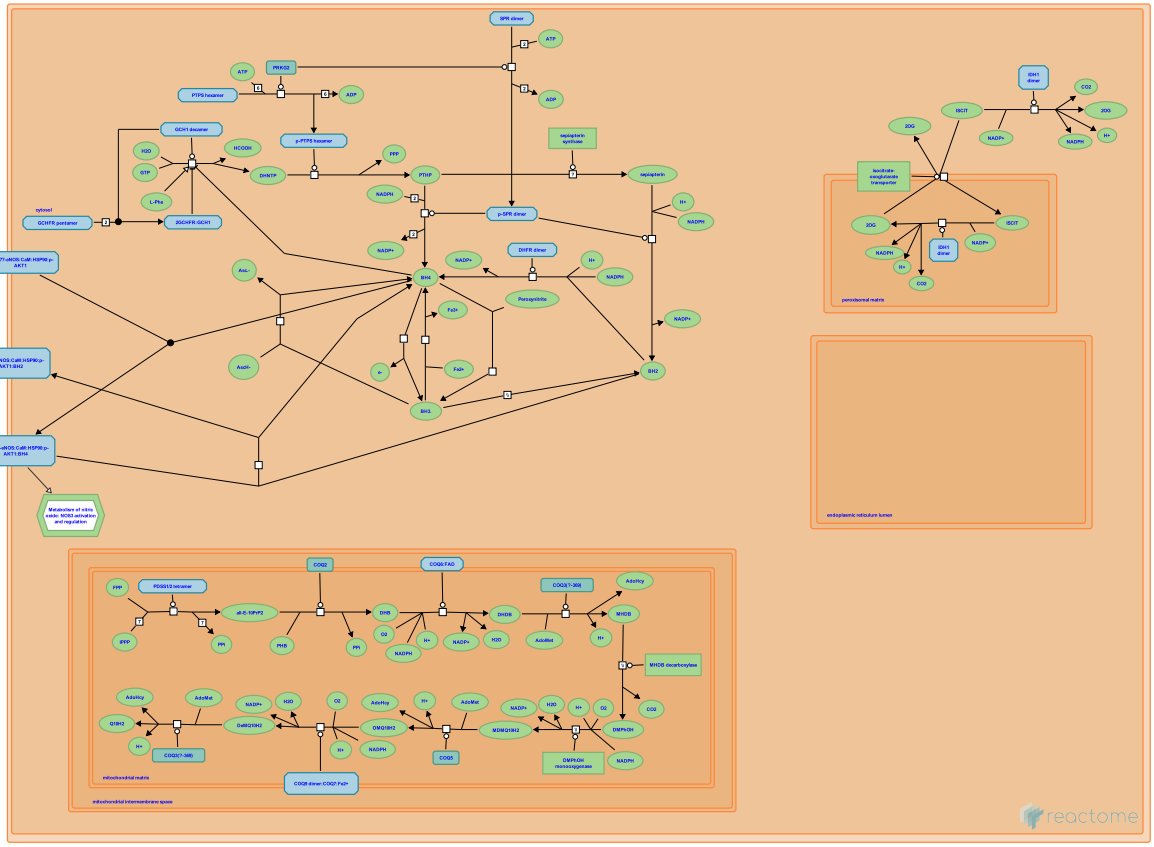
Metabolism of cofactors



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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.

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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. ↗

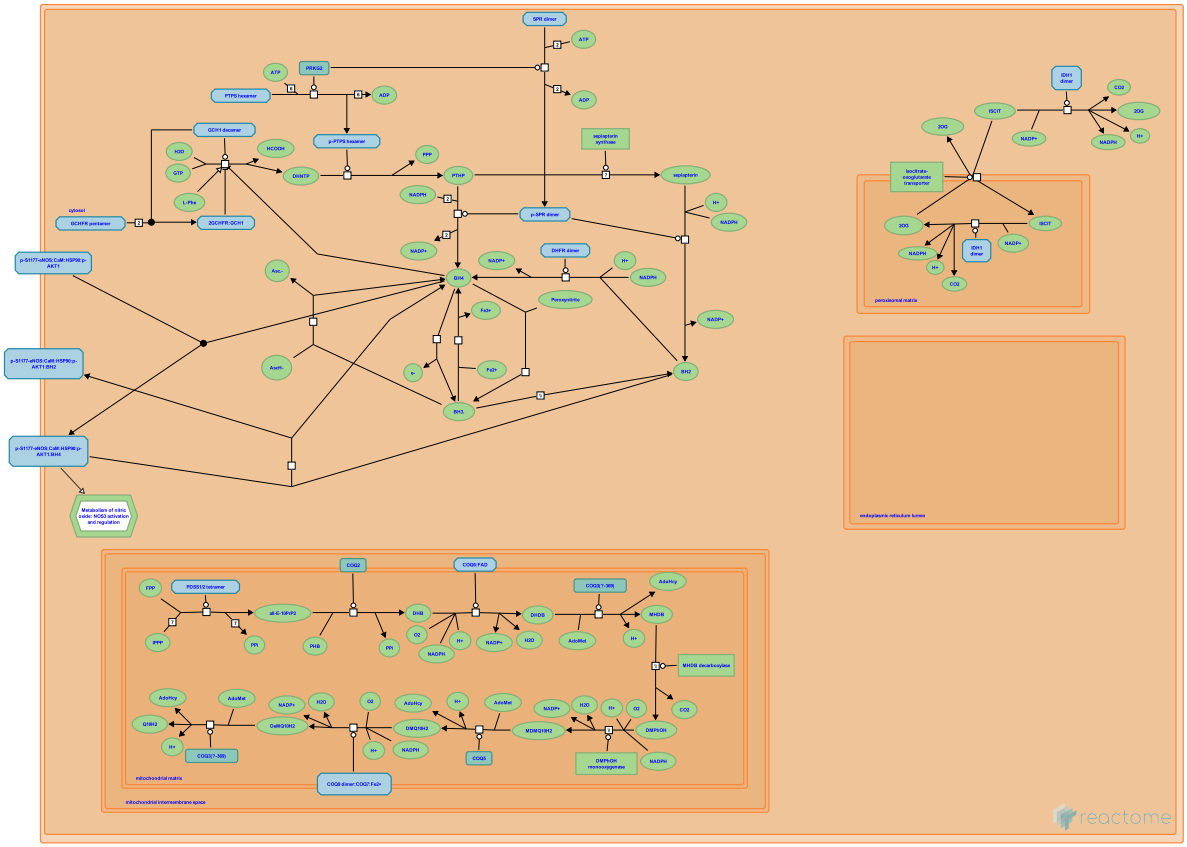
Fabregat, A., Korninger, F., Viteri, G., Sidiropoulos, K., Marin-Garcia, P., Ping, P. et al. (2018). Reactome graph database: Efficient access to complex pathway data. *PLoS computational biology, 14*, e1005968. ↗

Reactome database release: 74

This document contains 4 pathways (see Table of Contents)

Metabolism of cofactors ↗

Stable identifier: R-HSA-8978934



Many proteins depend for their activity on cofactors, associated ions and small molecules. This module contains annotations of processes involved in the synthesis of cofactors, either de novo or from essential molecules consumed in the diet (vitamins), as well as regeneration of active forms of cofactors (Lipmann 1984).

Literature references

Lipmann, F. (1984). A long life in times of great upheaval. *Annu. Rev. Biochem., 53*, 1-33. ↗

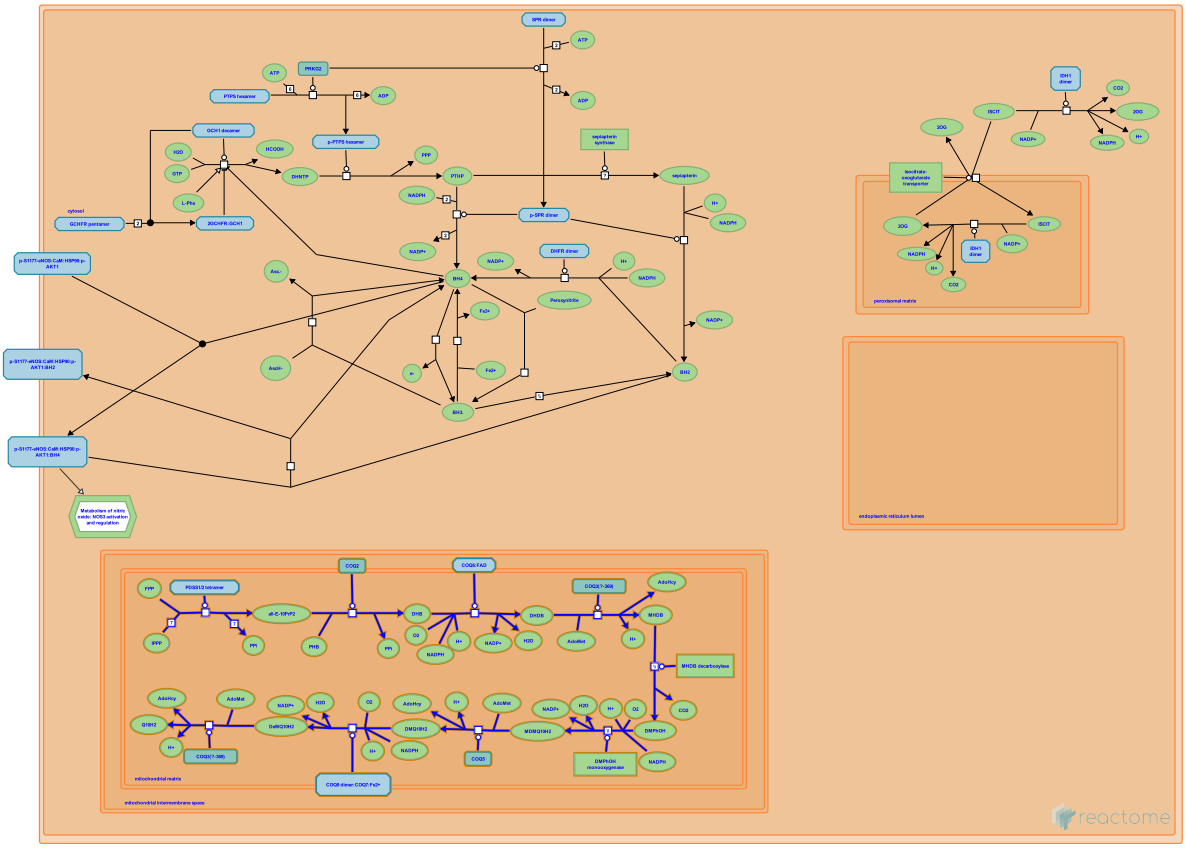
Editions

2009-01-08	Authored, Edited	D'Eustachio, P.
2009-02-27	Reviewed	Jassal, B.
2017-02-27	Revised	Jassal, B.

Ubiquinol biosynthesis ↗

Location: Metabolism of cofactors

Stable identifier: R-HSA-2142789



The length of the polyisoprenoid chain of ubiquinone aka coenzyme Q (Q), varies depending on the species involved: it is 6 in budding yeast, Saccharomyces cerevisiae, (Q6) and 10 in humans (Q10). Most ubiquinone is naturally reduced to ubiquinol (Q10H2 in humans) and it is this form which dominates in most human tissues. It functions as an ubiquitous coenzyme in redox reactions and its ability both to associate with complexes I and III of the electron transport chain and to move freely in the inner mitochondrial membrane are central to its role in electron transport. In eukaryotes ubiquinones/ubiquinols are also found in other membranes such as the endoplasmic reticulum, Golgi vesicles, lysosomes and peroxisomes.

Ubiquinol/ubiquinone is synthesized in the following way. Initially, the polyisoprenoid tail is assembled by a polyprenyl diphosphate synthase. Next, 4 hydroxybenzoate polyprenyltransferase (COQ2) catalyses the formation of the covalent linkage between the benzoquinone head group and the tail to produce 4 hydroxy 3 polyprenyl benzoic acid intermediate (DHB, 3 decaprenyl 4 hydroxybenzoic acid in humans). There follows modifications of the aromatic ring starting with hydroxylation, followed by O methylation, and decarboxylation to form the 2 methoxy 6 polyprenyl phenol intermediate (DMPhOH ; 2 methoxy 6 decaprenylphenol in humans). Following this, two additional methylations, one C methylation, and one O methylation step, finally generate the fully substituted hydroquinone, ubiquinol (Szkopinska 2000, Kagan & Quinn 2000, Tran & Clarke 2007, Kawamukai 2009).

Literature references

Kagan, VE., Quinn, PJ. (2000). Genetic Analysis of Coenzyme Q Biosynthesis, Coenzyme Q: Molecular Mechanisms in Health and Disease. *CRC Press*, 185-208.

Szkopinska, A. (2000). Ubiquinone. Biosynthesis of quinone ring and its isoprenoid side chain. Intracellular localization. *Acta Biochim Pol, 47*, 469-80. ↗

Tran, UC., Clarke, CF. (2007). Endogenous synthesis of coenzyme Q in eukaryotes. *Mitochondrion, 7*, S62-71. ↗

Kawamukai, M. (2009). Biosynthesis and bioproduction of coenzyme Q10 by yeasts and other organisms. *Biotechnol. Appl. Biochem., 53*, 217-26. ↗

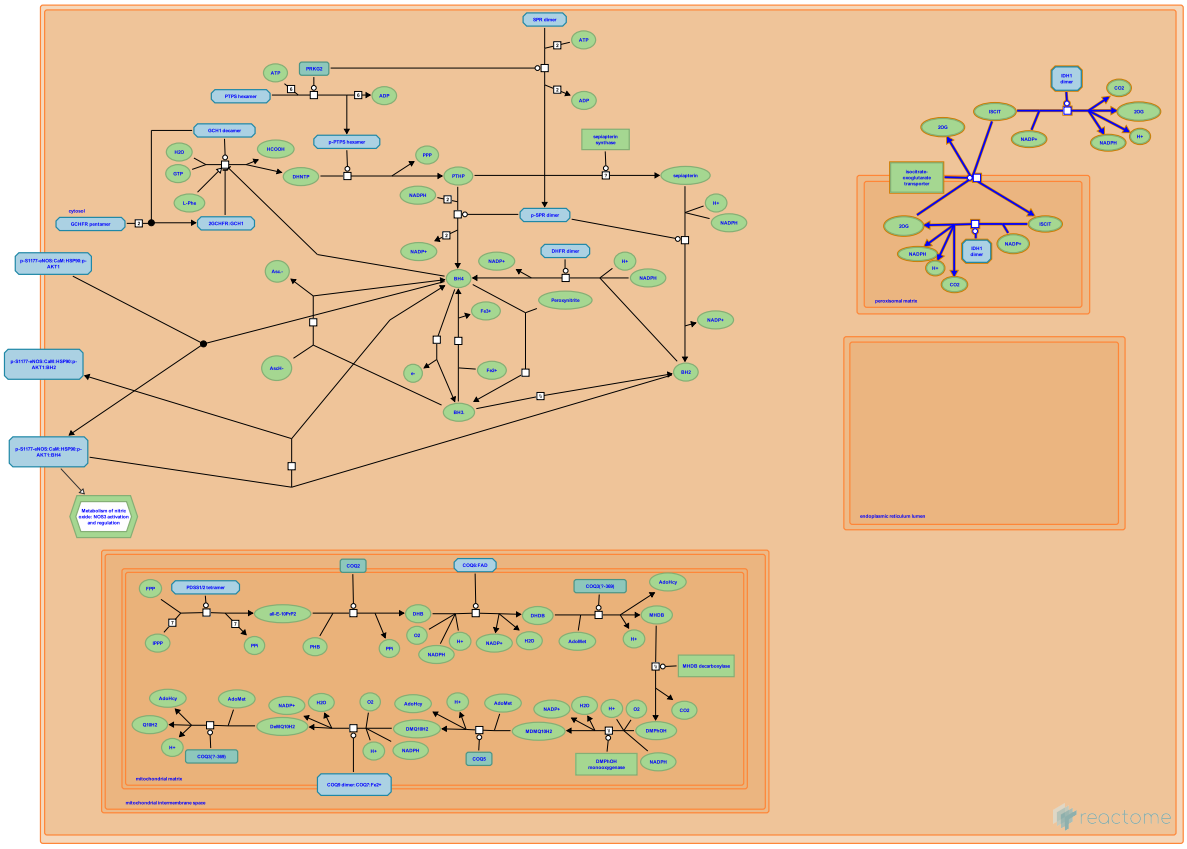
Editions

2012-03-15	Edited	Williams, MG.
2012-03-19	Authored	Williams, MG.
2013-02-05	Reviewed	Kawamukai, M.

NADPH regeneration ↗

Location: Metabolism of cofactors

Stable identifier: R-HSA-389542



The conversion of isocitrate to 2-oxoglutarate (alpha-ketoglutarate) with the concomitant synthesis of NADPH from NADP+ is thought to play a significant role in supplying NADPH for other reactions in both the cytosol and the peroxisome (Geisbrecht and Gould 1999). The activity of H6PD (Hexose-6-phosphate dehydrogenase) is thought to play a role in maintaining NADP+ : NADPH balance within the endoplasmic reticulum (Zielinska et al. 2011).

Literature references

Geisbrecht, BV., Gould, SJ. (1999). The human PICD gene encodes a cytoplasmic and peroxisomal NADP(+)-dependent isocitrate dehydrogenase. *J Biol Chem, 274*, 30527-33. ↗

Zielinska, AE., Walker, EA., Stewart, PM., Lavery, GG. (2011). Biochemistry and physiology of hexose-6-phosphate knockout mice. *Mol. Cell. Endocrinol., 336*, 213-8. ↗

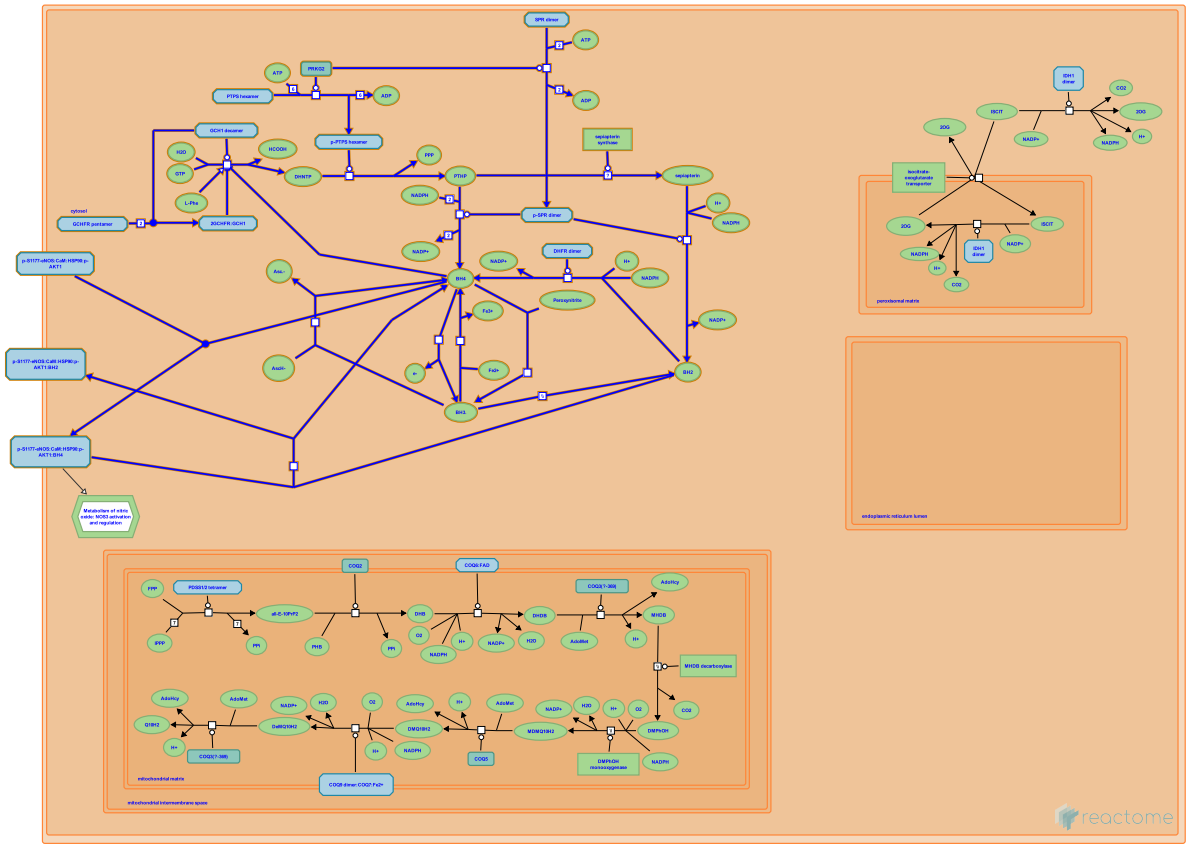
Editions

2009-01-08	Authored, Edited	D'Eustachio, P.
2009-02-27	Reviewed	Jassal, B.

Tetrahydrobiopterin (BH4) synthesis, recycling, salvage and regulation ↗

Location: Metabolism of cofactors

Stable identifier: R-HSA-1474151



Tetrahydrobiopterin (BH4) is an essential co-factor for the aromatic amino acid hydroxylases and glycerol ether monooxygenase and it regulates nitric oxide synthase (NOS) activity. Inherited BH4 deficiency leads to hyperphenylalaninemia, and dopamine and neurotransmitter deficiency in the brain. BH4 maintains enzymatic coupling to L-arginine oxidation to produce NO. Oxidation of BH4 to BH2 results in NOS uncoupling, resulting in superoxide (O2.-) formation rather than NO. Superoxide rapidly reacts with NO to produce peroxynitrite which can further uncouple NOS.

These reactive oxygen species (superoxide and peroxynitrite) can contribute to increased oxidative stress in the endothelium leading to atherosclerosis and hypertension (Thony et al. 2000, Crabtree and Channon 2011,Schulz et al. 2008, Schmidt and Alp 2007). The synthesis, recycling and effects of BH4 are shown here. Three enzymes are required for the de novo biosynthesis of BH4 and two enzymes for the recycling of BH4.

Literature references

Thöny, B., Auerbach, G., Blau, N. (2000). Tetrahydrobiopterin biosynthesis, regeneration and functions. *Biochem J, 347*, 1-16. ↗

Schmidt, TS., Alp, NJ. (2007). Mechanisms for the role of tetrahydrobiopterin in endothelial function and vascular disease. *Clin Sci (Lond), 113*, 47-63. ↗

Schulz, E., Jansen, T., Wenzel, P., Daiber, A., Münzel, T. (2008). Nitric oxide, tetrahydrobiopterin, oxidative stress, and endothelial dysfunction in hypertension. *Antioxid Redox Signal, 10*, 1115-26. ↗

Crabtree, MJ., Channon, KM. (2011). Synthesis and recycling of tetrahydrobiopterin in endothelial function and vascular disease. *Nitric Oxide, 25*, 81-8. ↗

Editions

2011-08-17	Authored, Edited	Jassal, B.
2011-08-23	Reviewed	D'Eustachio, P.

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