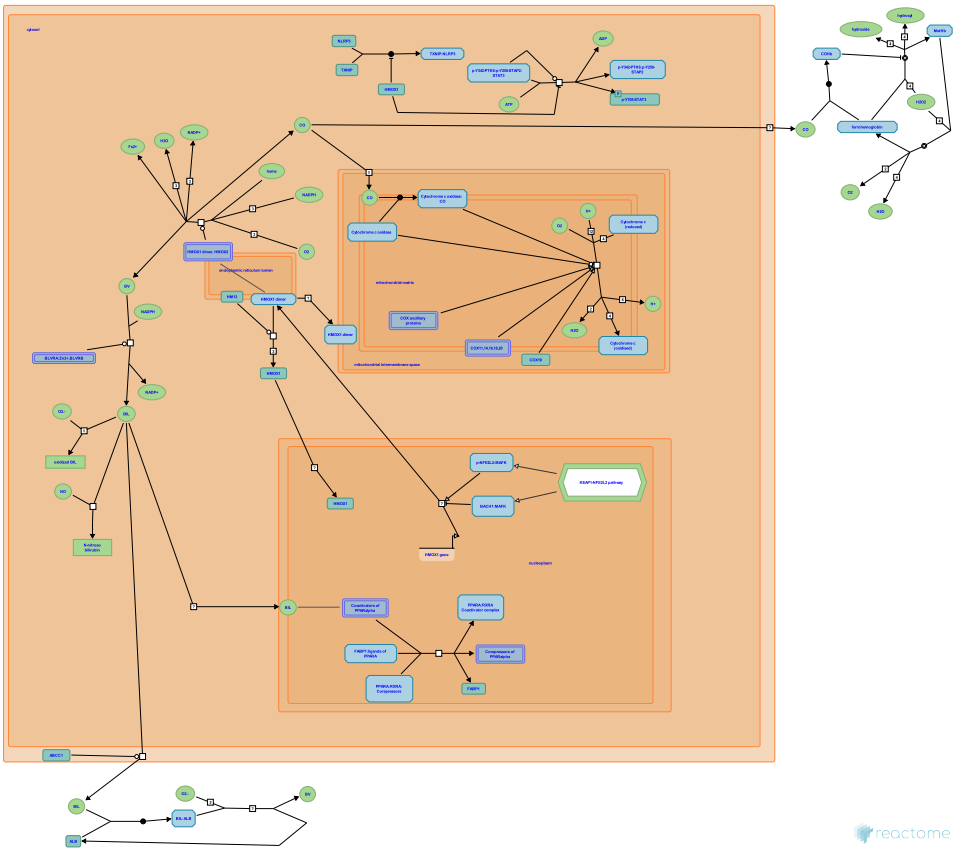
Cytoprotection by HMOX1



Barrientos, A., D'Eustachio, P., Inga, A., Jassal, B., Jupe, S., Kersten, S., Kufer, TA., May, B., Rittinger, K., Rothfels, K., Sassa, S., Somers, J., Stephan, R., Wong, E., Zaccara, S.

European Bioinformatics Institute, New York University Langone Medical Center, Ontario Institute for Cancer Research, Oregon Health and Science University.

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.

26/04/2024

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. ↗

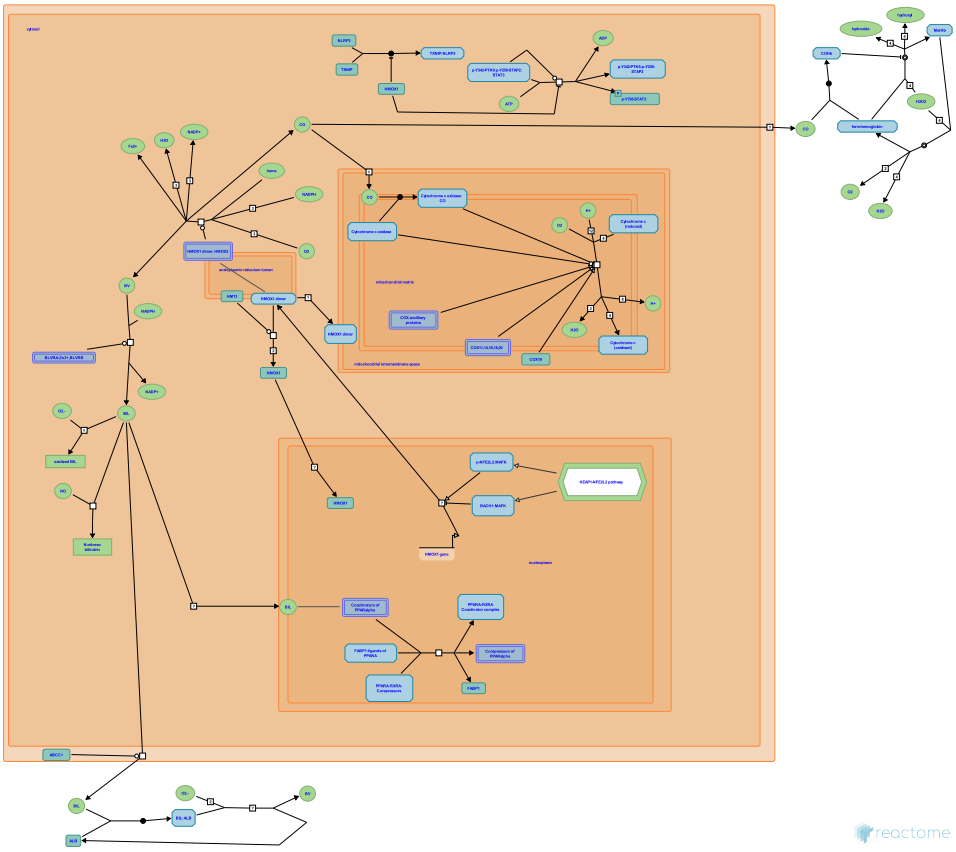
Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

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. ↗

Cytoprotection by HMOX1 ↗

Stable identifier: R-HSA-9707564



Expression of heme oxygenase 1 (HMOX1) is regulated by various indicators of cell stress, while HMOX2 is expressed constitutively. Both catalyze the breakdown of heme into biliverdin (BV), carbon monoxide (CO), and ferrous iron. Biliverdin is immediately reduced to bilirubin (BIL). Both bilirubin and carbon monoxide can localize to different compartments and outside the cell. Cytoprotection by HMOX1 is exerted directly by HMOX1 and by the antioxidant metabolites produced through the degradation of heme. Additionally, due to the reactive nature of labile heme, its degradation is intrinsically protective.

HMOX1 confers cytoprotection against cell death in various models of lung and vascular injury by inhibiting apoptosis, inflammation, and immune cell proliferation. It binds to the NACHT domain of NLRP3 inflammasome, blocking its activation. In mouse it directly binds STAT3 to control the generation of pathogenic Th17 cells during neutrophilic airway inflammation. It also blocks phosphorylation of STAT3 by PTK6 and co-inhibits Socs3, a negative feedback factor of Stat3 activation, as well as RORγt, thereby decreasing Th2 and Th17 immune responses, and alleviating airway inflammation.

The beneficial effects of the three products generated by HMOX1 differ not only in their inherent molecular mechanisms, but also in their downstream cellular targets. To date, this is the only enzymatic system known to exhibit such characteristics. Iron is a vital component of many biological systems and is capable of producing hydroxyl radicals via fenton chemistry. For this reason, iron is sequestered by the storage multimer ferritin and to prevent oxidative damage while maintaining the iron pool. On the other hand, the protective effects of bilirubin and CO are broadly recognized, which has led to their consideration as therapeutics for a range of diseases. Bilirubin has been recognized as one of the most potent antioxidants in nature, and moderate increases of its serum level have been shown in numerous large-scale population and epidemiological studies to have a protective effect against cardiovascular and metabolic disease. These effects are mediated by bilirubin scavenging of superoxide anions and reactive nitrogen species (RNS), and by activating the transcription factor PPAR-alpha.

CO and biliverdin/bilirubin, have been shown to exert protective effects in the liver against a number of stimuli, as in chronic hepatitis C and in transplanted liver grafts. CO possesses intriguing signaling properties affecting numerous critical cellular functions including but not limited to inflammation, cellular proliferation, and apoptotic cell death. Binding of CO with key ferrous hemoproteins serves as a posttranslational modification that regulates important processes as diverse as aerobic metabolism, oxidative stress, and mitochondrial bioenergetics. The most important of these is the mitochondrial cytochrome c oxidase (Cco). By locally blocking mitochondrial respiration the main source of reactive oxygen species (ROS) in the cell is switched off. Additionally CO enables efficient reduction of

methemoglobin (MetHb) by H2O2, thus preventing the generation of free heme in hemorrhagic diseases and malaria (Origassa and Câmara, 2013; Morse et al, 2009; Ryter et al, 2006; Cooper and Brown, 2008; Hinds and Stec, 2008).

Literature references

Câmara, N., Origassa, C. (2013). Cytoprotective role of heme oxygenase-1 and heme degradation derived end products in liver injury. *World journal of hepatology, 5*, 541-549.

Cooper, CE., Brown, GC. (2008). The inhibition of mitochondrial cytochrome oxidase by the gases carbon monoxide, nitric oxide, hydrogen cyanide and hydrogen sulfide: chemical mechanism and physiological significance. *J Bioenerg Biomembr, 40*, 533-9.

Stec, DE., Hinds, TD. (2018). Bilirubin, a Cardiometabolic Signaling Molecule. *Hypertension, 72*, 788-795.

Alam, J., Choi, AM., Ryter, SW. (2006). Heme oxygenase-1/carbon monoxide: from basic science to therapeutic applications. *Physiol Rev, 86*, 583-650.

Choi, AM., Morse, D., Ryter, SW., Lin, L. (2009). Heme oxygenase-1, a critical arbitrator of cell death pathways in lung injury and disease. *Free Radic Biol Med, 47*, 1-12.

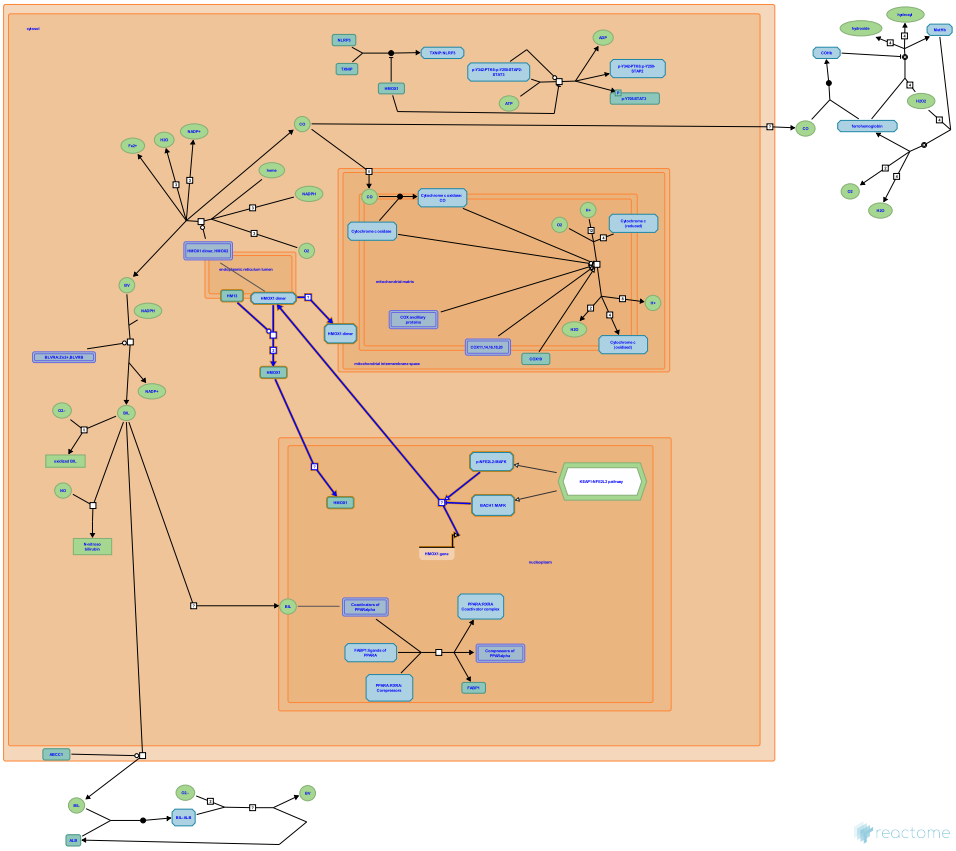
Editions

2020-11-12	Authored, Edited	Stephan, R.
2021-01-23	Reviewed	Somers, J.
2022-02-23	Revised	Rothfels, K.

Regulation of HMOX1 expression and activity ↗

Location: Cytoprotection by HMOX1

Stable identifier: R-HSA-9707587



Heme oxygenase 1 (HMOX1) is regulated at the level of gene transcription, mRNA translation, localization and degradation. Its gene is often activated under a wide range of stressful conditions. The transcriptional control of HMOX1 is determined by inducible regulatory elements localized in the 5′ region of the promoter, so called antioxidant response elements (ARE)(Raghunath et al, 2018).

AREs on the HMOX1 gene are ultimately controlled by the enhancing NFE2L2:MAFK dimer and the repressing BACH1:MAFK dimer, both of which are influenced by a multitude of processes. Less specific enhancement occurs via AP-1 (FOS:JUN) dimers (Funes et al, 2020).

HMOX1 activity depends on dimerization in the ER membrane. Its membrane localization is abandoned by cleavage of the membrane domain by HM13. The resulting soluble enzyme is found in the cytosol, mitochondria, and the nucleus (Schaefer et al, 2017).

Literature references

Sethi, G., Kumar, AP., Sundarraj, K., Perumal, E., Arfuso, F., Raghunath, A. et al. (2018). Antioxidant response elements: Discovery, classes, regulation and potential applications. *Redox Biol, 17*, 297-314. ↗

Behrends, S., Schaefer, B., Moriishi, K. (2017). Insights into the mechanism of isoenzyme-specific signal peptide peptidase-mediated translocation of heme oxygenase. *PLoS One, 12*, e0188344. ↗

Kalergis, AM., Fernández-Fierro, A., Funes, SC., Mackern-Oberti, JP., Bueno, SM., Covián, C. et al. (2020). Naturally Derived Heme-Oxygenase 1 Inducers and Their Therapeutic Application to Immune-Mediated Diseases. *Front Immunol, 11*, 1467. ↗

Alam, J., Choi, AM., Ryter, SW. (2006). Heme oxygenase-1/carbon monoxide: from basic science to therapeutic applications. *Physiol Rev, 86*, 583-650. ↗

Editions

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2022-02-24	Revised	Rothfels, K.

TXNIP binds NLRP3 ↗

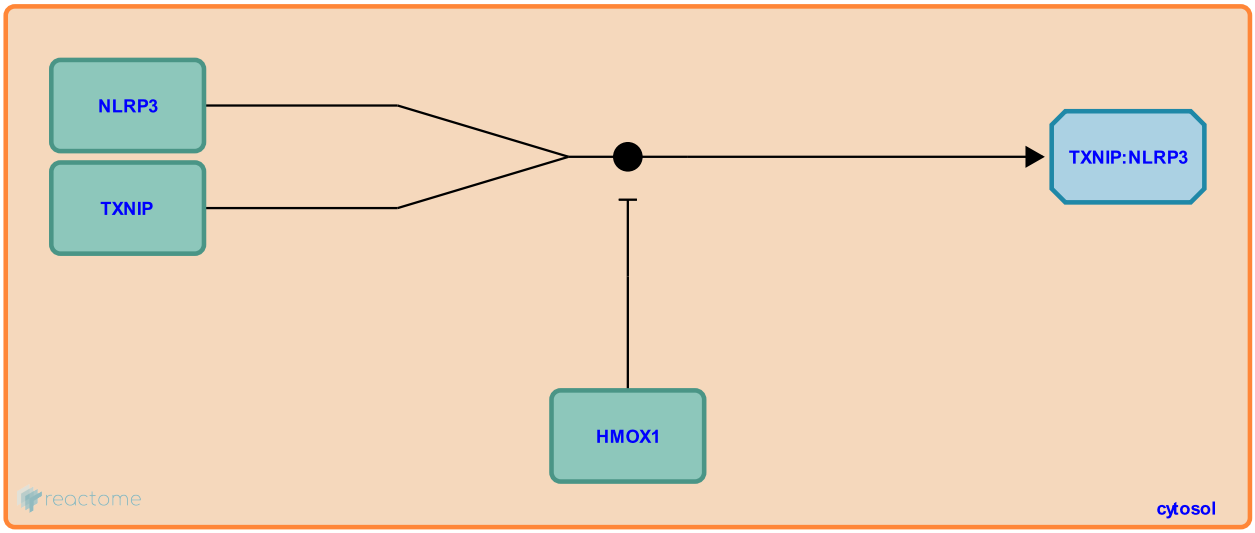
Location: Cytoprotection by HMOX1

Stable identifier: R-HSA-1250272

Type: binding

Compartments: cytosol

Inferred from: Txnip binds Nlrp3 (Mus musculus)



Thioredoxin-interacting protein (TXNIP) binds NLRP3. Reactive oxygen species (ROS) such as H2O2 increase this interaction, while the ROS inhibitor APDC blocks it (Zhou et al. 2010). This interaction is proposed to activate the NLRP3 inflammasome.

Heme oxygenase (HMOX1), besides its enzymatic activity of the dimeric membrane protein isoform, also occurs as soluble cytosolic protein. It is probably this form that binds to the NACHT domain of NLRP3, suppressing production of epithelial cell-derived cytokines induced by activation of the NLRP3 inflammasome, and protecting airway epithelium in asthma (Lv et al, 2018).

Literature references

Choi, I., Thorens, B., Tardivel, A., Zhou, R., Tschopp, J. (2010). Thioredoxin-interacting protein links oxidative stress to inflammasome activation. *Nat Immunol, 11*, 136-40. ↗

Editions

2011-04-28	Authored, Edited	Jupe, S.
2011-04-28	Reviewed	Kufer, TA.
2011-06-06	Reviewed	Rittinger, K., Wong, E.
2021-01-23	Reviewed	Somers, J.

PTK6 phosphorylates STAT3 ↗

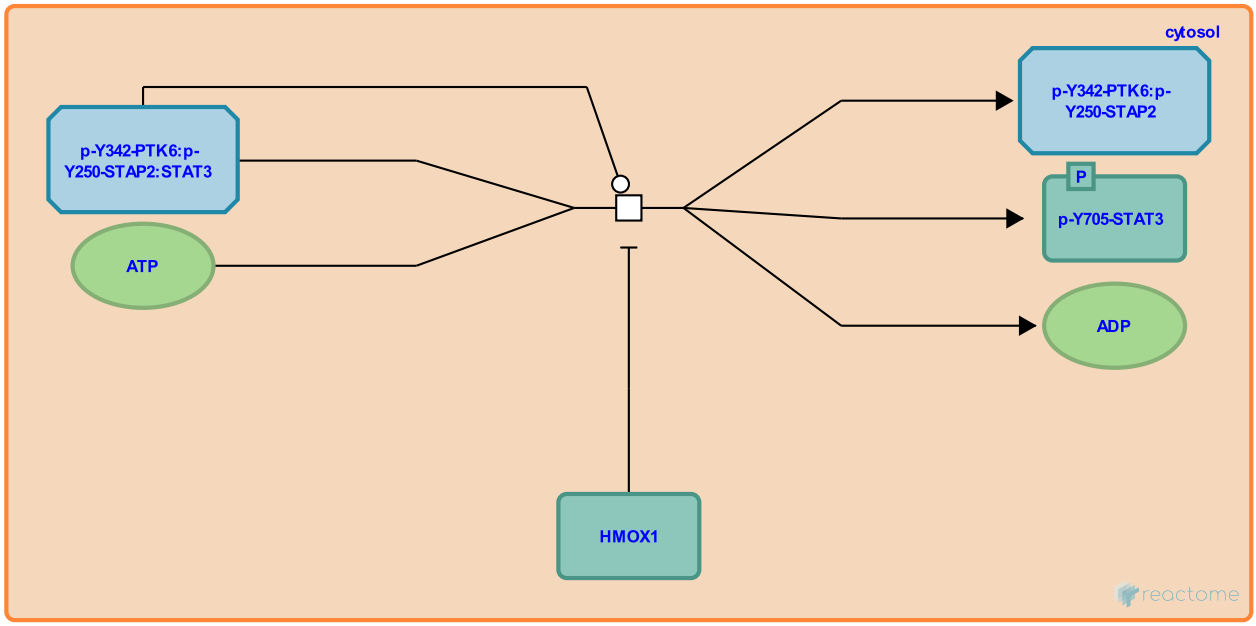
Location: Cytoprotection by HMOX1

Stable identifier: R-HSA-9709918

Type: transition

Compartments: cytosol

Inferred from: Ptk6 phosphorylates Stat3 (Mus musculus)



In humans, activated PTK6 (BRK) phosphorylates STAT3 on tyrosine residue Y705. PTK6-mediated phosphorylation of STAT3 is promoted by STAP2 and inhibited by SOCS3 (Liu et al. 2006, Ikeda et al. 2010).

In mouse, Ptk6-mediated phosphorylation of Stat3 is promoted by Stap2 and inhibited by Socs3. Heme oxygenase-1 (Hmox1) binds to tyrosine-705 and three domains on Stat3 (DNA-binding, linker, and transactivation domains), directly regulating Stat3 activation. Additionally it co-inhibits Socs3, a negative feedback factor of Stat3 activation, as well as RORγt, thereby decreasing Th2 and Th17 immune responses, and alleviating airway inflammation (Lin et al, 2020; Lin et al, 2017).

Literature references

Reich, NC., Gao, Y., Poli, V., Miller, WT., Liu, L., Qiu, H. (2006). Identification of STAT3 as a specific substrate of breast tumor kinase. *Oncogene, 25*, 4904-12. ↗

Miyasaka, Y., Matsuda, T., Mizushima, A., Nanbo, A., Ikeda, O., Sekine, Y. et al. (2010). Interactions of STAP-2 with Brk and STAT3 participate in cell growth of human breast cancer cells. *J. Biol. Chem., 285*, 38093-103. ↗

Editions

2020-12-14	Authored, Edited	Stephan, R.
2021-01-23	Reviewed	Somers, J.

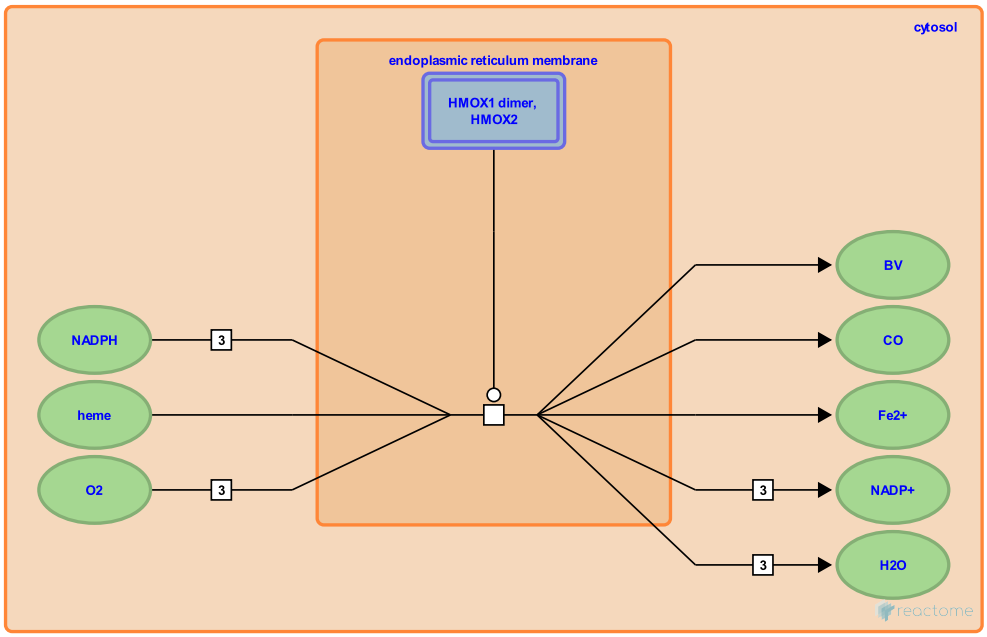
HMOX1 dimer, HMOX2 cleave heme ↗

Location: Cytoprotection by HMOX1

Stable identifier: R-HSA-189398

Type: transition

Compartments: endoplasmic reticulum membrane, cytosol



Heme oxygenases (HMOXs) cleaves the heme ring at the alpha-methene bridge to form bilverdin. This reaction forms the only endogenous source of carbon monoxide. HMOX1 is inducible and is thought to have an antioxidant role as it is activated in virtually all cell types and by many types of "oxidative stress" (Poss & Tonegawa 1997). HMOX1 forms dimers/oligomers in the endoplasmatic reticulum. This oligomerization is crucial for the stabilization and function of HMOX1 in the ER (Hwang et al. 2009). HMOX2 is non-inducible.

Followed by: CO translocates from cytosol to mitochondrial inner membrane, BLVRA:Zn2+, BLVRB reduce BV to BIL, CO translocates from cytosol to extracellular region

Editions

2006-11-20	Authored	Jassal, B.
2007-01-24	Reviewed	Sassa, S.
2009-05-19	Revised	D'Eustachio, P.
2020-11-23	Edited	Jassal, B.
2021-01-23	Reviewed	Somers, J.

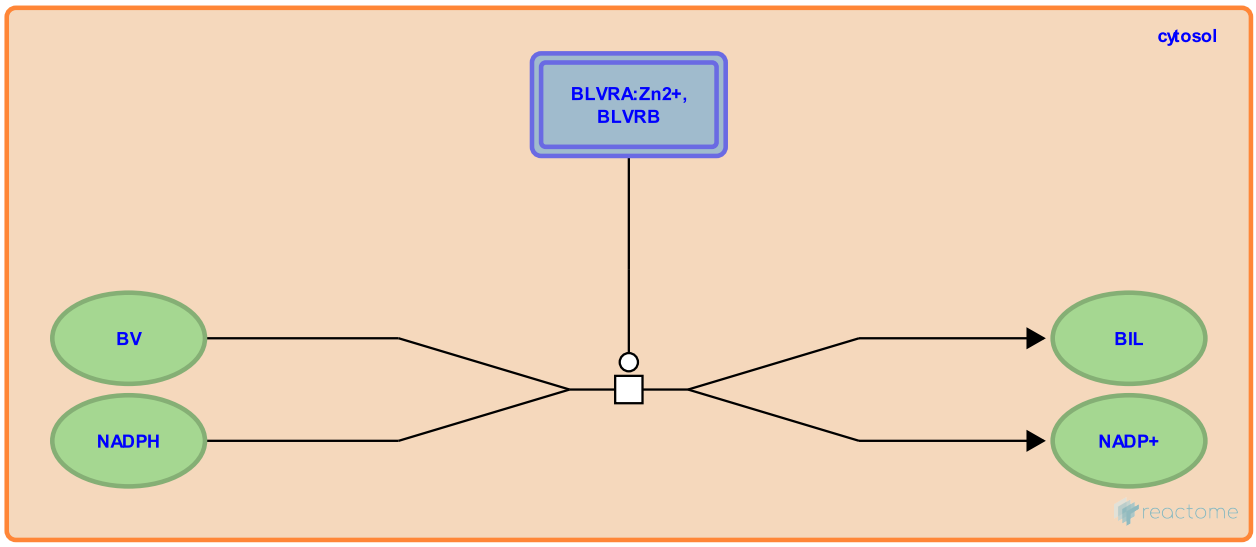
BLVRA:Zn2+, BLVRB reduce BV to BIL ↗

Location: Cytoprotection by HMOX1

Stable identifier: R-HSA-189384

Type: transition

Compartments: cytosol



Bilirubin (BIL) is the breakdown product of heme, causing death if allowed to accumulate in the blood. It is highly lipophilic and requires conjugation to become more water soluble to aid excretion. BIL is formed from the reduction of biliverdin (BV) by bilverdin reductases BLVRA and BLVRB (Cunningham et al. 2000, Fu et al. 2012, O'Brien et al. 2015).

Preceded by: HMOX1 dimer, HMOX2 cleave heme

Followed by: BIL scavenges NO, BIL scavenges O2.-, BIL translocates to the nucleus, ABCC1 transports BIL from cytosol to extracellular region (blood)

Literature references

Cunningham, O., Mantle, TJ., Gore, MG. (2000). Initial-rate kinetics of the flavin reductase reaction catalysed by human biliverdin-IXbeta reductase (BVR-B). *Biochem. J., 345*, 393-9. ↗

Fu, G., Doerksen, RJ., Liu, H. (2012). Molecular modeling to provide insight into the substrate binding and catalytic mechanism of human biliverdin-IXα reductase. *J Phys Chem B, 116*, 9580-94. ↗

Editions

2006-11-20	Authored	Jassal, B.
2007-01-24	Reviewed	Sassa, S.
2009-05-19	Revised	D'Eustachio, P.
2019-09-18	Edited, Revised	Jassal, B.
2021-01-23	Reviewed	Somers, J.

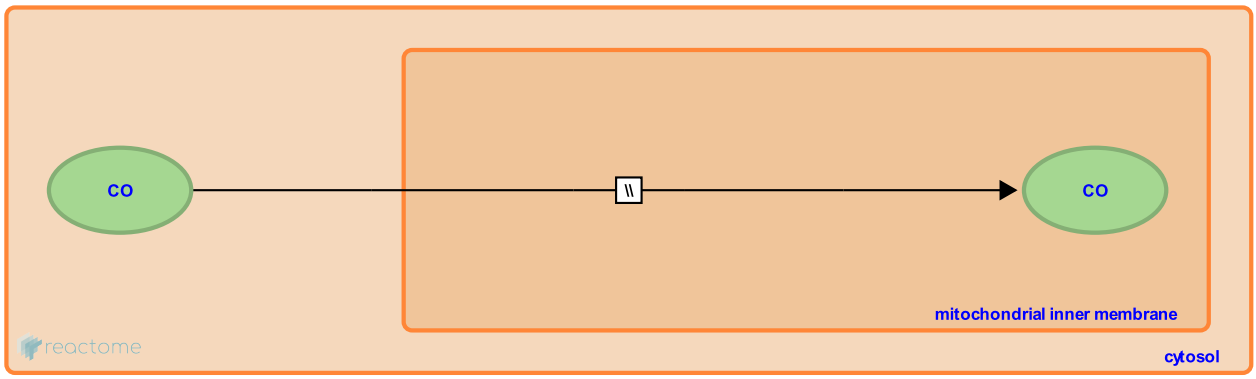
CO translocates from cytosol to mitochondrial inner membrane ↗

Location: Cytoprotection by HMOX1

Stable identifier: R-HSA-9709366

Type: omitted

Compartments: mitochondrial inner membrane, cytosol



As a light, unpolar molecule carbon monoxide (CO) is able to penetrate lipid membranes and so get access to proteins in the inner mitochondrial membrane (Alonso et al, 2003).

Preceded by: HMOX1 dimer, HMOX2 cleave heme

Followed by: CO binds to Cytochrome c oxidase

Literature references

Miró, O., López, S., Casademont, J., Alonso, JR., Cardellach, F. (2003). Carbon monoxide specifically inhibits cytochrome c oxidase of human mitochondrial respiratory chain. *Pharmacol Toxicol, 93*, 142-6. ↗

Editions

2020-12-03	Authored, Edited	Stephan, R.
2021-01-23	Reviewed	Somers, J.

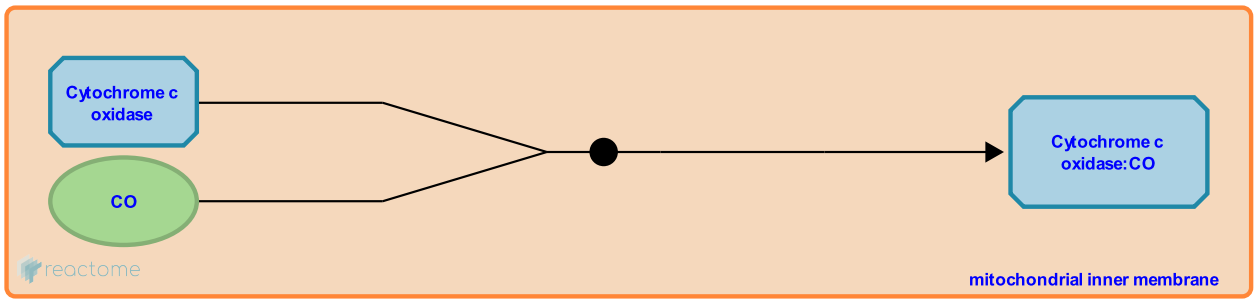
CO binds to Cytochrome c oxidase ↗

Location: Cytoprotection by HMOX1

Stable identifier: R-HSA-9709406

Type: binding

Compartments: mitochondrial inner membrane



Carbon monoxide (CO) toxicity is the result of a combination of tissue hypoxia and direct CO-mediated damage at a cellular level, since not all the signs and symptoms presented can be explained only by the formation of carboxyhaemoglobin. CO binds to cytochrome c oxidase, the terminal enzyme in the electron transfer chain, reducing its activity. Regulation of reactive oxygen species (ROS) generation is possibly one of the key components in CO signaling and its interaction with mitochondria but also other heme proteins that generate ROS, such as NADPH oxidase (Alonso et al, 2003; Zuckerbraun et al, 2007; Ishigami et al, 2017; Motterlini and Foresti, 2017).

Preceded by: CO translocates from cytosol to mitochondrial inner membrane

Literature references

Miró, O., López, S., Casademont, J., Alonso, JR., Cardellach, F. (2003). Carbon monoxide specifically inhibits cytochrome c oxidase of human mitochondrial respiratory chain. *Pharmacol Toxicol, 93*, 142-6. ↗

Nelson, G., Coe, JD., Fromme, R., Fromme, P., Yeh, SR., Conrad, CE. et al. (2017). Crystal structure of CO-bound cytochrome c oxidase determined by serial femtosecond X-ray crystallography at room temperature. *Proc Natl Acad Sci U S A, 114*, 8011-8016. ↗

Chin, BY., Zuckerbraun, BS., Bilban, M., d'Avila, JC., Rao, J., Otterbein, LE. et al. (2007). Carbon monoxide signals via inhibition of cytochrome c oxidase and generation of mitochondrial reactive oxygen species. *FASEB J, 21*, 1099-106. ↗

Editions

2020-12-03	Authored, Edited	Stephan, R.
2021-01-23	Reviewed	Somers, J.

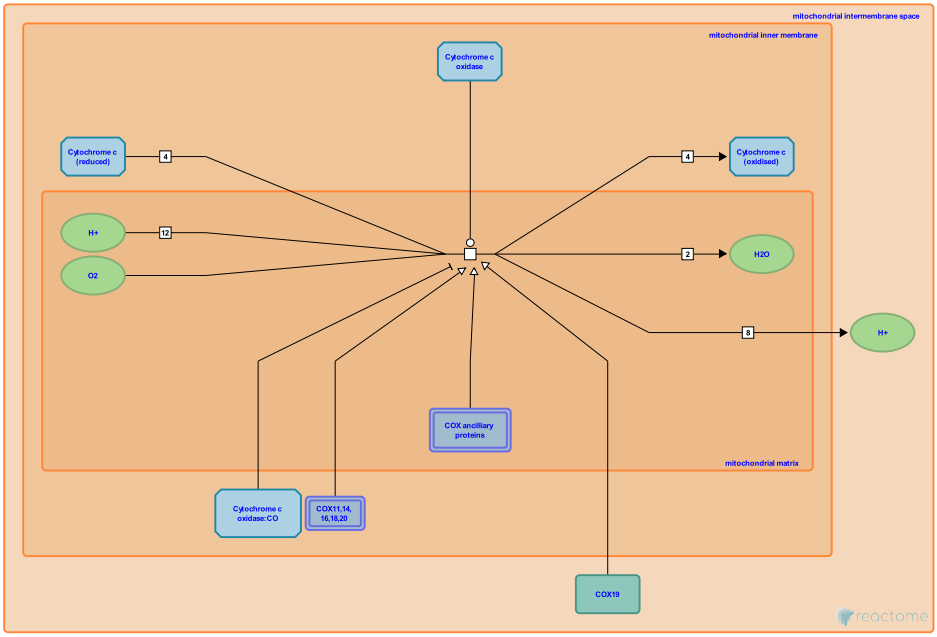
Electron transfer from reduced cytochrome c to molecular oxygen ↗

Location: Cytoprotection by HMOX1

Stable identifier: R-HSA-163214

Type: transition

Compartments: mitochondrial matrix, mitochondrial intermembrane space, mitochondrial inner membrane



Complex IV (COX, cytochrome c oxidase) contains the hemeprotein cytochrome a and a3. It also contains copper atoms which undergo a transition from Cu+ to Cu2+ during the transfer of electrons through the complex to molecular oxygen. A bimetallic centre containing a copper atom and a heme-linked iron protein binds oxygen after 4 electrons have been picked up. Water, the final product of oxygen reduction, is then released. Oxygen is the final electron acceptor in the respiratory chain. The overall reaction can be summed as

4Cyt c (red.) + 12H+ (in) + O2 = 4Cyt c (ox.) + 2H2O + 8H+ (out)

Four protons are taken up from the matrix side of the membrane to form the water (scalar protons). Wikstrom (1977) suggests 4 protons are additionally transferred out from the matrix to the intermembrane space.

COX ancillary proteins mediate membrane insertion, catalytic core processing, copper transport and insertion into core subunits and heme A biosynthesis (Stilburek et al. 2006, Fontanesi et al. 2006, Soto et al. 2012). To date, all Mendelian disorders presenting COX deficiency have been assigned to mutations in ancillary factors, with the exception of an infantile encephalomyopathy caused by a defective COX6B1 and an exocrine pancreatic insufficiency caused by a defective COX4I2 gene (Soto et al. 2012). Balsa et al have shown that NDUFA4, formerly considered to be a constituent of NADH dehydrogenase (Complex I), is instead a component of the cytochrome c oxidase (CIV) (Balsa et al. 2012). Patients with NDUFA4 mutations display COX deficiencies (Pitceathly et al. 2013).

Carbon monoxide (CO) readily inhibits oxygen consumption by mitochondrial cytochrome oxidase. This inhibition is responsible for much of its toxicity when it is applied externally to the body. However, CO has been implicated in normal cellular signalling, especially in anti-inflammatory effects. The addition of antioxidants or inhibition of complex III of the electron transport chain by antimycin A attenuates the inhibitory effects of CO on lipopolysaccharide (LPS)-induced NLRP3 formation and TNF-alpha secretion, and blocked CO-induced p38 MAPK phosphorylation. These effects may be mediated via inhibition of cytochrome c oxidase and its generation of mitochondrial reactive oxygen species (Alonso et al, 2003; Zuckerbraun et al, 2007; Cooper and Brown, 2008; Jung et al, 2014; Ishigami et al, 2017).

Literature references

Schultz, BE., Chan, SI. (2001). Structures and proton-pumping strategies of mitochondrial respiratory. *Annu Rev Biophys Biomol Struct, 30*, 23-65. ↗

Soto, IC., Horn, D., Barrientos, A., Fontanesi, F. (2006). Assembly of mitochondrial cytochrome c-oxidase, a complicated and highly regulated cellular process. *Am. J. Physiol., Cell Physiol., 291*, C1129-47. ↗

Hurles, ME., Rahman, S., Taanman, JW., Woodward, CE., Sweeney, MG., Foley, AR. et al. (2013). NDUFA4 mutations underlie dysfunction of a cytochrome c oxidase subunit linked to human neurological disease. *Cell Rep, 3*, 1795-805. ↗

Calvo, E., Balsa, E., Marco, R., Szklarczyk, R., Enríquez, JA., Landázuri, MO. et al. (2012). NDUFA4 is a subunit of complex IV of the mammalian electron transport chain. *Cell Metab., 16*, 378-86. ↗

Wikstrom, MK. (1977). Proton pump coupled to cytochrome c oxidase in mitochondria. *Nature, 266*, 271-3. ↗

Editions

2005-04-25	Edited	Jassal, B.
2005-06-28	Authored	Jassal, B.
2014-09-02	Revised	Barrientos, A.
2015-02-11	Revised	Jassal, B.
2016-02-04	Reviewed	Inga, A., Zaccara, S.
2021-01-23	Reviewed	Somers, J.

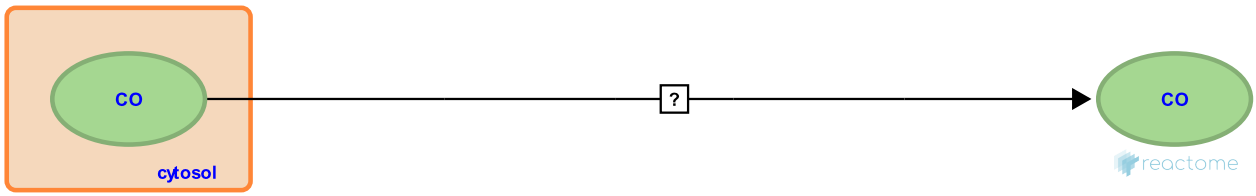
CO translocates from cytosol to extracellular region ↗

Location: Cytoprotection by HMOX1

Stable identifier: R-HSA-9709396

Type: uncertain

Compartments: extracellular region, cytosol



As a light, unpolar molecule carbon monoxide is able to penetrate lipid membranes and to escape the cell (Sher et al, 2012).

Preceded by: HMOX1 dimer, HMOX2 cleave heme

Followed by: CO binds to free ferrohemoglobin, H2O2 reduces MetHb

Literature references

Shaklai, M., Sher, EA., Shaklai, N. (2012). Carbon monoxide promotes respiratory hemoproteins iron reduction using peroxides as electron donors. *PLoS One, 7*, e33039. ↗

Editions

2020-12-03	Authored, Edited	Stephan, R.
2021-01-23	Reviewed	Somers, J.

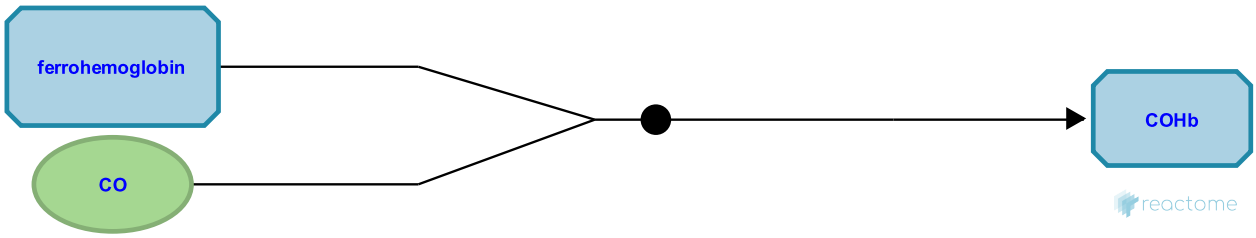
CO binds to free ferrohemoglobin ↗

Location: Cytoprotection by HMOX1

Stable identifier: R-HSA-9709317

Type: binding

Compartments: extracellular region



Carbon monoxide (CO) tightly binds to free ferrohemoglobin, preventing its oxidation to methemoglobin by reactive oxygen species. The reaction is fast and quickly removes CO from the local environment if free hemoglobin is present (Cera et al, 1987; Sher et al, 2012).

Preceded by: H2O2 reduces MetHb, CO translocates from cytosol to extracellular region

Literature references

Shaklai, M., Sher, EA., Shaklai, N. (2012). Carbon monoxide promotes respiratory hemoproteins iron reduction using peroxides as electron donors. *PLoS One, 7*, e33039. ↗

Connelly, PR., Di Cera, E., Doyle, ML., Gill, SJ. (1987). Carbon monoxide binding to human hemoglobin A0. *Biochemistry, 26*, 6494-502. ↗

Editions

2020-12-03	Authored, Edited	Stephan, R.
2021-01-23	Reviewed	Somers, J.

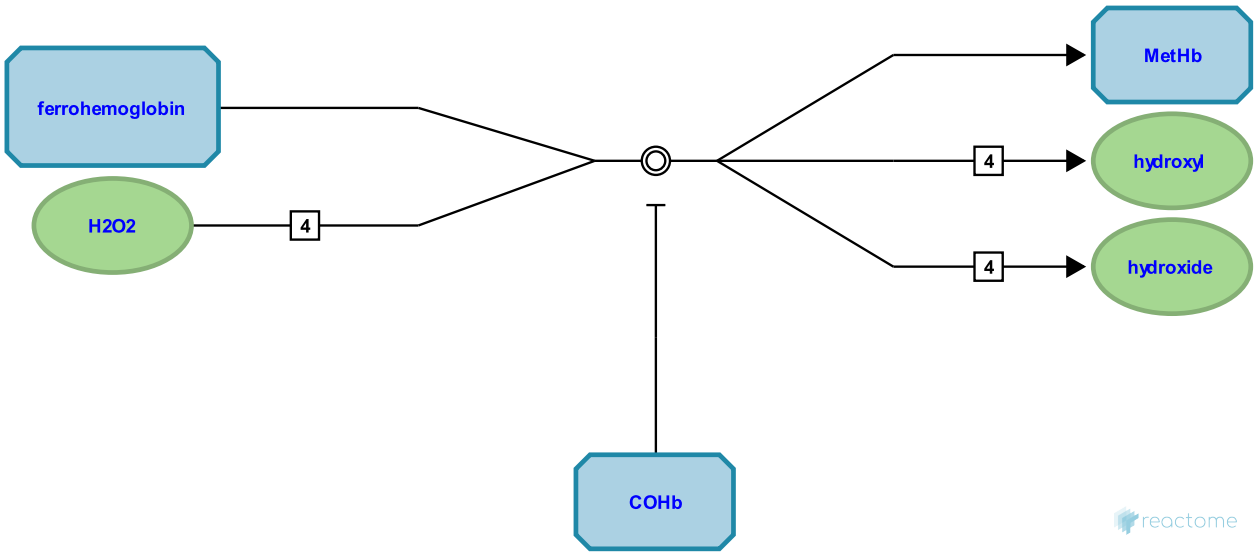
H2O2 oxidises ferrohemoglobin to MetHb ↗

Location: Cytoprotection by HMOX1

Stable identifier: R-HSA-9707504

Type: dissociation

Compartments: extracellular region



Extracellular ferrous (Fe2+) hemoglobin (FeHM) is readily oxidized into methemoglobin (MetHb) in the presence of reactive oxygen species (ROS) like hydrogen peroxide (H2O2) (Gouveia et al, 2017; Sadrzadeh et al, 1984).

Carbon monoxide (CO) tightly binds to free ferrohemoglobin, preventing its oxidation to methemoglobin by reactive oxygen species. The reaction is fast and quickly removes CO from the local environment if free hemoglobin is present (Cera et al, 1987; Sher et al, 2012).

Followed by: H2O2 reduces MetHb

Literature references

Eaton, JW., Graf, E., Panter, SS., Hallaway, PE., Sadrzadeh, SM. (1984). Hemoglobin. A biologic fenton reagent. *J Biol Chem, 259*, 14354-6. ↗

Acker, JP., Kanias, T. (2010). Biopreservation of red blood cells--the struggle with hemoglobin oxidation. *FEBS J, 277*, 343-56. ↗

Editions

2020-11-12	Authored	Stephan, R.
2020-11-19	Edited	Stephan, R.
2021-01-23	Reviewed	Somers, J.

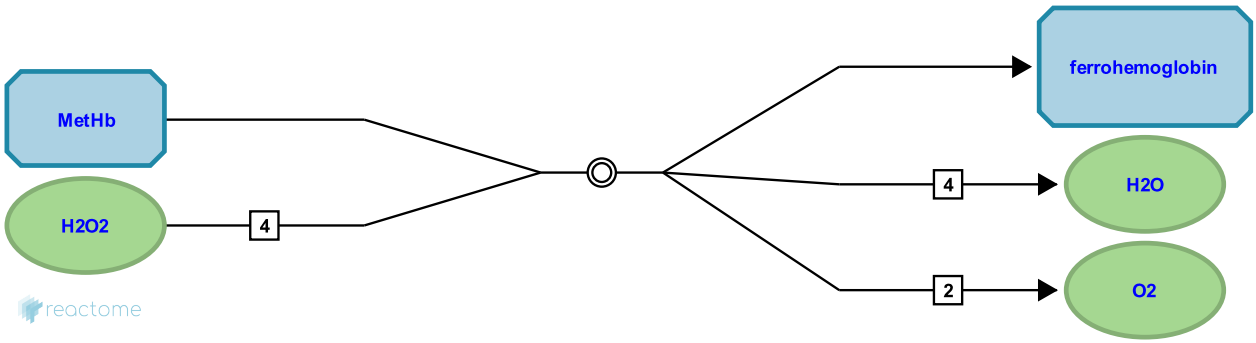
H2O2 reduces MetHb ↗

Location: Cytoprotection by HMOX1

Stable identifier: R-HSA-9709360

Type: dissociation

Compartments: extracellular region



Hydrogen peroxide (H2O2) can reduce methemoglobin (metHb) but this is a slow reaction. However, the fast and practically irreversible reaction of ferrous heme-iron in ferrohemoglobin with carbon monoxide (CO) results in a shift of the equilibrium towards the carboxy forms of hemoglobin. The main impact of CO is not reduction of ferric heme-iron per se, but rather its arrest in the ferrous carboxy complex, a practically irreversible process. Equilibrium is then shifted via Le Chatelier's principle. Therefore, the net result of the reaction appears to be replacement of injurious plasma components, metHb and H2O2, by physiological, harmless, metabolites (Sher et al, 2012).

Preceded by: H2O2 oxidises ferrohemoglobin to MetHb, CO translocates from cytosol to extracellular region

Followed by: CO binds to free ferrohemoglobin

Literature references

Shaklai, M., Sher, EA., Shaklai, N. (2012). Carbon monoxide promotes respiratory hemoproteins iron reduction using peroxides as electron donors. *PLoS One, 7*, e33039. ↗

Editions

2020-12-03	Authored, Edited	Stephan, R.
2021-01-23	Reviewed	Somers, J.

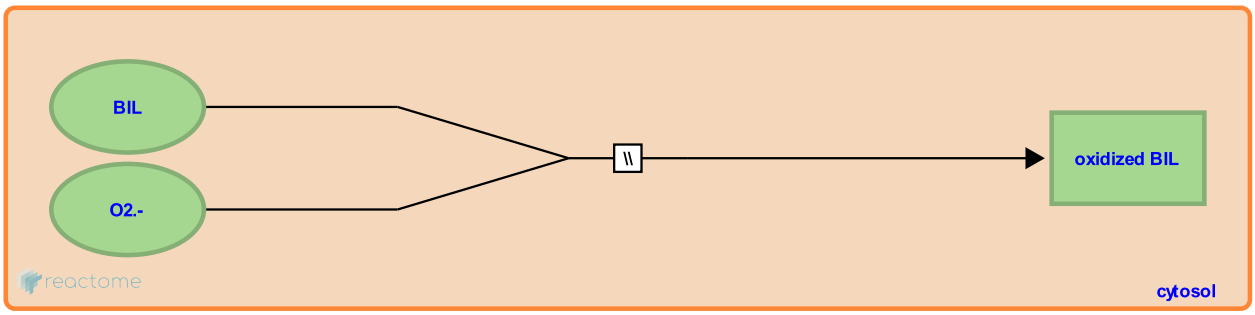
BIL scavenges O2.- ↗

Location: Cytoprotection by HMOX1

Stable identifier: R-HSA-9709879

Type: omitted

Compartments: cytosol



Bilirubin (BIL) is a physiologic antioxidant. It has a unique redox activity towards superoxide radicals (O2•−) which it readily scavenges. Bilirubin's redox activity is particularly important in the brain, where it prevents excitotoxicity and neuronal death by scavenging O2•− during NMDA neurotransmission (Vasavda et al, 2019).

Preceded by: BLVRA:Zn2+, BLVRB reduce BV to BIL

Literature references

Ricco, C., Tokhunts, R., Saavedra, HG., Albacarys, L., Kothari, R., Vasavda, C. et al. (2019). Bilirubin Links Heme Metabolism to Neuroprotection by Scavenging Superoxide. *Cell Chem Biol, 26*, 1450-1460.e7. ↗

Editions

2020-12-14	Authored, Edited	Stephan, R.
2021-01-23	Reviewed	Somers, J.

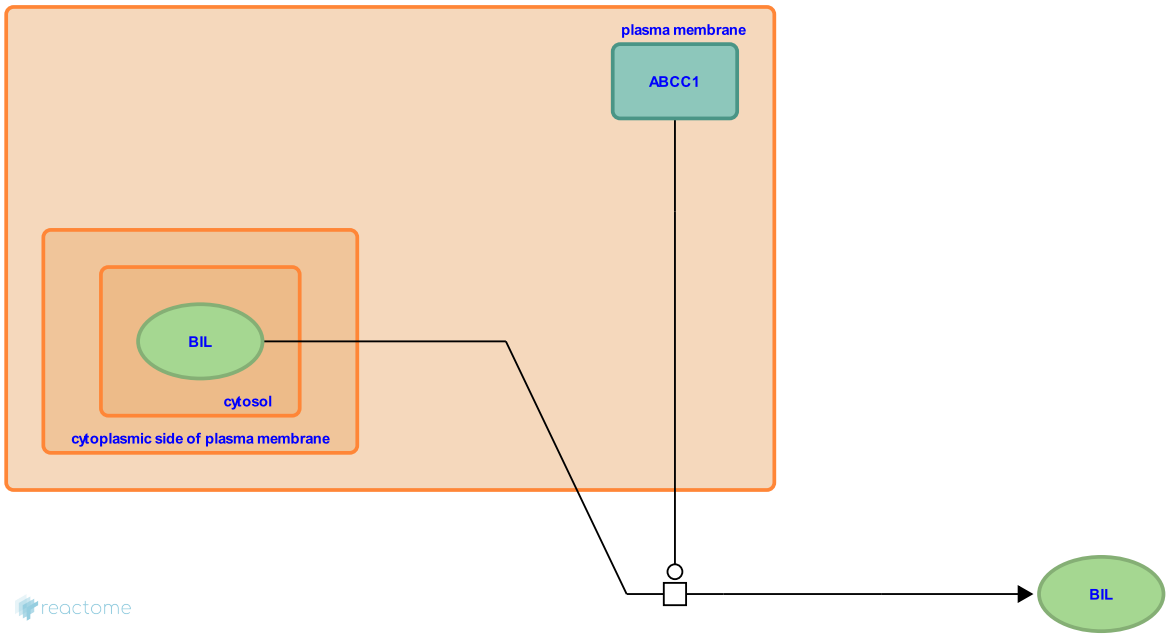
ABCC1 transports BIL from cytosol to extracellular region (blood) ↗

Location: Cytoprotection by HMOX1

Stable identifier: R-HSA-9661405

Type: transition

Compartments: extracellular region, cytosol



Bilirubin (BIL), formed in erythroid cells, exits the cell to be transported to the liver for conjugation and ultimately, excretion. BIL possibly leaves the cell by simple diffusion as it is highly lipophilic (Kamisako et al. 2000). However, the multidrug resistance-associated protein 1 (ABCC1 aka MRP1) is known to mediate the ATP-dependent export of organic anions and drugs from cells. Unconjugated bilirubin (BIL) may also be exported from cells by ABCC1 (Rigato et al. 2004).

Preceded by: BLVRA:Zn2+, BLVRB reduce BV to BIL

Followed by: BIL binds ALB

Literature references

Ostrow, JD., Fernetti, C., Tiribelli, C., Rigato, I., Pascolo, L. (2004). The human multidrug-resistance-associated protein MRP1 mediates ATP-dependent transport of unconjugated bilirubin. *Biochem. J., 383*, 335-41. ↗

Takeuchi, K., Gabazza, EC., Kamisako, T., Adachi, Y., Ishihara, T., Kobayashi, Y. et al. (2000). Recent advances in bilirubin metabolism research: the molecular mechanism of hepatocyte bilirubin transport and its clinical relevance. *J. Gastroenterol., 35*, 659-64. ↗

Editions

2019-09-16	Authored, Edited	Jassal, B.
2019-10-03	Reviewed	D'Eustachio, P.
2021-01-23	Reviewed	Somers, J.

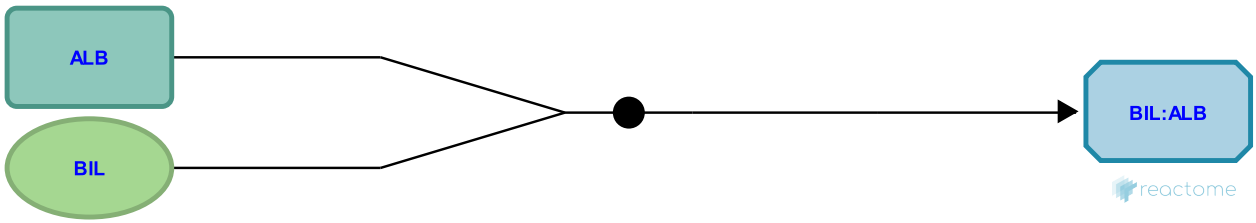
BIL binds ALB ↗

Location: Cytoprotection by HMOX1

Stable identifier: R-HSA-9661432

Type: binding

Compartments: extracellular region



The serum protein albumin (ALB) binds unconjugated bilirubin (BIL), preventing BIL toxicity (Griffiths et al. 1975, Weisiger et al. 2001). ALB-bound BIL is a water-soluble complex and is transported to the liver where it is selectively absorbed by hepatocytes.

Preceded by: ABCC1 transports BIL from cytosol to extracellular region (blood)

Followed by: BIL:ALB scavenges O2.-

Literature references

Diamond, I., Dextraze, P., Griffiths, WC. (1975). The albumin binding of unconjugated bilirubin in serum. *Clin. Biochem., 8*, 254-60. ↗

Weisiger, RA., Webster, CC., Ostrow, JD., Tiribelli, C., Pascolo, L., Mukerjee, P. et al. (2001). Affinity of human serum albumin for bilirubin varies with albumin concentration and buffer composition: results of a novel ultrafiltration method. *J. Biol. Chem., 276*, 29953-60. ↗

Editions

2019-09-16	Authored, Edited	Jassal, B.
2019-10-03	Reviewed	D'Eustachio, P.
2021-01-23	Reviewed	Somers, J.

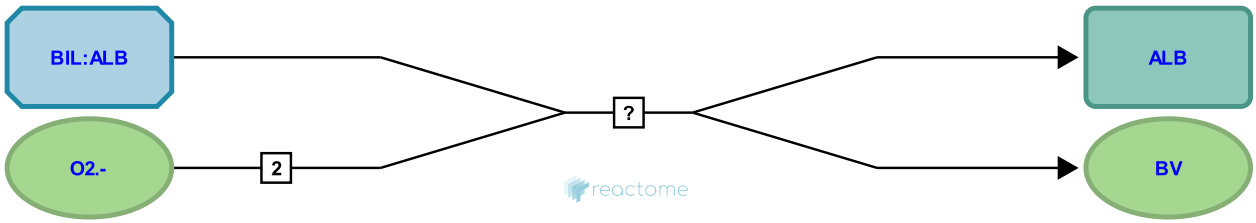
BIL:ALB scavenges O2.-

Location: Cytoprotection by HMOX1

Stable identifier: R-HSA-9709883

Type: uncertain

Compartments: extracellular region



Like unbound bilirubin (BIL) the bilirubin-albumin complex (BIL:ALB) scavenges superoxide. Small amounts of plasma bilirubin are sufficient to prevent oxidation of albumin-bound fatty acids as well as of the protein itself. This indicates a role for BIL:ALB as a physiological antioxidant in plasma and the extravascular space. There is however no evidence for a fully circular mechanism where all bilirubin is oxidized back to biliverdin to be available again as antioxidant (Stocker et al, 1987; Maghzal et al, 2009).

Preceded by: BIL binds ALB

Literature references

Ames, BN., Glazer, AN., Stocker, R. (1987). Antioxidant activity of albumin-bound bilirubin. *Proc Natl Acad Sci U S A, 84*, 5918-22.

Li, C., Stocker, R., Maghzal, GJ., Leck, MC., Collinson, E. (2009). Limited role for the bilirubin-biliverdin redox amplification cycle in the cellular antioxidant protection by biliverdin reductase. *J Biol Chem, 284*, 29251-9.

Editions

2020-12-14	Authored, Edited	Stephan, R.
2021-01-23	Reviewed	Somers, J.

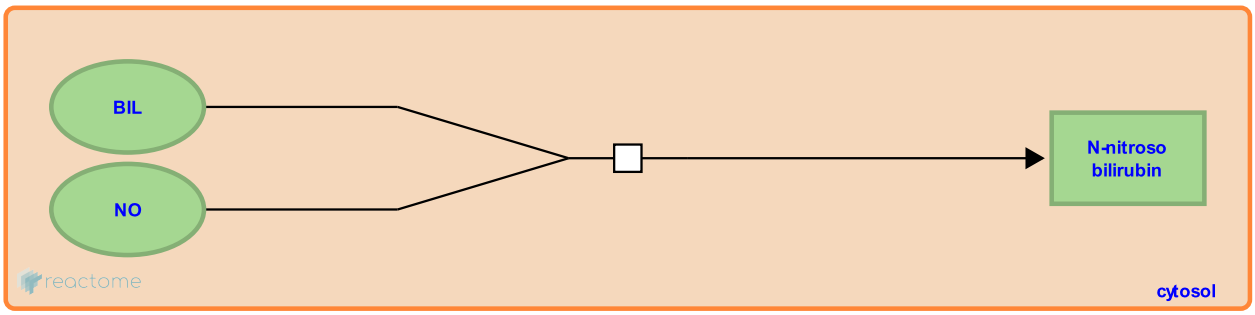
BIL scavenges NO ↗

Location: Cytoprotection by HMOX1

Stable identifier: R-HSA-9709885

Type: transition

Compartments: cytosol



Bilirubin (BIL) can serve as an endogenous scavenger of both nitric oxide (NO) and reactive nitrogen species, thus widening the protective role of bilirubin to other reactive species originating within the cellular environment. This ability is quite important in explaining some of the pathophysiological mechanisms involved in the cytoprotective function of the bile pigment against NO-related pathologies such as atherosclerosis, liver disease and neurodegenerative disorders (Mancuso et al, 2006; Kaur et al, 2003; Mancuso et al, 2003).

Preceded by: BLVRA:Zn2+, BLVRB reduce BV to BIL

Literature references

Motterlini, R., Mancuso, C., Mordente, A., Di Stasio, E., Bonsignore, A. (2003). Bilirubin and S-nitrosothiols interaction: evidence for a possible role of bilirubin as a scavenger of nitric oxide. *Biochem Pharmacol, 66*, 2355-63. ↗

Motterlini, R., Hughes, MN., Naughton, P., Foresti, R., Kaur, H., Green, CJ. (2003). Interaction of bilirubin and biliverdin with reactive nitrogen species. *FEBS Lett, 543*, 113-9. ↗

Editions

2020-12-14	Authored, Edited	Stephan, R.
2021-01-23	Reviewed	Somers, J.

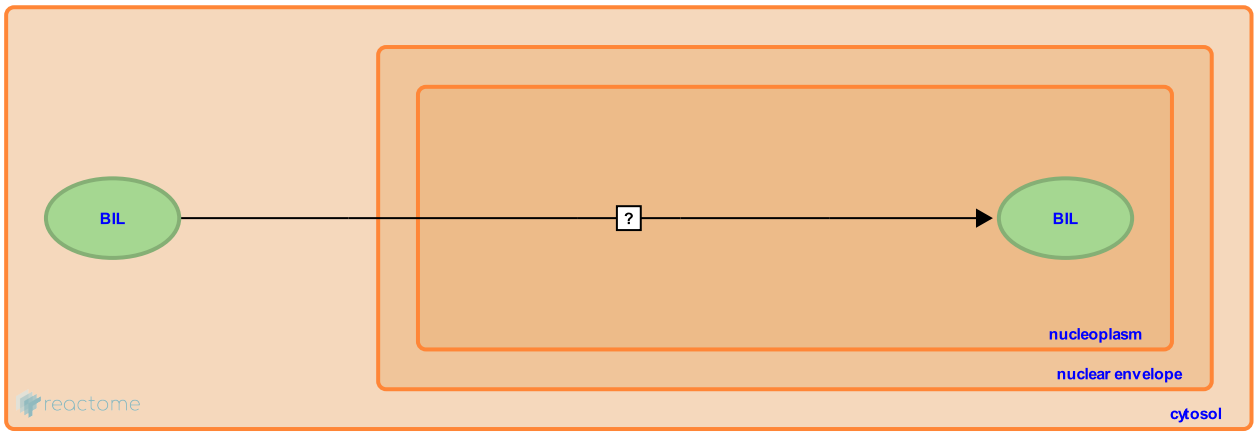
BIL translocates to the nucleus ↗

Location: Cytoprotection by HMOX1

Stable identifier: R-HSA-9709878

Type: uncertain

Compartments: nucleoplasm, cytosol



An unknown transport protein is responsible for the translocation of bilirubin (BIL) to the nucleus where it has been shown to be present (Park et al, 2016).

Preceded by: BLVRA:Zn2+, BLVRB reduce BV to BIL

Literature references

Rhee, HW., Park, JS., Nam, E., Lim, MH., Lee, HK. (2016). In Cellulo Mapping of Subcellular Localized Bilirubin. *ACS Chem Biol, 11*, 2177-85. ↗

Editions

2020-12-14	Authored, Edited	Stephan, R.
2021-01-23	Reviewed	Somers, J.

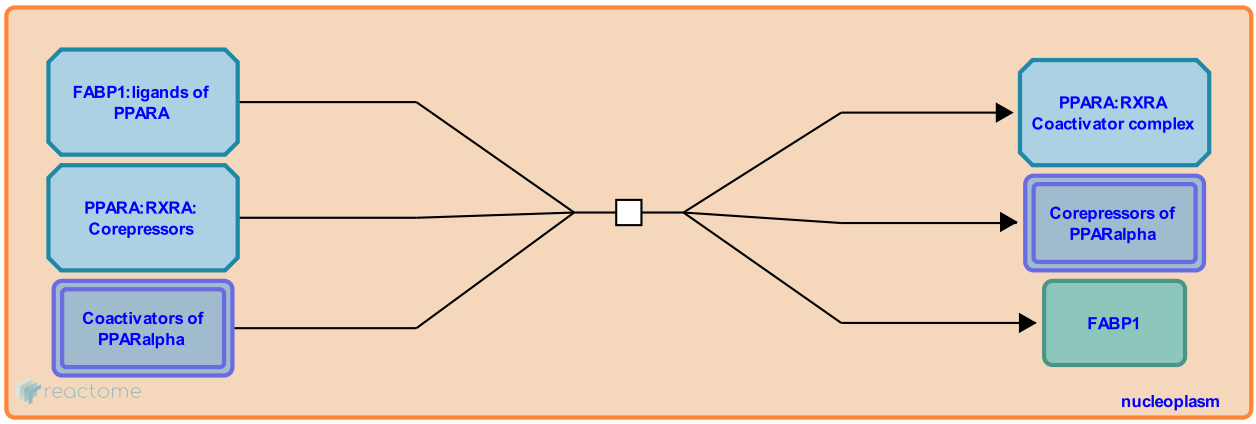
Fatty acid ligands activate PPARA ↗

Location: Cytoprotection by HMOX1

Stable identifier: R-HSA-400143

Type: transition

Compartments: nucleoplasm



PPAR-alpha is activated by binding polyunsaturated fatty acids especially those having 18-22 carbon groups and 2-6 double bonds. These ligands bind the C-terminal region of PPAR-alpha and include linoleic acid, linolenic acids, arachidonic acid, and eicosapentaenoic acid. The fibrate drugs are also agonists of PPAR-alpha.
Binding of a ligand causes a conformational change in PPAR-alpha so that it recruits coactivators. By analogy with the closely related receptor PPAR-gamma, PPAR-alpha probably binds TBL1 and TBLR1, which are responsible for recruiting the 19S proteasome to degrade corepressors during the exchange of corepressors for coactivators. The coactivators belong to the CBP-SRC-HAT complex (CBP/p300, SRC1, SRC2, SRC3, CARM1, SWI/SNF, BAF60C, PRIC320, and PRIC285), the ASC complex (PRIP/ASC2, PIMT), and the TRAP-DRIP-ARC-MEDIATOR complex (TRAP130, PBP/TRAP220). The coactivators contain LXXLL motifs (Nuclear Receptor Boxes) that interact with the AF-2 region in nuclear receptors such as PPAR-alpha. Additionally bilirubin binds to PPAR-alpha and acts as coactivator.

Literature references

Payne, HR., Storey, SM., Hostetler, HA., Schroeder, F., Kier, AB., McIntosh, AL. et al. (2009). L-FABP directly interacts with PPARalpha in cultured primary hepatocytes. *J Lipid Res, 50*, 1663-75. ↗

Yu, S., Reddy, JK. (2007). Transcription coactivators for peroxisome proliferator-activated receptors. *Biochim Biophys Acta, 1771*, 936-51. ↗

Kersten, S. (2008). Peroxisome proliferator activated receptors and lipoprotein metabolism. *PPAR Res, 2008*, 132960. ↗

Qi, C., Reddy, JK., Zhu, Y. (2000). Peroxisome proliferator-activated receptors, coactivators, and downstream targets. *Cell Biochem Biophys, 32*, 187-204. ↗

Rose, DW., Aggarwal, A., Perissi, V., Rosenfeld, MG., Glass, CK. (2004). A corepressor/coactivator exchange complex required for transcriptional activation by nuclear receptors and other regulated transcription factors. *Cell, 116*, 511-26. ↗

Editions

2009-05-30	Authored, Edited	May, B.
2009-06-08	Reviewed	Kersten, S.
2009-06-08	Edited	May, B.
2021-01-23	Reviewed	Somers, J.

Table of Contents