

Location: Metabolism of porphyrins

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-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 uroporphyringen 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 uroporphyringen 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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Editions

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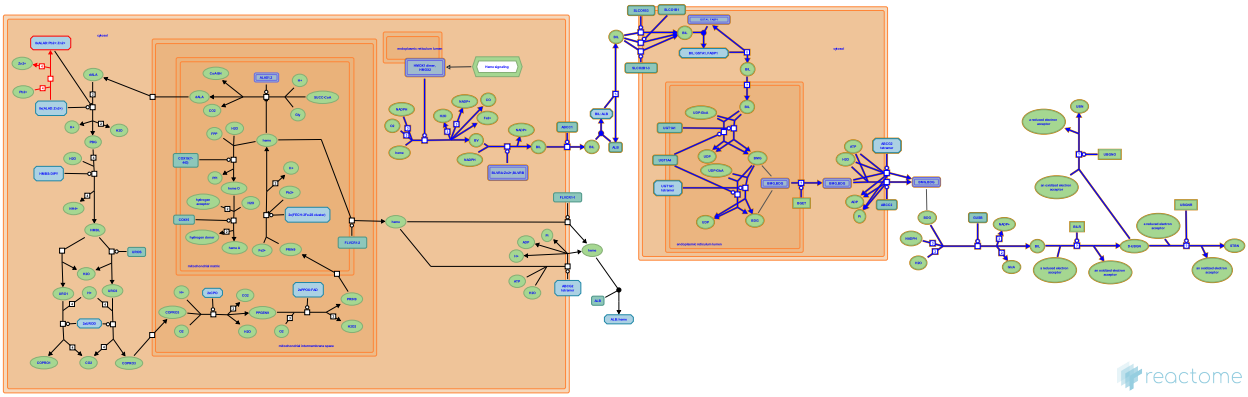
2019-09-18	Revised	Jassal, B.
2023-11-22	Revised	D'Eustachio, P.

Heme degradation ↗

Location: Metabolism of porphyrins

Stable identifier: R-HSA-189483



Most of the heme degraded in humans comes from hemoglobin. Approximately 6-8 grams of hemoglobin is degraded daily which is equivalent to approximately 300 milligrams of heme per day. Heme is not recycled so it must be degraded and excreted. The iron, however, is conserved. There are two steps to heme degradation;
1. cleavage of the heme ring by a microsomal heme oxygenase producing biliverdin
2. biliverdin is reduced to bilirubin.
Bilirubin can then be conjugated with glucuronic acid and excreted.

Literature references

Soares, MP., Otterbein, LE., Yamashita, K., Bach, FH. (2003). Heme oxygenase-1: unleashing the protective properties of heme. *Trends Immunol, 24*, 449-55. ↗

Editions

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2009-05-19	Revised	D'Eustachio, P.
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