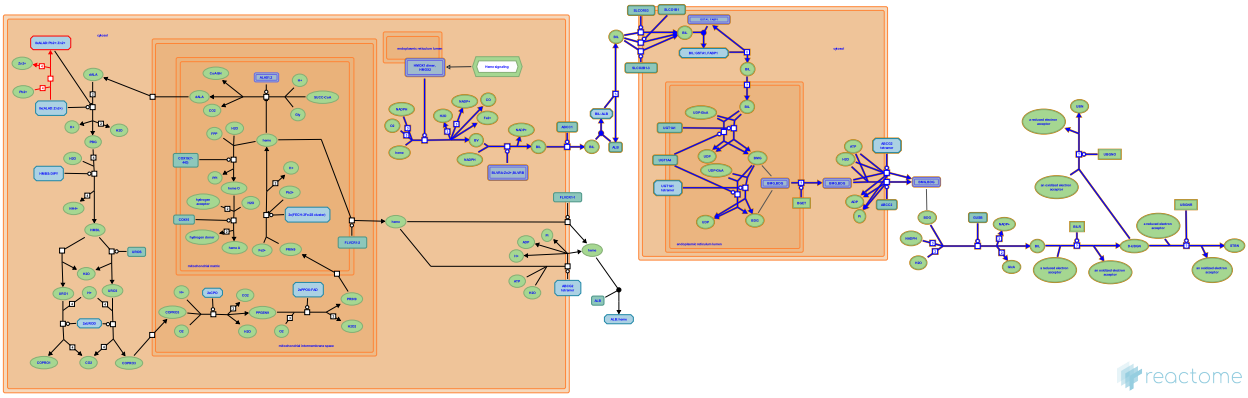
Heme degradation



D'Eustachio, P., Jassal, B., Sassa, S., Somers, J.

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.

04/05/2024

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. ↗

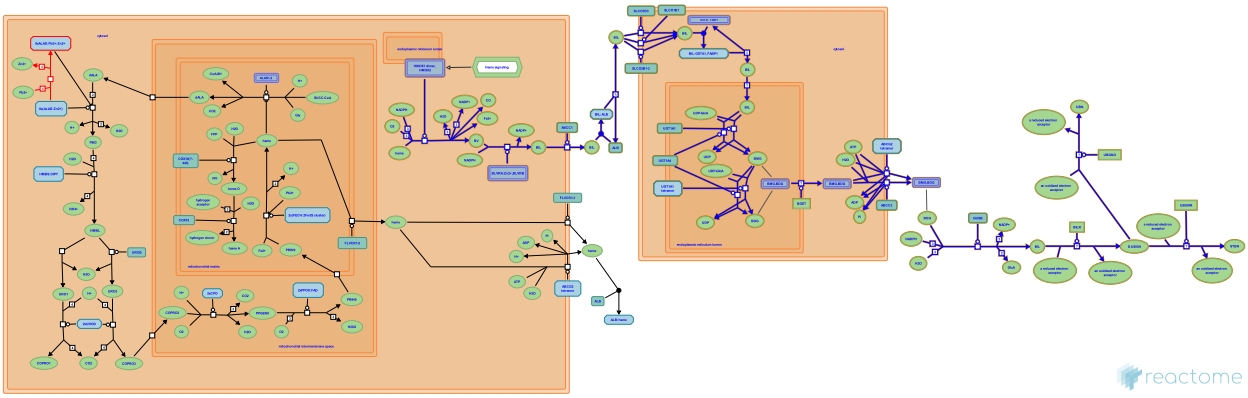
Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

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. ↗

Heme degradation ↗

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

2007-01-24	Reviewed	Sassa, S.
2009-05-19	Revised	D'Eustachio, P.
2019-09-18	Revised	Jassal, B.

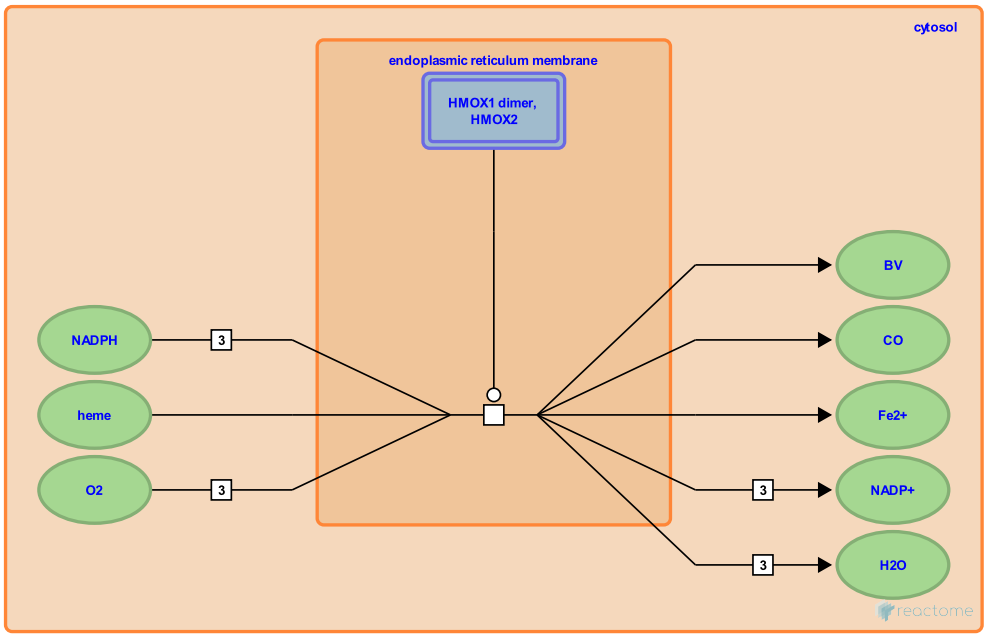
HMOX1 dimer, HMOX2 cleave heme ↗

Location: Heme degradation

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: BLVRA:Zn2+, BLVRB reduce BV to BIL

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.

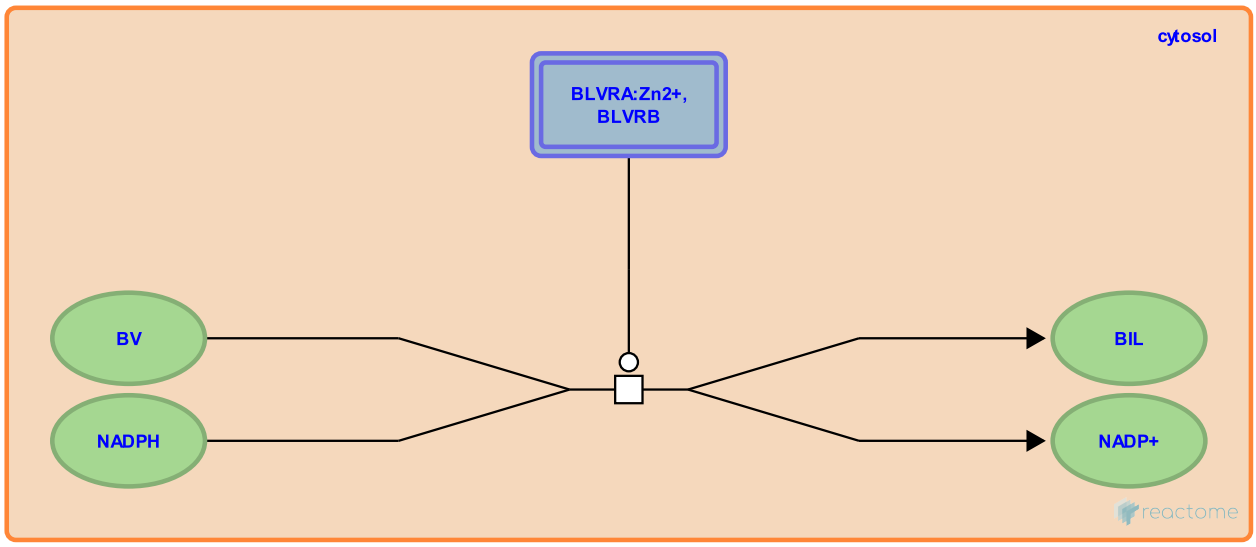
BLVRA:Zn2+, BLVRB reduce BV to BIL ↗

Location: Heme degradation

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: 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.

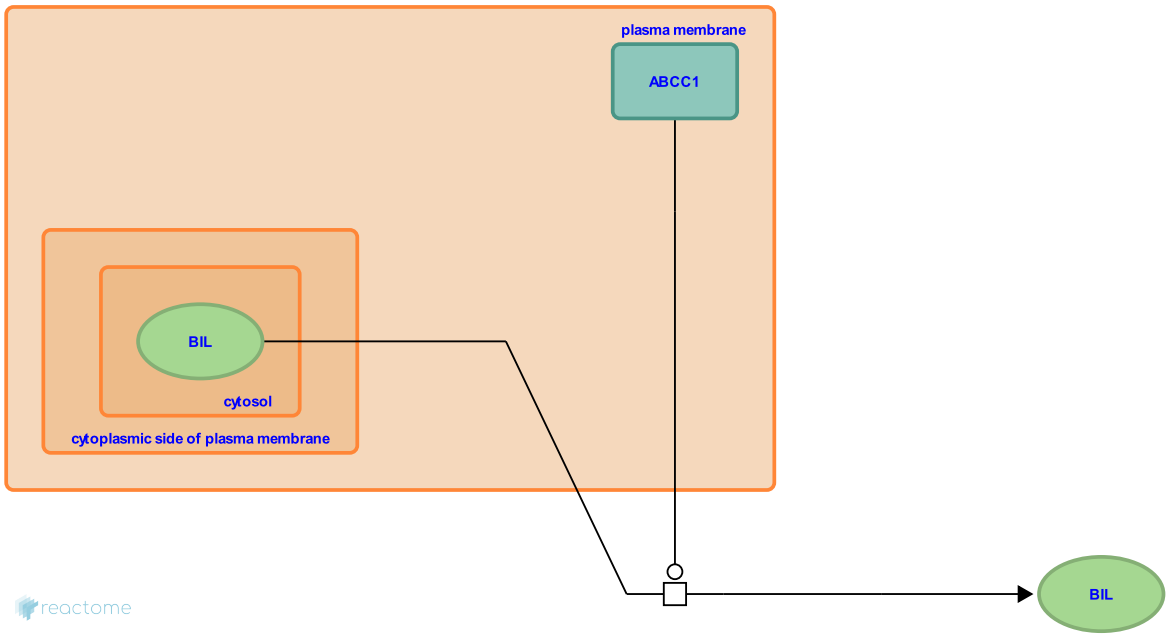
ABCC1 transports BIL from cytosol to extracellular region (blood) ↗

Location: Heme degradation

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.

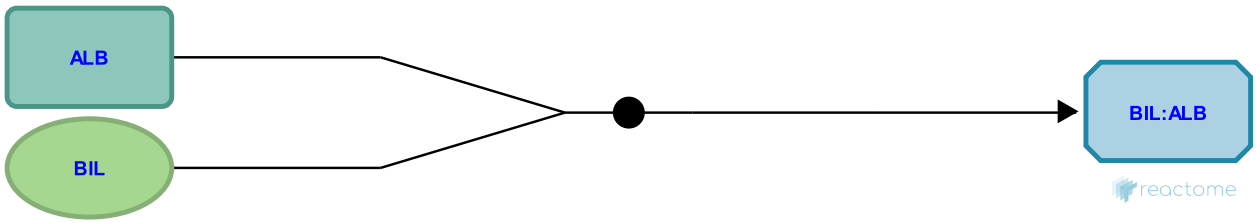
BIL binds ALB ↗

Location: Heme degradation

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 dissociates

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.
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2021-01-23	Reviewed	Somers, J.

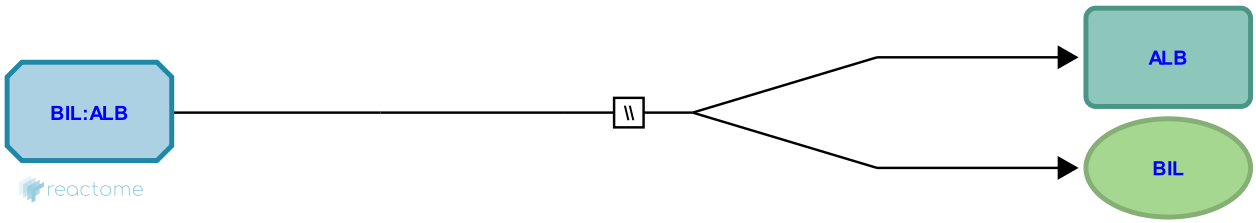
BIL:ALB dissociates ↗

Location: Heme degradation

Stable identifier: R-HSA-9661425

Type: omitted

Compartments: extracellular region



When the bilirubin-albumin complex (BIL:ALB) reaches the liver, the highly permeable hepatic circulation facilitates the complex to reach the sinusoidal side of the hepatocyte. The exact mechanism of unbound BIL uptake is unclear but may proceed like this. BIL in complex with ALB is reversible and a tiny fraction of of free BIL is present in plasma in equilibrium with BIL:ALB. Hence this free BIL may be taken up at a rate determined by its plasma concentration. As free BIL is taken up, more BIL is released from ALB and becomes available for uptake (Bhagavan & Ha 2015).

Preceded by: BIL binds ALB

Followed by: SLCO2B1-3 transports BIL from extracellular region (blood) to cytosol (hepatocyte), SLCO1B1 transports BIL from extracellular region (blood) to cytosol (hepatocyte), SLCO1B3 transports BIL from extracellular region (blood) to cytosol (hepatocyte)

Literature references

Ha, CE., Bhagavan, NV. (2015). Chapter 27 - Metabolism of Iron and Heme, Essentials of Medical Biochemistry (Second Edition).

Cui, Y., König, J., Buchholz, U., Leier, I., Keppler, D. (2001). Hepatic uptake of bilirubin and its conjugates by the human organic anion transporter SLC21A6. *J. Biol. Chem., 276*, 9626-30. ↗

Editions

2019-09-16	Authored, Edited	Jassal, B.
2019-10-03	Reviewed	D'Eustachio, P.

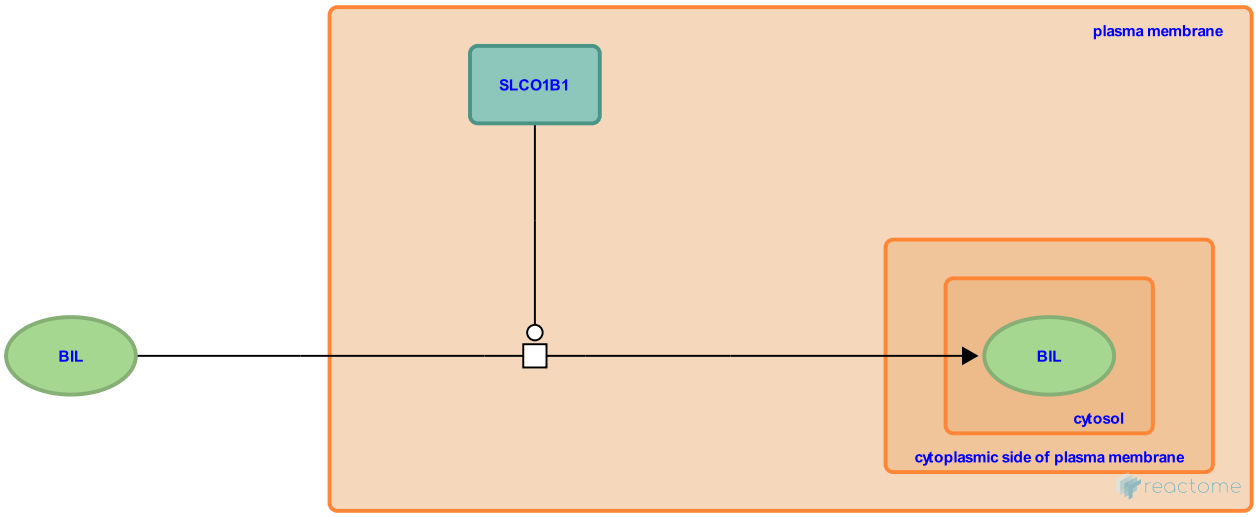
SLCO1B1 transports BIL from extracellular region (blood) to cytosol (hepatocyte) ↗

Location: Heme degradation

Stable identifier: R-HSA-9661397

Type: transition

Compartments: plasma membrane, extracellular region, cytosol



Bilirubin (BIL), the end product of heme catabolism, is taken up from the blood circulation into the liver. The organic anion transporting polypeptide SLCO1B1 (OATP, OATP2, OATPC, SLC21A6), localised on the basolateral (sinusoidal side) hepatocyte membrane, can mediate the uptake of BIL and various other lipophilic anions into the human liver (Konig et al. 2000, Cui et al. 2001).

Preceded by: BIL:ALB dissociates

Followed by: BIL binds GSTA1, FABP1

Literature references

Cui, Y., König, J., Buchholz, U., Leier, I., Keppler, D. (2001). Hepatic uptake of bilirubin and its conjugates by the human organic anion transporter SLC21A6. *J. Biol. Chem., 276*, 9626-30. ↗

Konig, J., Nies, AT., Keppler, D., Cui, Y. (2000). A novel human organic anion transporting polypeptide localized to the basolateral hepatocyte membrane. *Am J Physiol Gastrointest Liver Physiol, 278*, G156-G164. ↗

Editions

2019-09-16	Authored, Edited	Jassal, B.
2019-10-03	Reviewed	D'Eustachio, P.

SLCO2B1-3 transports BIL from extracellular region (blood) to cytosol (hepatocyte)

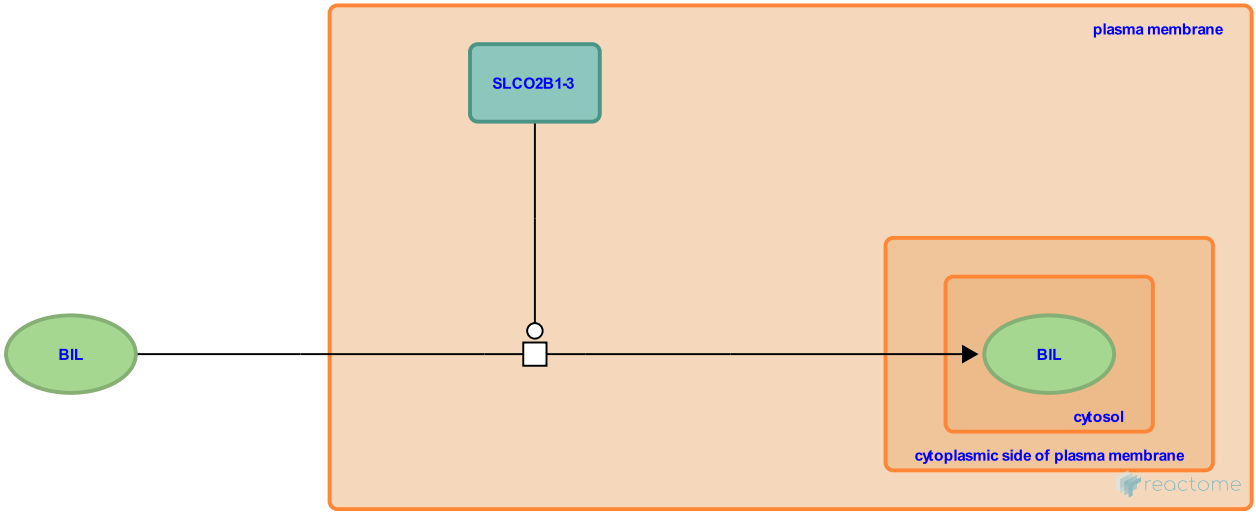
↗

Location: Heme degradation

Stable identifier: R-HSA-9661723

Type: transition

Compartments: plasma membrane, extracellular region, cytosol



Bilirubin (BIL), the end product of heme catabolism, is taken up from the blood circulation into the liver. The solute carrier organic anion transporter family member 2B1 (SLCO2B1, aka OATPRP2, OATPB, SLC21A9), localised on the basolateral (sinusoidal side) hepatocyte membrane, can mediate the uptake of BIL and various other lipophilic anions into the human liver (Kullak-Ublick et al. 2001). The predominant isoform in the liver is SLCO2B1 isoform 3 (Knauer et al. 2013).

Preceded by: BIL:ALB dissociates

Followed by: BIL binds GSTA1, FABP1

Literature references

Fattinger, K., Landmann, L., Huber, R., Meier, PJ., Hagenbuch, B., Kullak-Ublick, GA. et al. (2001). Organic anion-transporting polypeptide B (OATP-B) and its functional comparison with three other OATPs of human liver. *Gastroenterology, 120*, 525-33. ↗

Knauer, MJ., Girdwood, AJ., Tirona, RG., Kim, RB. (2013). Transport function and transcriptional regulation of a liver-enriched human organic anion transporting polypeptide 2B1 transcriptional start site variant. *Mol. Pharmacol. , 83*, 1218-28. ↗

Editions

2019-09-18	Authored, Edited	Jassal, B.
2019-10-03	Reviewed	D'Eustachio, P.

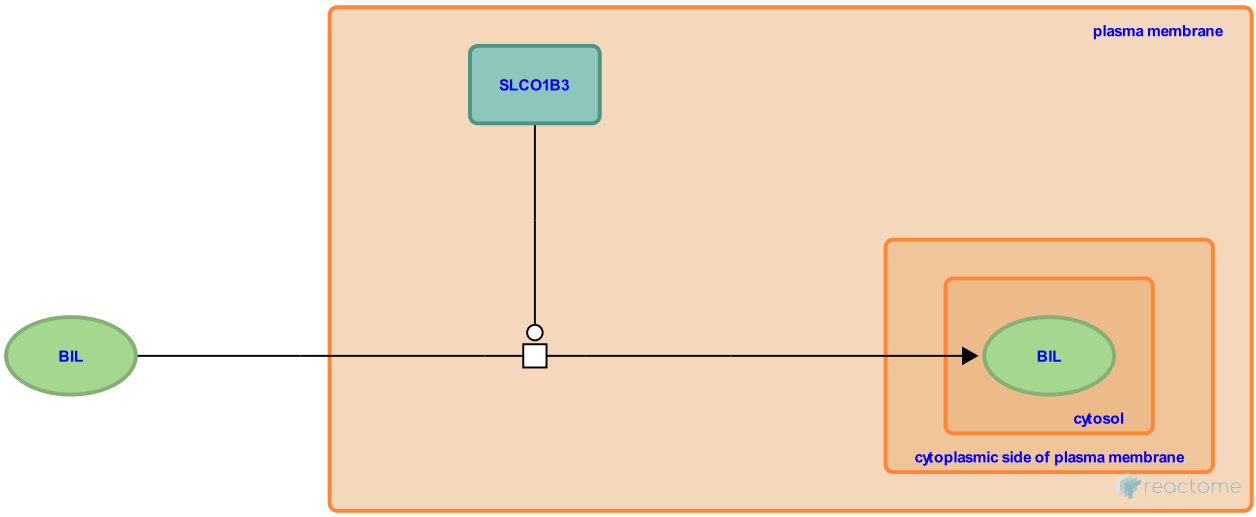
SLCO1B3 transports BIL from extracellular region (blood) to cytosol (hepatocyte) ↗

Location: Heme degradation

Stable identifier: R-HSA-9661799

Type: transition

Compartments: plasma membrane, extracellular region, cytosol



Bilirubin (BIL), the end product of heme catabolism, is taken up from the blood circulation into the liver. The organic anion transporting polypeptide (SLCO1B3, aka OATP-8, LST2, SLC21A8), localised on the basolateral (sinusoidal side) hepatocyte membrane, can mediate the uptake of BIL and various other lipophilic anions into the human liver (van de Steeg et al. 2012).

Preceded by: BIL:ALB dissociates

Followed by: BIL binds GSTA1, FABP1

Literature references

Nosková, L., Kmoch, S., al-Edreesi, M., Jirsa, M., Wagenaar, E., Sticová, E. et al. (2012). Complete OATP1B1 and OATP1B3 deficiency causes human Rotor syndrome by interrupting conjugated bilirubin reuptake into the liver. *J. Clin. Invest., 122*, 519-28. ↗

Editions

2019-09-18	Authored, Edited	Jassal, B.
2019-10-03	Reviewed	D'Eustachio, P.

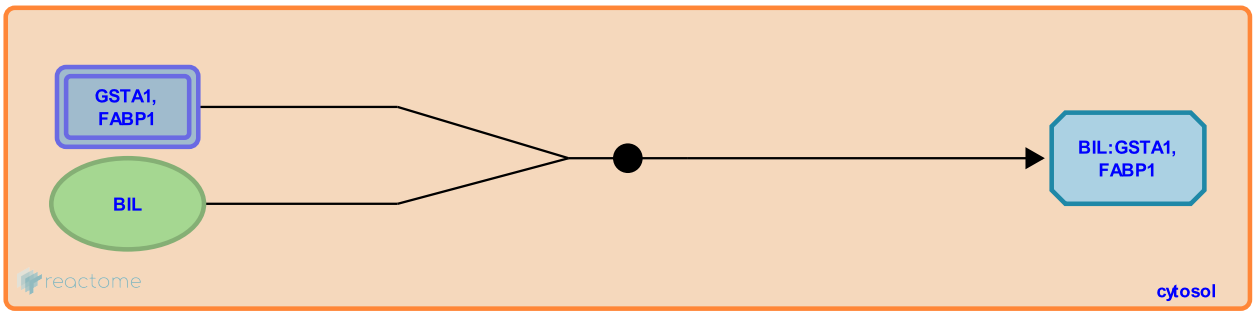
BIL binds GSTA1, FABP1 ↗

Location: Heme degradation

Stable identifier: R-HSA-9663511

Type: binding

Compartments: cytosol



Upon entry into the hepatocyte, bilirubin (BIL) can bind to one of two cytosolic binding proteins; glutathione S-transferase A1 (GSTA1 aka ligandin, Y-protein), a major cytosolic protein that has both transport and detoxification functions or fatty acid-binding protein (FABP1 aka Z-protein) (Levi et al. 1969, Simons & Jagt 1980, Arias 2012). It is assumed GSTA1 transports BIL to the ER where it is detoxified by conjugation with a glucuronosyl moiety.

Preceded by: SLCO2B1-3 transports BIL from extracellular region (blood) to cytosol (hepatocyte), SLCO1B1 transports BIL from extracellular region (blood) to cytosol (hepatocyte), SLCO1B3 transports BIL from extracellular region (blood) to cytosol (hepatocyte)

Followed by: BIL dissociates from GSTA1, FABP1

Literature references

Gatmaitan, Z., Levi, AJ., Arias, IM. (1969). Two hepatic cytoplasmic protein fractions, Y and Z, and their possible role in the hepatic uptake of bilirubin, sulfobromophthalein, and other anions. *J. Clin. Invest., 48*, 2156-67. ↗

Simons, PC., Jagt, DL. (1980). Bilirubin binding to human liver ligandin (glutathione S-transferase). *J. Biol. Chem., 255* , 4740-4. ↗

Editions

2019-10-02	Authored, Edited	Jassal, B.
2019-10-03	Reviewed	D'Eustachio, P.

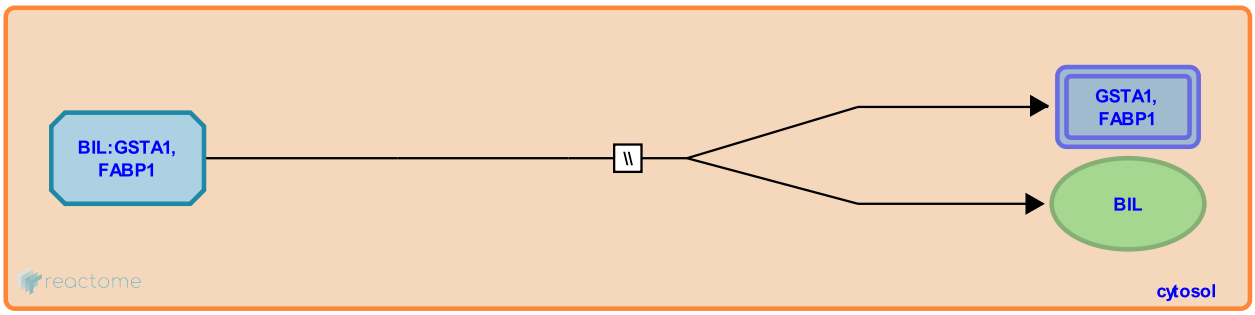
BIL dissociates from GSTA1, FABP1 ↗

Location: Heme degradation

Stable identifier: R-HSA-9663492

Type: omitted

Compartments: cytosol



Once GSTA1 and FABP1 proteins transport bilirubin to the ER, it is assumed they must dissociate from BIL ((Levi et al. 1969, Simons & Jagt 1980) to allow its translocation, most likely by simple diffusion, into the ER lumen.

Preceded by: BIL binds GSTA1, FABP1

Followed by: BIL translocates from the cytosol to the ER lumen

Literature references

Gatmaitan, Z., Levi, AJ., Arias, IM. (1969). Two hepatic cytoplasmic protein fractions, Y and Z, and their possible role in the hepatic uptake of bilirubin, sulfobromophthalein, and other anions. *J. Clin. Invest., 48*, 2156-67. ↗

Simons, PC., Jagt, DL. (1980). Bilirubin binding to human liver ligandin (glutathione S-transferase). *J. Biol. Chem., 255* , 4740-4. ↗

Editions

2019-10-02	Authored, Edited	Jassal, B.
2019-10-03	Reviewed	D'Eustachio, P.

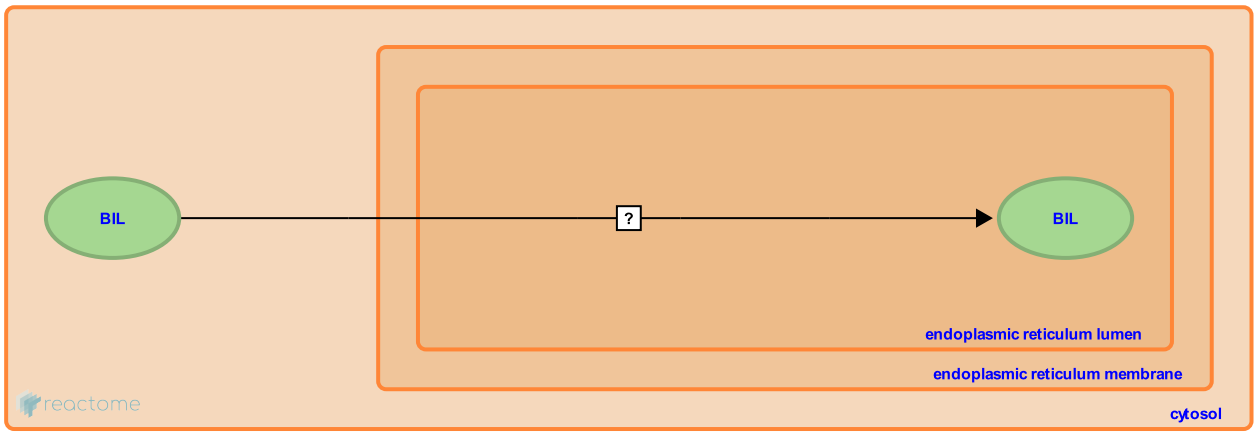
BIL translocates from the cytosol to the ER lumen ↗

Location: Heme degradation

Stable identifier: R-HSA-189381

Type: uncertain

Compartments: endoplasmic reticulum lumen, cytosol



The enzyme which catalyzes the conjugation of bilirubin (UGT1A1) is found in the ER. Bilirubin translocates to the ER, probably by simple diffusion, to be glucuronylated (Schröter 1972). To date, no transporter has been identified for this process (Fujiwara & Itoh 2014).

Preceded by: BIL dissociates from GSTA1, FABP1

Followed by: UGT1A1 transfers GlcA from UDP-GlcA to BIL to form BMG, UGT1A4 transfers GlcA from UDP-GlcA to BIL to form BMG

Literature references

Itoh, T., Fujiwara, R. (2014). Extensive protein-protein interactions involving UDP-glucuronosyltransferase (UGT) 2B7 in human liver microsomes. *Drug Metab. Pharmacokinet., 29*, 259-65. ↗

Schröter, W. (1972). [Intracellular bilirubin transport and the membrane of the hepatic endoplasmic reticulum: new aspects in the development of transitory bilirubinemia of the newborn]. *Monatsschr Kinderheilkd, 120*, 119-22. ↗

Editions

2007-01-24	Reviewed	Sassa, S.
2009-05-19	Revised	D'Eustachio, P.
2019-09-18	Revised	Jassal, B.

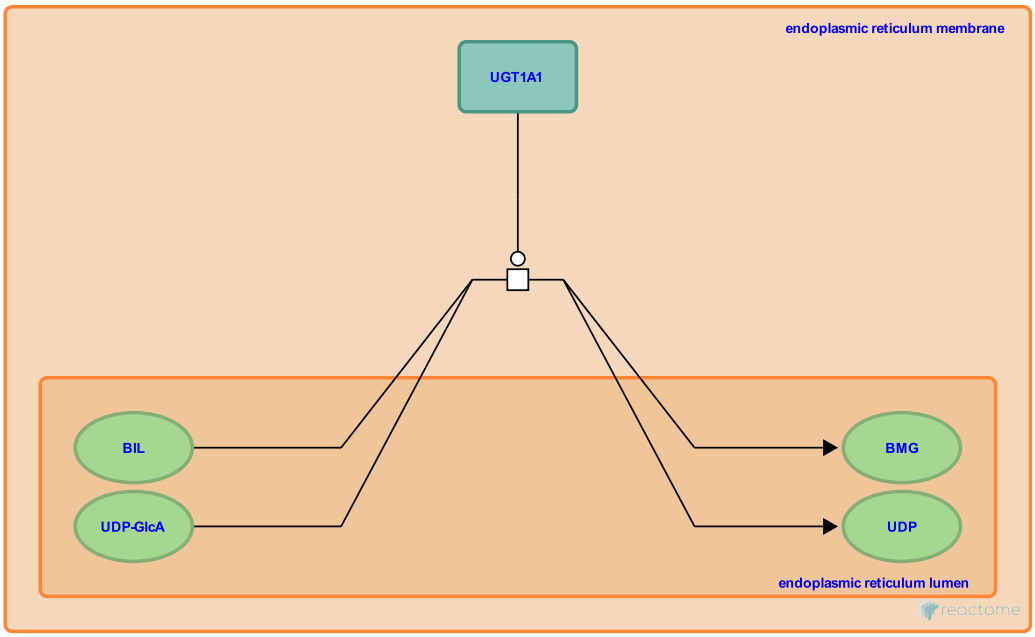
UGT1A1 transfers GlcA from UDP-GlcA to BIL to form BMG ↗

Location: Heme degradation

Stable identifier: R-HSA-9632039

Type: transition

Compartments: endoplasmic reticulum membrane, endoplasmic reticulum lumen



Bilirubin (BIL) is a breakdown product of heme. Its accumulation in the blood can be fatal. It is highly lipophilic and thus requires conjugation to become more water soluble to aid excretion. Both UGT1A1 tetramer and UGT1A4 can transfer glucuronic acid (GlcA) to bilirubin to form either its monoglucuronide (BMG) or diglucuronide (BDG) conjugates (Bosma et al. 1994, Ritter et al. 1992, Peters & Jansen 1986, Gorden et al. 1983, Choudhury et al. 1981, Fevery et al. 1971).

Preceded by: BIL translocates from the cytosol to the ER lumen

Followed by: BMG, BDG translocates from ER lumen to cytosol

Literature references

Owens, IS., Chen, F., Ritter, JK., Kimura, S., Sheen, YY., Yeatman, MT. et al. (1992). A novel complex locus UGT1 encodes human bilirubin, phenol, and other UDP-glucuronosyltransferase isozymes with identical carboxyl termini . *J. Biol. Chem., 267*, 3257-61. ↗

Goldhoorn, B., Bosma, PJ., Jansen, PL., Oude, Elferink R., Bakker, C., Seppen, J. et al. (1994). Bilirubin UDP-glucuronosyltransferase 1 is the only relevant bilirubin glucuronidating isoform in man. *J Biol Chem, 269*, 17960-4. ↗

Editions

2005-02-23	Authored	Jassal, B.
2010-05-08	Reviewed	D'Eustachio, P.
2010-05-27	Edited	Jassal, B.
2014-07-01	Revised	Jassal, B.

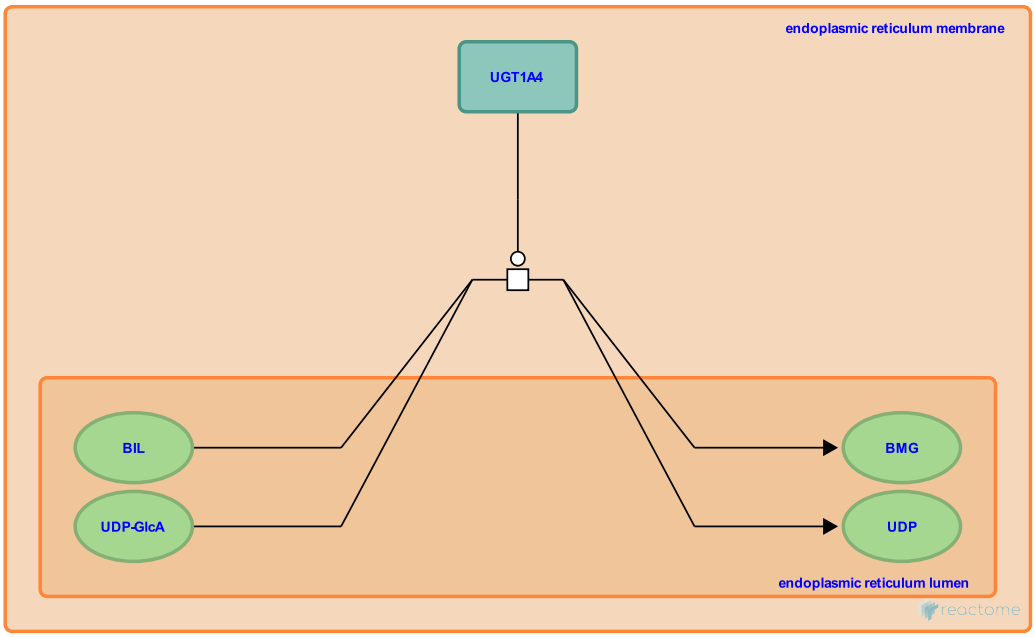
UGT1A4 transfers GlcA from UDP-GlcA to BIL to form BMG ↗

Location: Heme degradation

Stable identifier: R-HSA-159194

Type: transition

Compartments: endoplasmic reticulum membrane, endoplasmic reticulum lumen



Bilirubin (BIL) is a breakdown product of heme. Its accumulation in the blood can be fatal. It is highly lipophilic and thus requires conjugation to become more water soluble to aid excretion. Both UGT1A1 tetramer and UGT1A4 can transfer glucuronic acid (GlcA) to bilirubin to form either its monoglucuronide (BMG) or diglucuronide (BDG) conjugates (Bosma et al. 1994, Ritter et al. 1992, Peters & Jansen 1986, Gorden et al. 1983, Choudhury et al. 1981, Fevery et al. 1971).

Preceded by: BIL translocates from the cytosol to the ER lumen

Followed by: UGT1A4 transfers GlcA from UDP-GlcA to BMG to form BDG, BMG, BDG translocates from ER lumen to cytosol, UGT1A1 tetramer transfers GlcA from UDP-GlcA to BMG to form BDG

Literature references

Michiels, R., Van, Damme B., Heirwegh, KP., Fevery, J., De Groote, J. (1972). Bilirubin conjugates in bile of man and rat in the normal state and in liver disease. *J Clin Invest, 51*, 2482-92. ↗

Goresky, CA., Gordon, ER., Sommerer, U. (1983). The hepatic microsomal formation of bilirubin diglucuronide. *J Biol Chem, 258*, 15028-36. ↗

Shouval, R., Wu, G., Chowdhury, JR., Chowdhury, NR., Arias, IM. (1981). Bilirubin mono- and diglucuronide formation by human liver in vitro: assay by high-pressure liquid chromatography. *Hepatology, 1*, 622-7. ↗

Owens, IS., Chen, F., Ritter, JK., Kimura, S., Sheen, YY., Yeatman, MT. et al. (1992). A novel complex locus UGT1 encodes human bilirubin, phenol, and other UDP-glucuronosyltransferase isozymes with identical carboxyl termini . *J. Biol. Chem., 267*, 3257-61. ↗

Jansen, PL., Peters, WH. (1986). Microsomal UDP-glucuronyltransferase-catalyzed bilirubin diglucuronide formation in human liver. *J Hepatol, 2*, 182-94. ↗

Editions

2005-02-23	Authored	Jassal, B.
2010-05-08	Reviewed	D'Eustachio, P.
2010-05-27	Edited	Jassal, B.
2014-07-01	Revised	Jassal, B.

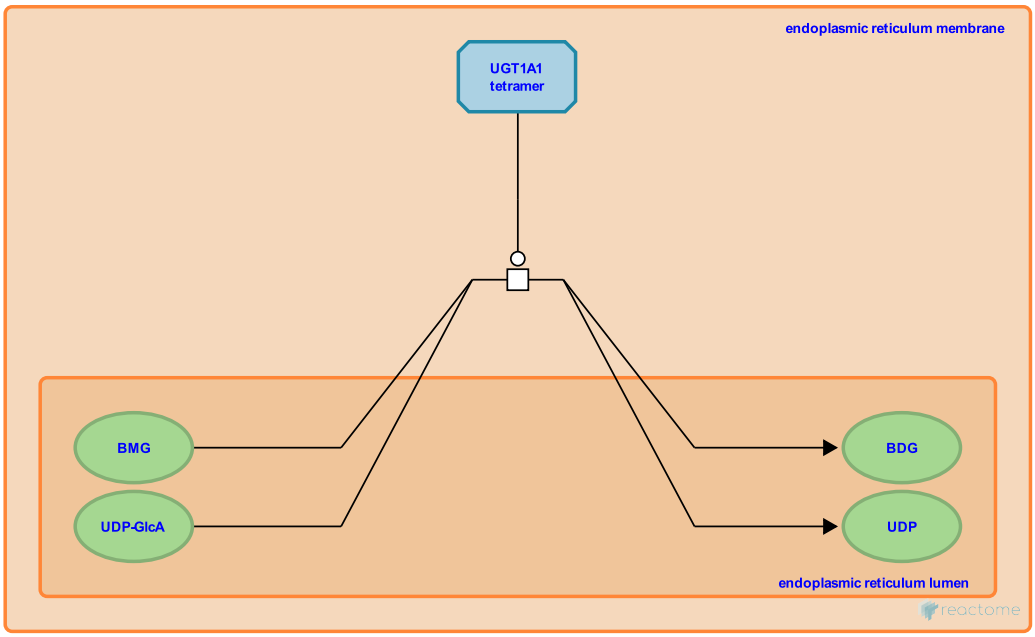
UGT1A1 tetramer transfers GlcA from UDP-GlcA to BMG to form BDG ↗

Location: Heme degradation

Stable identifier: R-HSA-9632038

Type: transition

Compartments: endoplasmic reticulum membrane, endoplasmic reticulum lumen



The principal conjugate of bilirubin in bile is bilirubin diglucuronide (BDG). The monomeric forms of UGT1A1 (Bilirubin UDP-glucuronyltransferase 1) only conjugates the first step of bilirubin conjugation to form the monoglucuronide. A tetrameric form of UGT1A1 can transfer glucuronic acid (GlcA) to bilirubin (BIL) and bilirubin monoglucuronide (BMG) to form both the monoglucuronide and the diglucuronide (BDG) conjugates respectively (Peters & Jansen 1986, Gorden et al. 1983, Choudhury et al. 1981, Fevery et al. 1971).

Preceded by: UGT1A4 transfers GlcA from UDP-GlcA to BIL to form BMG

Followed by: BMG, BDG translocates from ER lumen to cytosol

Literature references

Michiels, R., Van, Damme B., Heirwegh, KP., Fevery, J., De Groote, J. (1972). Bilirubin conjugates in bile of man and rat in the normal state and in liver disease. *J Clin Invest, 51*, 2482-92. ↗

Goresky, CA., Gordon, ER., Sommerer, U. (1983). The hepatic microsomal formation of bilirubin diglucuronide. *J Biol Chem, 258*, 15028-36. ↗

Shouval, R., Wu, G., Chowdhury, JR., Chowdhury, NR., Arias, IM. (1981). Bilirubin mono- and diglucuronide formation by human liver in vitro: assay by high-pressure liquid chromatography. *Hepatology, 1*, 622-7. ↗

Jansen, PL., Peters, WH. (1986). Microsomal UDP-glucuronyltransferase-catalyzed bilirubin diglucuronide formation in human liver. *J Hepatol, 2*, 182-94. ↗

Editions

2005-02-23	Authored	Jassal, B.
2010-05-08	Reviewed	D'Eustachio, P.
2010-05-27	Edited	Jassal, B.
2014-07-01	Revised	Jassal, B.

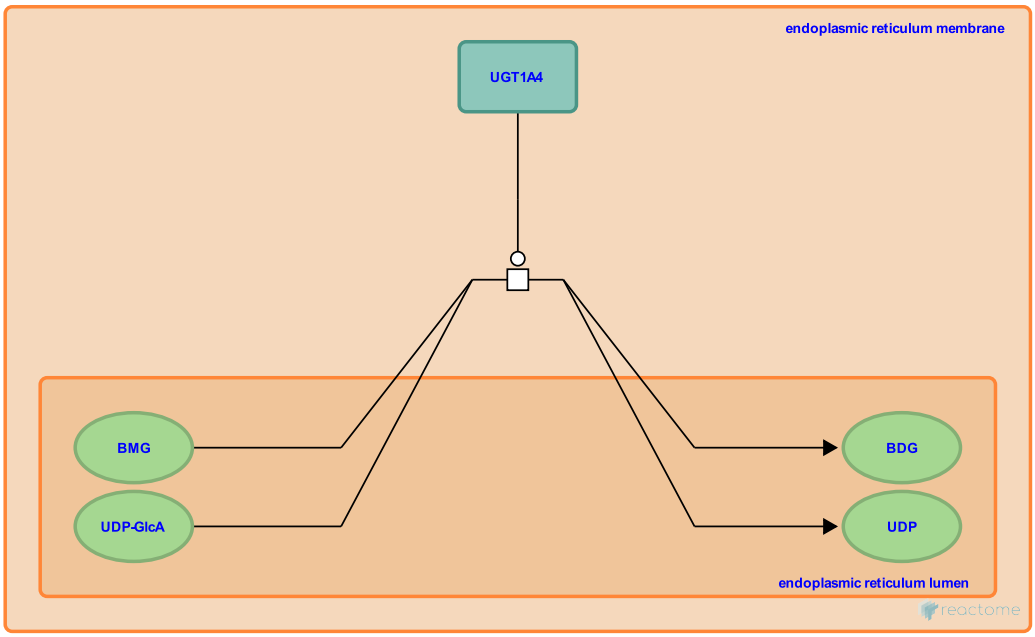
UGT1A4 transfers GlcA from UDP-GlcA to BMG to form BDG ↗

Location: Heme degradation

Stable identifier: R-HSA-159179

Type: transition

Compartments: endoplasmic reticulum membrane, endoplasmic reticulum lumen



The principal conjugate of bilirubin in bile is bilirubin diglucuronide (BDG). UGT1A4 can transfer glucuronic acid (GlcA) to bilirubin (BIL) and bilirubin monoglucuronide (BMG) to form both the monoglucuronide and the diglucuronide (BDG) conjugates respectively (Ritter et al. 1992).

Preceded by: UGT1A4 transfers GlcA from UDP-GlcA to BIL to form BMG

Followed by: BMG, BDG translocates from ER lumen to cytosol

Literature references

Owens, IS., Chen, F., Ritter, JK., Kimura, S., Sheen, YY., Yeatman, MT. et al. (1992). A novel complex locus UGT1 encodes human bilirubin, phenol, and other UDP-glucuronosyltransferase isozymes with identical carboxyl termini . *J. Biol. Chem., 267*, 3257-61. ↗

Editions

2005-02-23	Authored	Jassal, B.
2010-05-08	Reviewed	D'Eustachio, P.
2010-05-27	Edited	Jassal, B.
2014-07-01	Revised	Jassal, B.

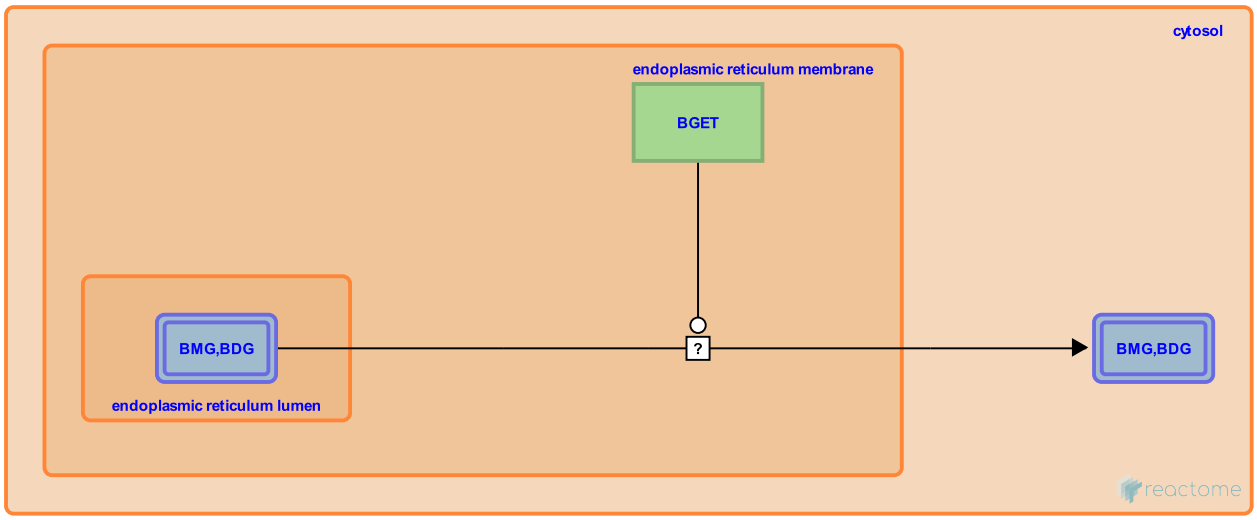
BMG, BDG translocates from ER lumen to cytosol ↗

Location: Heme degradation

Stable identifier: R-HSA-9661446

Type: uncertain

Compartments: endoplasmic reticulum membrane, endoplasmic reticulum lumen, cytosol



To be excreted from the cell, mono- and di-glucuronated bilirubin (BMG, BDG respectively) translocate from the ER lumen to the cytosol. Glucuronated bilirubin is a much more hydrophilic substance than bilirubin so the assumption is some form of active transport is required for this translocation. No transporter has been identified yet but tentatively, we assign the name bilirubin glucuronide efflux transporter (BGET) (Erlinger et al. 2014, Rowland et al. 2013).

Preceded by: UGT1A4 transfers GlcA from UDP-GlcA to BMG to form BDG, UGT1A4 transfers GlcA from UDP-GlcA to BIL to form BMG, UGT1A1 transfers GlcA from UDP-GlcA to BIL to form BMG, UGT1A1 tetramer transfers GlcA from UDP-GlcA to BMG to form BDG

Followed by: ABCG2 tetramer transports BMG,BDG from cytosol to extracellular region, ABCC2 transports BMG,BDG from cytosol to extracellular region

Literature references

Miners, JO., Rowland, A., Mackenzie, PI. (2013). The UDP-glucuronosyltransferases: their role in drug metabolism and detoxification. *Int. J. Biochem. Cell Biol., 45*, 1121-32. ↗

Erlinger, S., Dhumeaux, D., Arias, IM. (2014). Inherited disorders of bilirubin transport and conjugation: new insights into molecular mechanisms and consequences. *Gastroenterology, 146*, 1625-38. ↗

Editions

2019-09-16	Authored, Edited	Jassal, B.
2019-10-03	Reviewed	D'Eustachio, P.

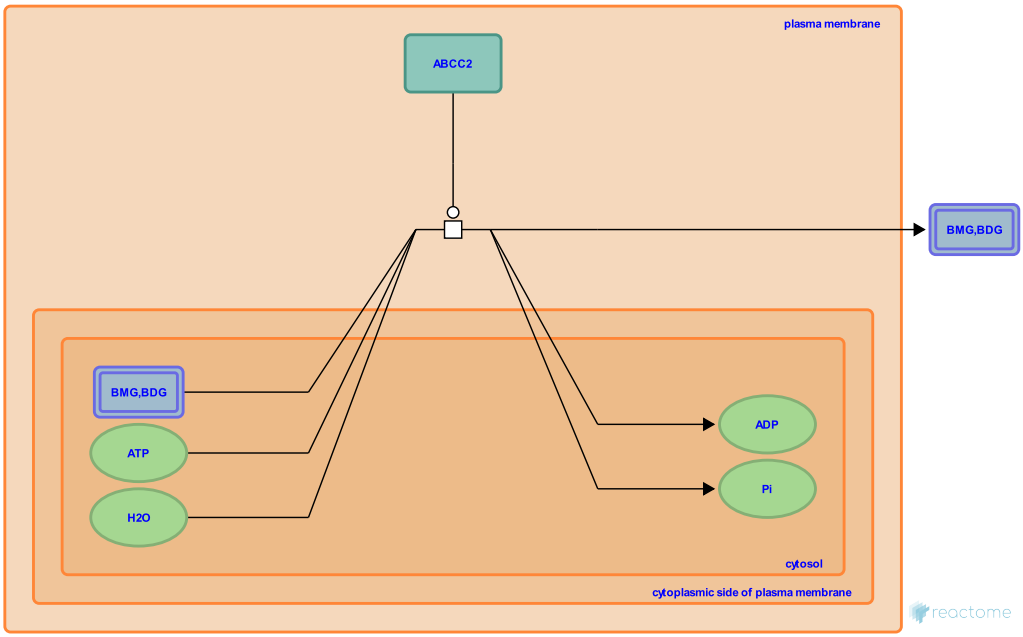
ABCC2 transports BMG,BDG from cytosol to extracellular region ↗

Location: Heme degradation

Stable identifier: R-HSA-5679041

Type: transition

Compartments: plasma membrane, extracellular region, cytosol



Canalicular multispecific organic anion transporter 1 (ABCC2 aka multidrug resistance-associated protein 2, MRP2), in addition to transporting many organic anions, mediates the ATP-dependent transport of glutathione and glucuronate conjugates from hepatocytes into bile. In the reaction annotated here, ABCC2 specifically transports, with high affinity and efficiency, mono- and di-glucuronated bilirubin (BMG, BDG respectively) into bile (Kamisako et al. 1999). ABCC2 is located on the canalicular membrane of hepatocytes. Bilirubin, the end product of heme breakdown, is an important constituent of bile and is responsible for its characteristic colour.

Preceded by: BMG, BDG translocates from ER lumen to cytosol

Followed by: Bacterial GUSB hydrolyses BDG to BIL

Literature references

Cui, Y., Kamisako, T., König, J., Buchholz, U., Leier, I., Hummel-Eisenbeiss, J. et al. (1999). Transport of monoglucuronosyl and bisglucuronosyl bilirubin by recombinant human and rat multidrug resistance protein 2. *Hepatology, 30*, 485-90. ↗

Editions

2011-07-19	Edited	Jassal, B.
2015-03-02	Authored	Jassal, B.
2015-11-16	Reviewed	D'Eustachio, P.
2019-09-18	Revised	Jassal, B.

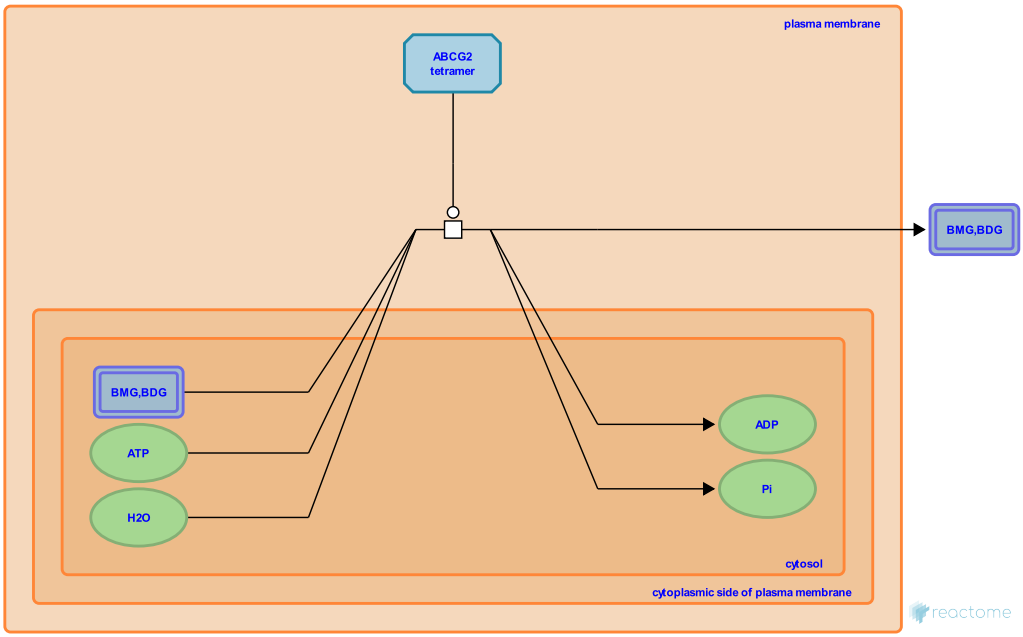
ABCG2 tetramer transports BMG,BDG from cytosol to extracellular region ↗

Location: Heme degradation

Stable identifier: R-HSA-9661417

Type: transition

Compartments: plasma membrane, extracellular region, cytosol



Bilirubin glucuronides (BMG and BDG) are transported out of hepatocytes through their apical surfaces into the bile ducts, mainly by ABCC2 (MRP2) but also by the tetrameric efflux pump ATP-binding cassette sub-family G member 2 (ABCG2) (Xu et al. 2004).

Preceded by: BMG, BDG translocates from ER lumen to cytosol

Followed by: Bacterial GUSB hydrolyses BDG to BIL

Literature references

Liu, Y., Xu, J., Bates, S., Zhang, JT., Yang, Y. (2004). Characterization of oligomeric human half-ABC transporter ATP-binding cassette G2. *J. Biol. Chem., 279*, 19781-9. ↗

Editions

2019-09-16	Authored, Edited	Jassal, B.
2019-10-03	Reviewed	D'Eustachio, P.

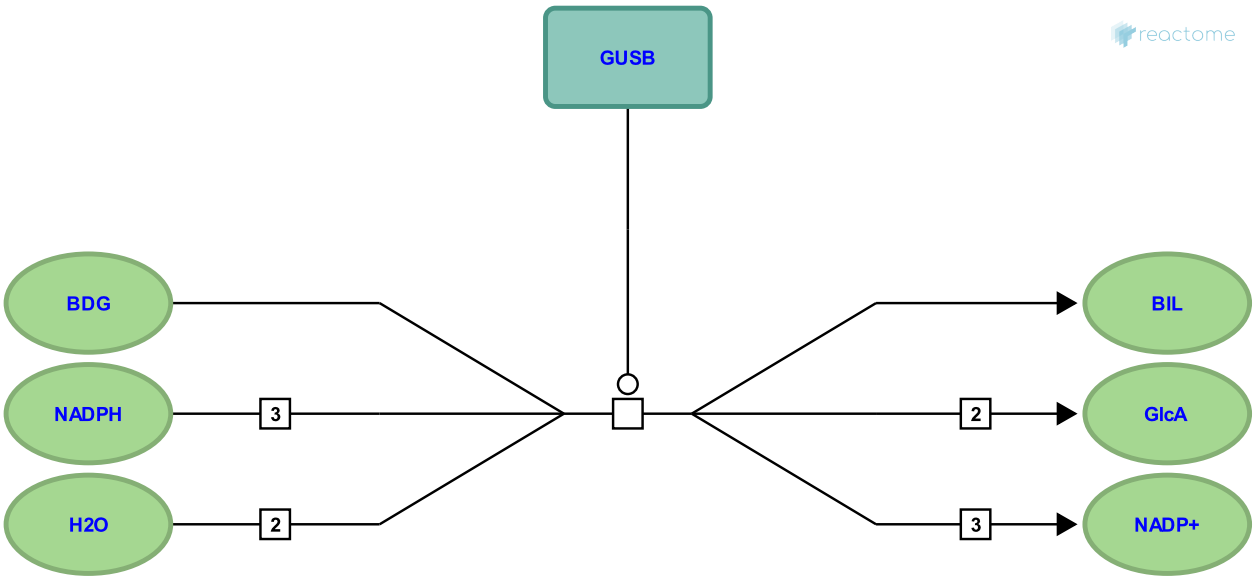
Bacterial GUSB hydrolyses BDG to BIL ↗

Location: Heme degradation

Stable identifier: R-HSA-9661820

Type: transition

Compartments: extracellular region



Bilirubin diglucuronide (BDG) is a substrate for microbial β-glucuronidase, which can cleave the glucuronosyl moieties and liberate bilirubin for reabsorption through the basolateral surfaces of the intestines where it can undergo further metabolism or pass directly back into the circulation. This process, known as enterohepatic circulation, can extend the half-life of bilirubin while adding to the total serum bilirubin load (Seyfried et al. 1976). Conjugated bilirubin is excreted in bile through the duodenum, where it can be unconjugated by enteric bacteria (Kim et al. 1995). Many bacterial β-glucuronidases can cleave the glucuronosyl moieties from conjugated bilirubins in the human gut. In vitro assays reveal the C. perfringens species produce beta-glucuronidase enzyme activity that is at least 30-fold higher than other bacterial species (Leung et al. 2001).

Urobilinogen (D-urobilinogen) is closely related to two other compounds: mesobilirubinogen (I-urobilinogen) and stercobilinogen (L-urobilinogen). Somewhat confusingly, all three compounds are frequently collectively referred to as "urobilinogens".

Preceded by: ABCG2 tetramer transports BMG,BDG from cytosol to extracellular region, ABCC2 transports BMG,BDG from cytosol to extracellular region

Followed by: An unknown BILR reduces BIL to D-UBGN

Literature references

Han, MJ., Jin, YH., Jung, EA., Kobashi, K., Kim, DH. (1995). Purification and characterization of beta-glucuronidase from Escherichia coli HGU-3, a human intestinal bacterium. *Biol. Pharm. Bull., 18*, 1184-8. ↗

Seyfried, H., Leithner, C., Penner, E., Klicpera, M. (1976). [Bilirubin metabolism (author's transl)]. *Wien. Klin. Wochenschr., 88*, 477-82. ↗

Chan, RC., Cheng, AF., Leung, JW., Liu, YL., Inciardi, JF., Leung, PS. (2001). Expression of bacterial beta-glucuronidase in human bile: an in vitro study. *Gastrointest. Endosc., 54*, 346-50. ↗

Editions

2019-09-19	Authored, Edited	Jassal, B.
2019-10-03	Reviewed	D'Eustachio, P.

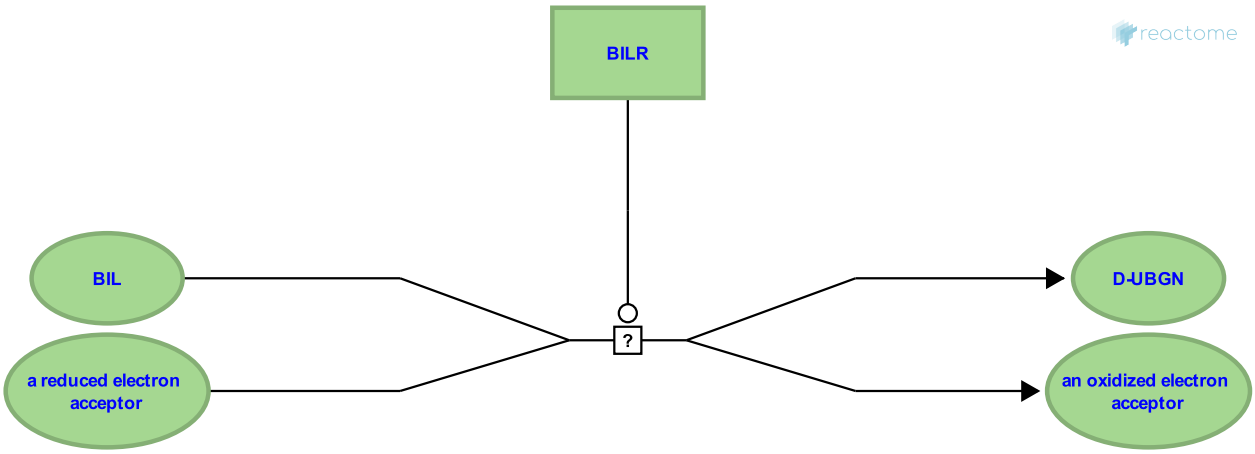
An unknown BILR reduces BIL to D-UBGN ↗

Location: Heme degradation

Stable identifier: R-HSA-9661745

Type: uncertain

Compartments: extracellular region



Microbes present in the large intestine reduce bilirubin (BIL) to D-urobilinogen (D-UBGN) (Troxler et al. 1968, Watson et al. 1958, Vitek et al. 2006). The identity of the bilirubin reductase (BILR) is unknown (Koníčková et al. 2012). Some D-UBGN can be reabsorbed into the portal circulation and delivered to the liver where it is recycled back into the biliary flow.

Preceded by: Bacterial GUSB hydrolyses BDG to BIL

Followed by: An unknown oxidase oxidises D-UBGN to UBN, An unknown reductase reduces D-UBGN to STBN

Literature references

Dawber, NH., Troxler, RF., Lester, R. (1968). Synthesis of urobilinogen by broken cell preparations of intestinal bacteria. *Gastroenterology, 54*, 568-74. ↗

LOWRY, PT., Watson, CJ., Campbell, M. (1958). Preferential reduction of conjugated bilirubin to urobilinogen by normal fecal flora. *Proc. Soc. Exp. Biol. Med., 98*, 707-11. ↗

Muchová, L., Ubik, K., Majer, F., Malina, J., Branný, P., Zelenka, J. et al. (2006). Identification of bilirubin reduction products formed by Clostridium perfringens isolated from human neonatal fecal flora. *J. Chromatogr. B Analyt. Technol. Biomed. Life Sci., 833*, 149-57. ↗

Lešetický, L., Konícková, R., Vítek, L., Štícha, M., Zelenka, J., Jirásková, A. (2012). Reduction of bilirubin ditaurate by the intestinal bacterium Clostridium perfringens. *Acta Biochim. Pol., 59*, 289-92. ↗

Editions

2019-09-18	Authored, Edited	Jassal, B.
2019-10-03	Reviewed	D'Eustachio, P.

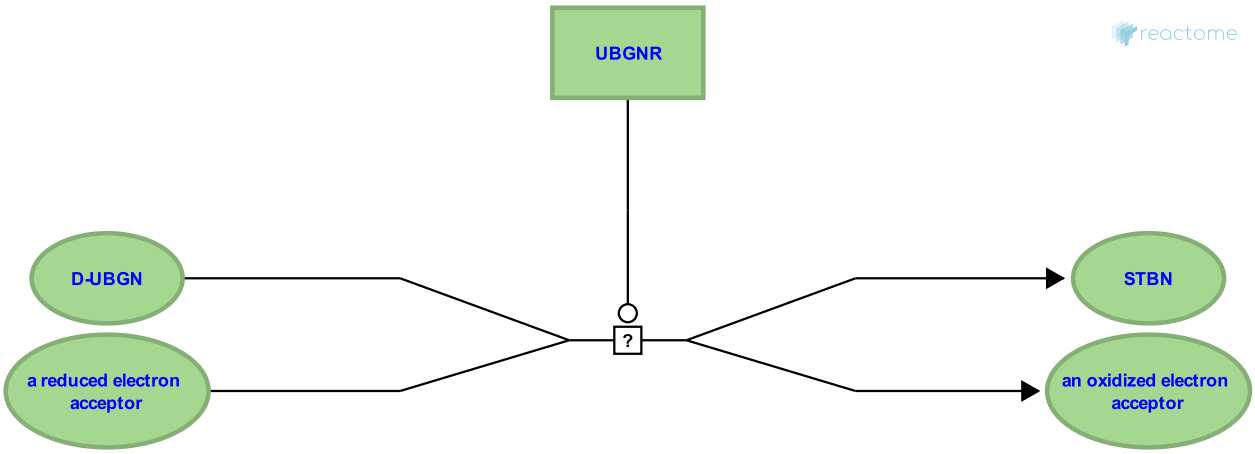
An unknown reductase reduces D-UBGN to STBN ↗

Location: Heme degradation

Stable identifier: R-HSA-9661726

Type: uncertain

Compartments: extracellular region



The D-urobilinogen (D-UBGN) that remains in the intestine is directly reduced to stercobilin (STBN) by unknown bacterial reductases. Stercobilins oxidize to form brownish pigments which lead to the characteristic brown colour found in normal feces (Vitek et al. 2006). STBN can also be reduced to stercobilinogen (L-urobilinogen), which can then be further oxidized to STBN. This constitutes the "enterohepatic urobilinogen cycle."

Preceded by: An unknown BILR reduces BIL to D-UBGN

Literature references

Muchová, L., Ubik, K., Majer, F., Malina, J., Branný, P., Zelenka, J. et al. (2006). Identification of bilirubin reduction products formed by Clostridium perfringens isolated from human neonatal fecal flora. *J. Chromatogr. B Analyt. Technol. Biomed. Life Sci., 833*, 149-57. ↗

Editions

2019-09-18	Authored, Edited	Jassal, B.
2019-10-03	Reviewed	D'Eustachio, P.

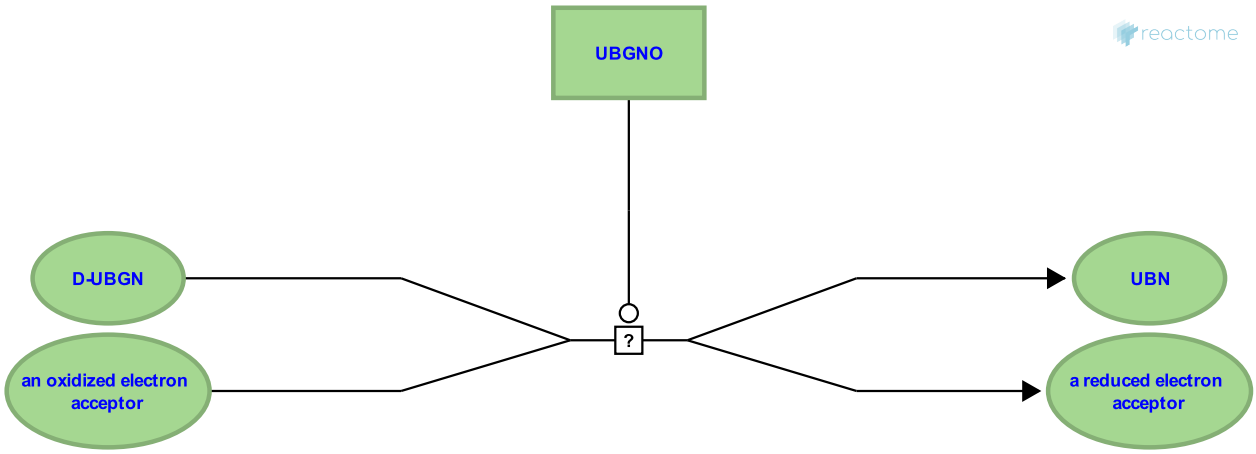
An unknown oxidase oxidises D-UBGN to UBN ↗

Location: Heme degradation

Stable identifier: R-HSA-9661710

Type: uncertain

Compartments: extracellular region



The D urobilinogen (D UBGN) that remains in the intestine is directly reduced to stercobilin (STBN) or oxidised to urobilin (UBN), a yellow pigment seen in urine (Rupe & Fetter 1981). How this oxidation is mediated is unknown (Hamoud et al. 2018).

Preceded by: An unknown BILR reduces BIL to D-UBGN

Literature references

Fetter, MC., Rupe, CO. (1981). Urinary urobilinogen determined by a mercuric chloride procedure. *Clin. Chem., 27*, 1385-7. ↗

Editions

2019-09-18	Authored, Edited	Jassal, B.
2019-10-03	Reviewed	D'Eustachio, P.

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