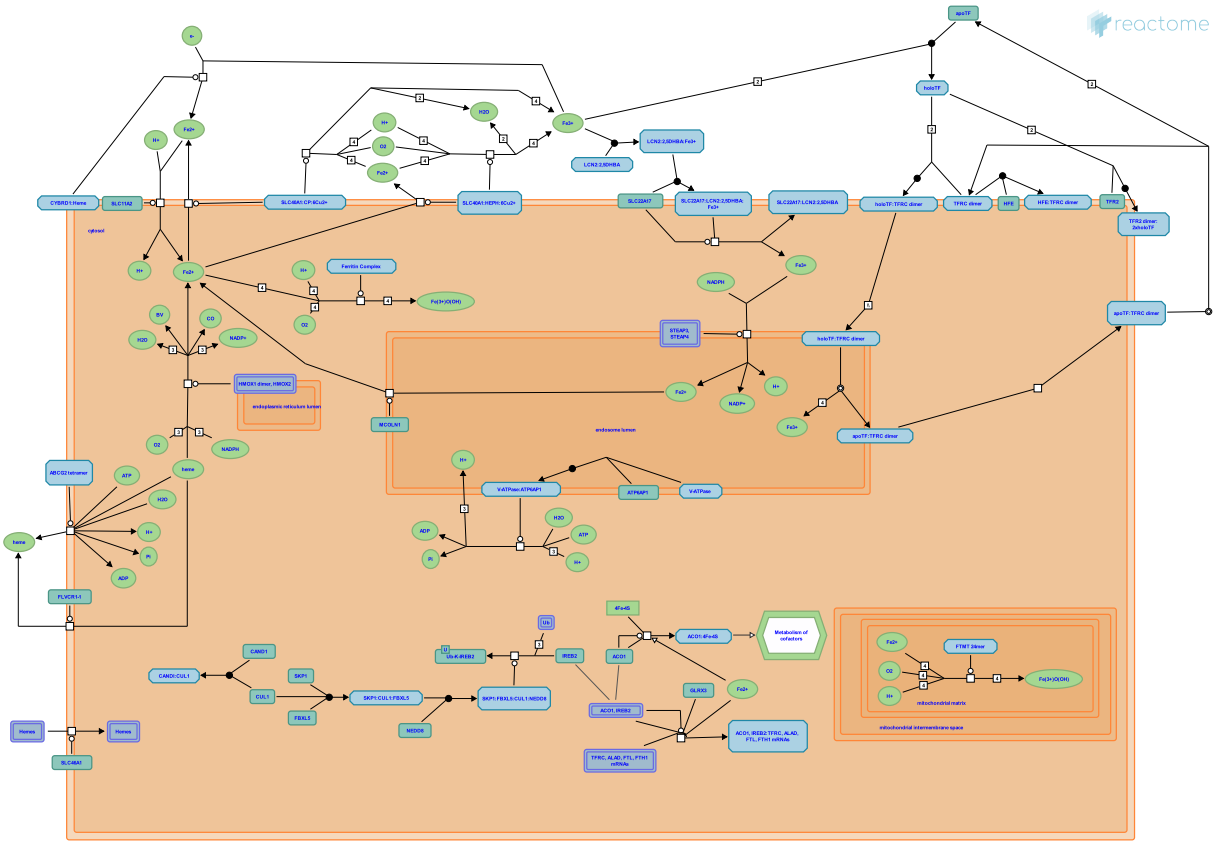
Iron uptake and transport



Chen, C., D'Eustachio, P., He, L., Hill, DP., Jassal, B., Sassa, S., Somers, J., Stephan, R.

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

14/09/2024

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. ↗

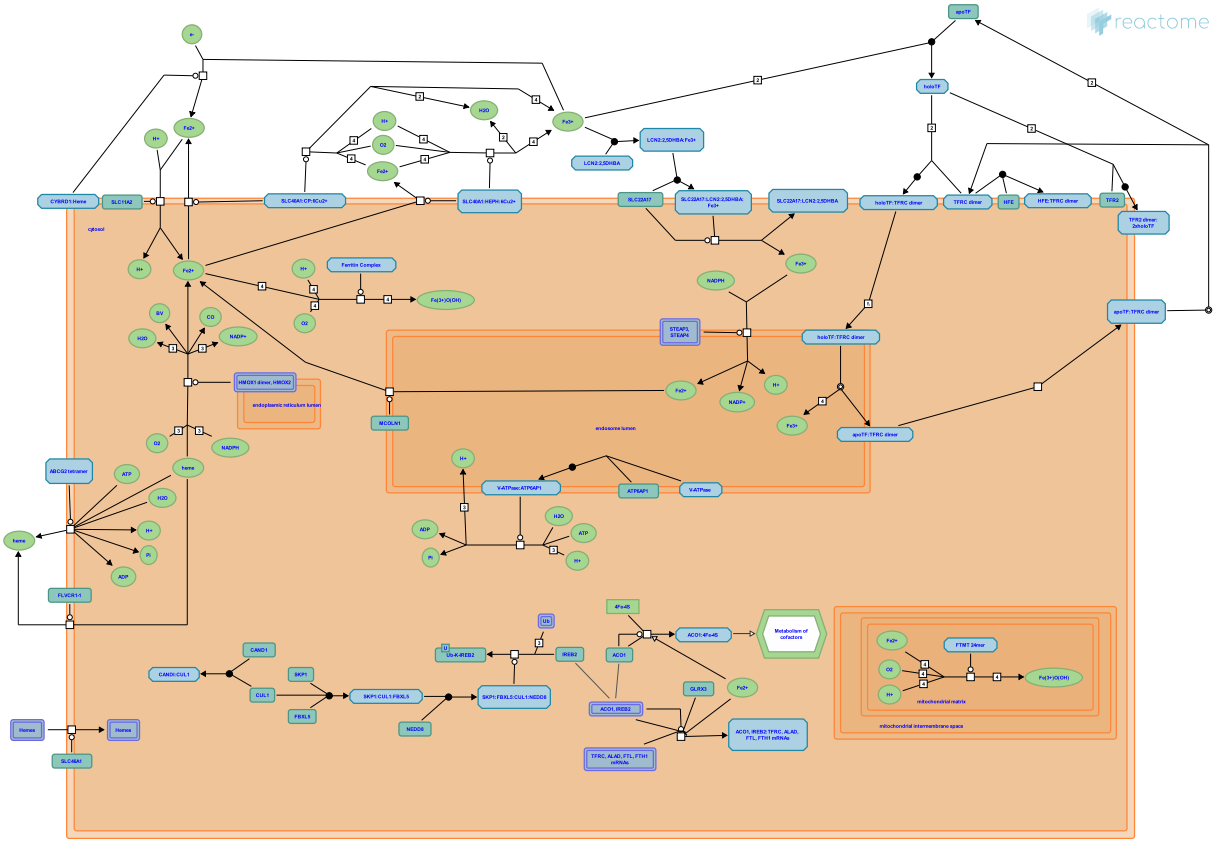
Fabregat, A., Korninger, F., Viteri, G., Sidiropoulos, K., Marin-Garcia, P., Ping, P. et al. (2018). Reactome graph database: Efficient access to complex pathway data. *PLoS computational biology, 14*, e1005968. ↗

Reactome database release: 89

This document contains 2 pathways and 22 reactions (see Table of Contents)

Iron uptake and transport ↗

Stable identifier: R-HSA-917937



The transport of iron between cells is mediated by transferrin. However, iron can also enter and leave cells not only by itself, but also in the form of heme and siderophores. When entering the cell via the main path (by transferrin endocytosis), its goal is not the (still elusive) chelated iron pool in the cytosol nor the lysosomes but the mitochondria, where heme is synthesized and iron-sulfur clusters are assembled (Kurz et al,2008, Hower et al 2009, Richardson et al 2010).

Literature references

Torti, FM., Torti, SV., Shulaev, V., Mendes, P., Hower, V., Laubenbacher, R. et al. (2009). A general map of iron metabolism and tissue-specific subnetworks. *Mol Biosyst, 5*, 422-43. ↗

Ponka, P., Richardson, DR., Whitnall, M., Becker, EM., Sheftel, AD., Lane, DJ. et al. (2010). Mitochondrial iron trafficking and the integration of iron metabolism between the mitochondrion and cytosol. *Proc Natl Acad Sci U S A, 107*, 10775-82. ↗

Gustafsson, B., Kurz, T., Brunk, UT., Terman, A. (2008). Lysosomes in iron metabolism, ageing and apoptosis. *Histochem Cell Biol, 129*, 389-406. ↗

Editions

2010-06-30	Authored	Stephan, R.
2010-07-30	Edited	Jassal, B.
2010-11-05	Reviewed	D'Eustachio, P.
2014-06-09	Revised	Jassal, B.
2017-01-11	Revised	D'Eustachio, P.
2024-02-16	Reviewed	Hill, DP.

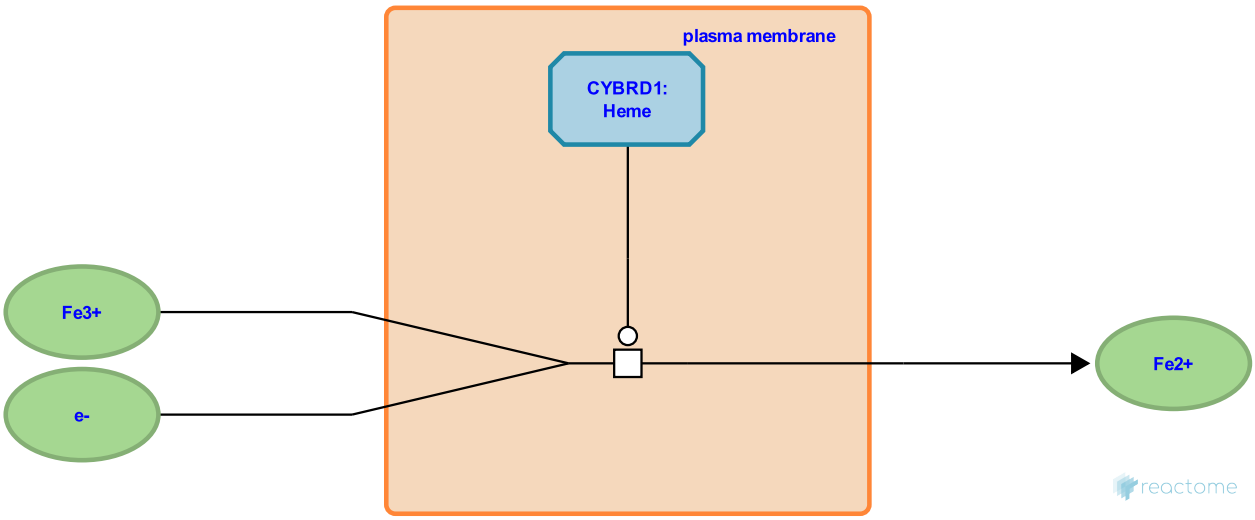
CYBRD1:Heme reduces Fe3+ to Fe2+

Location: Iron uptake and transport

Stable identifier: R-HSA-917805

Type: transition

Compartments: plasma membrane, extracellular region



Cytochrome b reductase 1 not only reduces ferrous iron in the brush-border membrane but also in the airways. It is upregulated on iron starvation. However, its electron donor molecule is still unknown (Oakhill et al, 2007; Turi et al, 2006).

Followed by: SLC11A2 cotransports Fe2+, H+ from extracellular region to cytosol

Literature references

McKie, AT., Ghio, AJ., Piantadosi, CA., Mamo, LB., Crissman, K., Wang, X. et al. (2006). Duodenal cytochrome b: a novel ferrireductase in airway epithelial cells. *Am J Physiol Lung Cell Mol Physiol, 291*, L272-80.

McKie, AT., Cammack, R., Gareta, EG., Oakhill, JS., Marritt, SJ. (2008). Functional characterization of human duodenal cytochrome b (Cybrd1): Redox properties in relation to iron and ascorbate metabolism. *Biochim Biophys Acta, 1777*, 260-8.

Editions

2010-07-05	Authored	Stephan, R.
2010-07-30	Edited	Jassal, B.
2010-11-05	Reviewed	D'Eustachio, P.

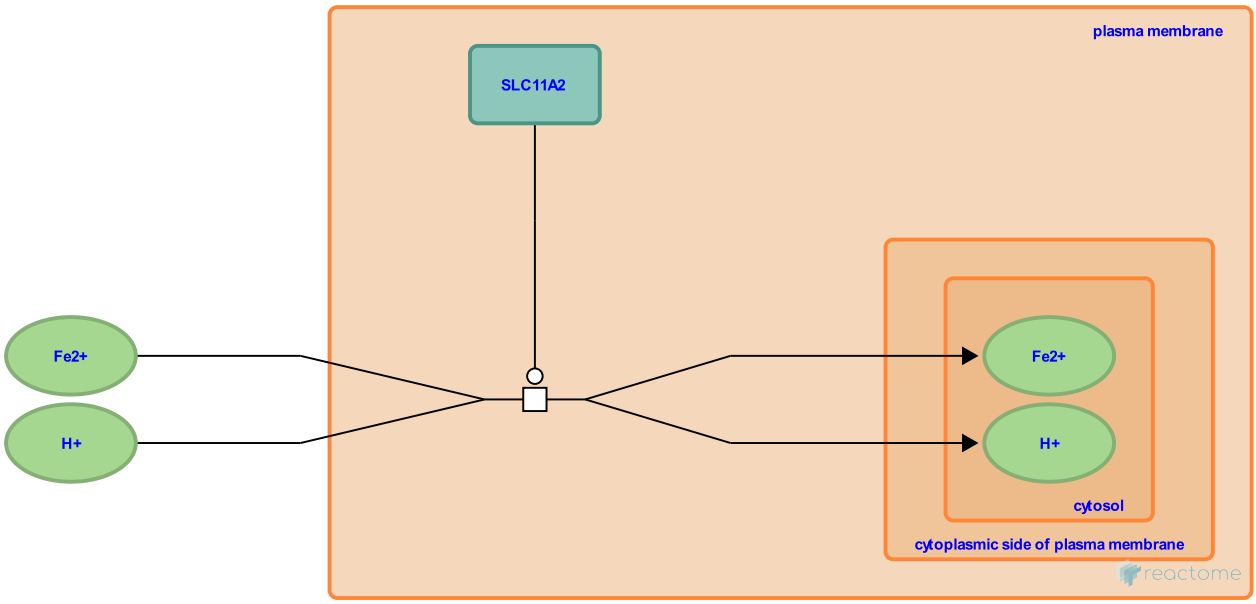
SLC11A2 cotransports Fe2+, H+ from extracellular region to cytosol ↗

Location: Iron uptake and transport

Stable identifier: R-HSA-435349

Type: transition

Compartments: plasma membrane



The primary site for absorption of dietary iron is the duodenum. Ferrous iron (Fe2+) is taken up from the gut lumen across the apical membranes of enterocytes and released into the portal vein circulation across basolateral membranes. The human gene SLC11A2 encodes the divalent cation transporter DCT1 (NRAMP2, Natural resistance-associated macrophage protein 2). DCT1 resides on the apical membrane of enterocytes and mediates the uptake of many metal ions, particularly ferrous iron, into these cells (Tandy et al. 2000).

Preceded by: CYBRD1:Heme reduces Fe3+ to Fe2+

Followed by: SLC40A1:CP:6Cu2+ transports Fe2+ from cytosol to extracellular region

Literature references

Dedes, M., Williams, M., Ramesh, B., Leggett, A., Tandy, S., Lopez-Jimenez, M. et al. (2000). Nramp2 expression is associated with pH-dependent iron uptake across the apical membrane of human intestinal Caco-2 cells. *J Biol Chem, 275*, 1023-9. ↗

Editions

2009-08-21	Edited	Jassal, B.
2009-09-09	Authored	Jassal, B.
2009-11-12	Reviewed	He, L.

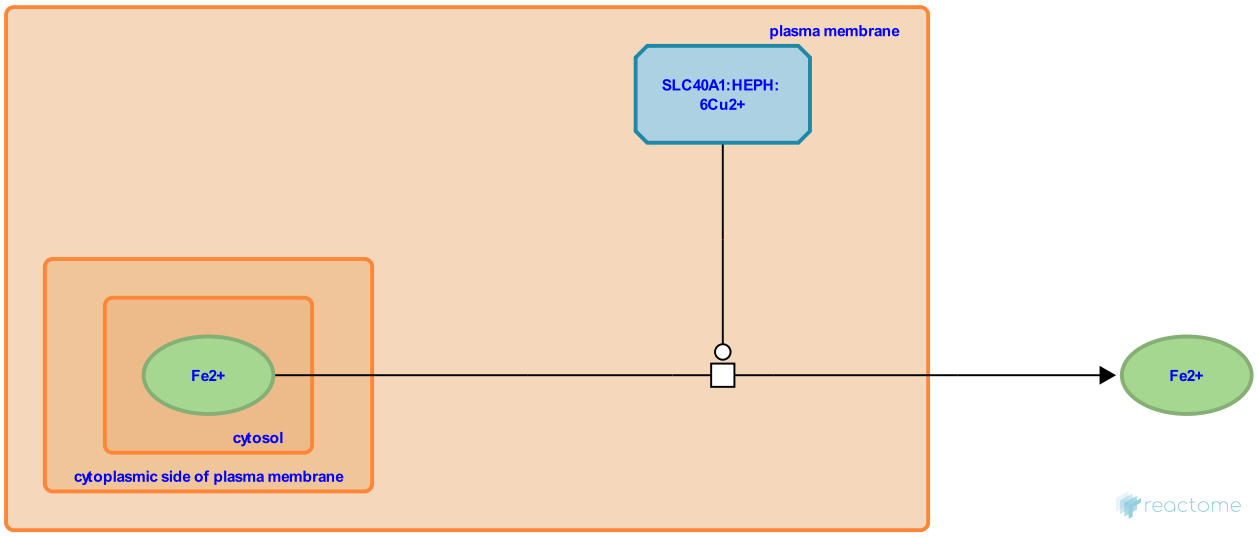
SLC40A1:HEPH:6Cu2+ transports Fe2+ from cytosol to extracellular region ↗

Location: Iron uptake and transport

Stable identifier: R-HSA-442368

Type: transition

Compartments: plasma membrane



The primary site for absorption of dietary iron is the duodenum. Ferrous iron (Fe2+) is taken up from the gut lumen across the apical membranes of enterocytes and released into the portal vein circulation across basolateral membranes.
The human gene SLC40A1 encodes the metal transporter protein MTP1 (aka ferroportin or IREG1). This protein resides on the basolateral membrane of enterocytes and mediates ferrous iron efflux into the portal vein (Schimanski et al. 2005). MTP1 colocalizes with hephaestin (HEPH) which stablizes MTP1 and is necessary for the efflux reaction to occur (Han & Kim 2007, Chen et al. 2009). As well as the dudenum, MTP1 is also highly expressed on macrophages (where it mediates iron efflux from the breakdown of haem) and the placenta (where it may mediate the transport of iron from maternal to foetal circulation). It is also expressed in muscle and spleen.

Followed by: SLC40A1:HEPH:6Cu2+ oxidises 4Fe2+ to 4Fe3+

Literature references

Viprakasit, V., Cowley, D., Bastin, JM., Schimanski, LM., Robson, KJ., Townsend, AR. et al. (2005). In vitro functional analysis of human ferroportin (FPN) and hemochromatosis-associated FPN mutations. *Blood, 105*, 4096-102. ↗

Kim, EY., Han, O. (2007). Colocalization of ferroportin-1 with hephaestin on the basolateral membrane of human intestinal absorptive cells. *J Cell Biochem, 101*, 1000-10. ↗

Vulpe, C., Attieh, ZK., van der Hee, RM., Huang, G., Chen, H., Dang, T. (2009). Decreased hephaestin expression and activity leads to decreased iron efflux from differentiated Caco2 cells. *J Cell Biochem, 107*, 803-8. ↗

Editions

2009-08-21	Edited	Jassal, B.
2009-09-25	Authored	Jassal, B.
2009-11-12	Reviewed	He, L.

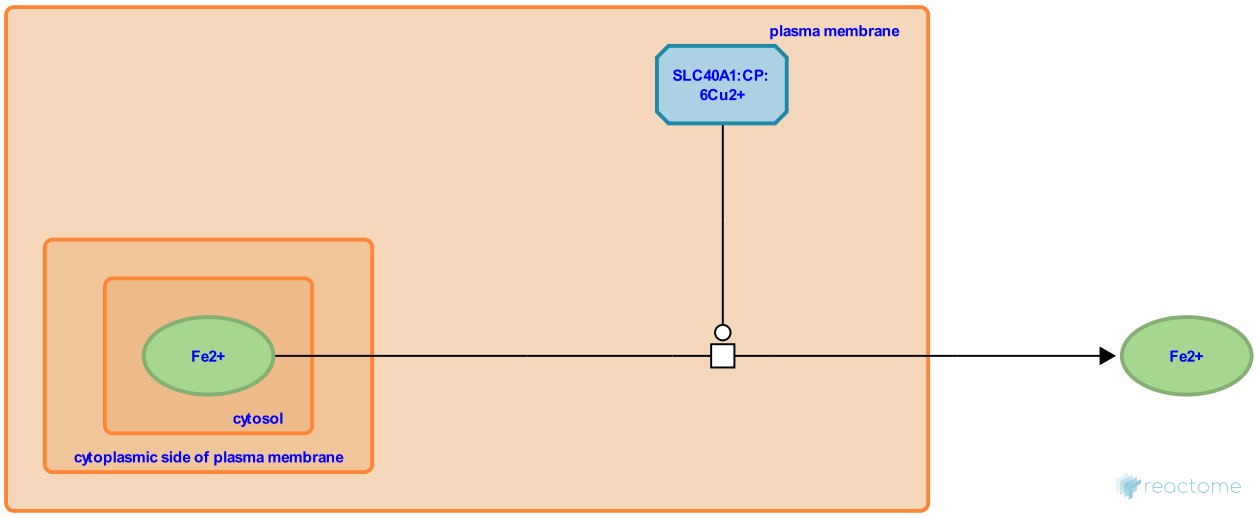
SLC40A1:CP:6Cu2+ transports Fe2+ from cytosol to extracellular region ↗

Location: Iron uptake and transport

Stable identifier: R-HSA-904830

Type: transition

Compartments: plasma membrane



SLC40A1 (MTP1 aka ferroportin or IREG1) is highly expressed on macrophages where it mediates iron efflux from the breakdown of haem (Schimanski et al. 2005). SLC40A1 colocalizes with ceruloplasmin (CP) which stablizes SLC40A1 and is necessary for the efflux reaction to occur (Texel et al. 2008). Six copper ions are required as cofactor. Ceruloplasmin (CP) also catalyses the conversion of iron from ferrous (Fe2+) to ferric form (Fe3+), thereby assisting in its transport in the plasma in association with transferrin, which can only carry iron in the ferric state. As well as being expressed on macrophages, SLC40A1 is also highly expressed in the duodenum, placenta (where it may mediate the transport of iron from maternal to foetal circulation), muscle and spleen.

Preceded by: SLC11A2 cotransports Fe2+, H+ from extracellular region to cytosol

Literature references

Viprakasit, V., Cowley, D., Bastin, JM., Schimanski, LM., Robson, KJ., Townsend, AR. et al. (2005). In vitro functional analysis of human ferroportin (FPN) and hemochromatosis-associated FPN mutations. *Blood, 105*, 4096-102. ↗

Xu, X., Texel, SJ., Harris, ZL. (2008). Ceruloplasmin in neurodegenerative diseases. *Biochem Soc Trans, 36*, 1277-81. ↗

Editions

2009-08-21	Edited	Jassal, B.
2009-09-25	Authored	Jassal, B.
2009-11-12	Reviewed	He, L.
2014-08-29	Revised	Jassal, B.

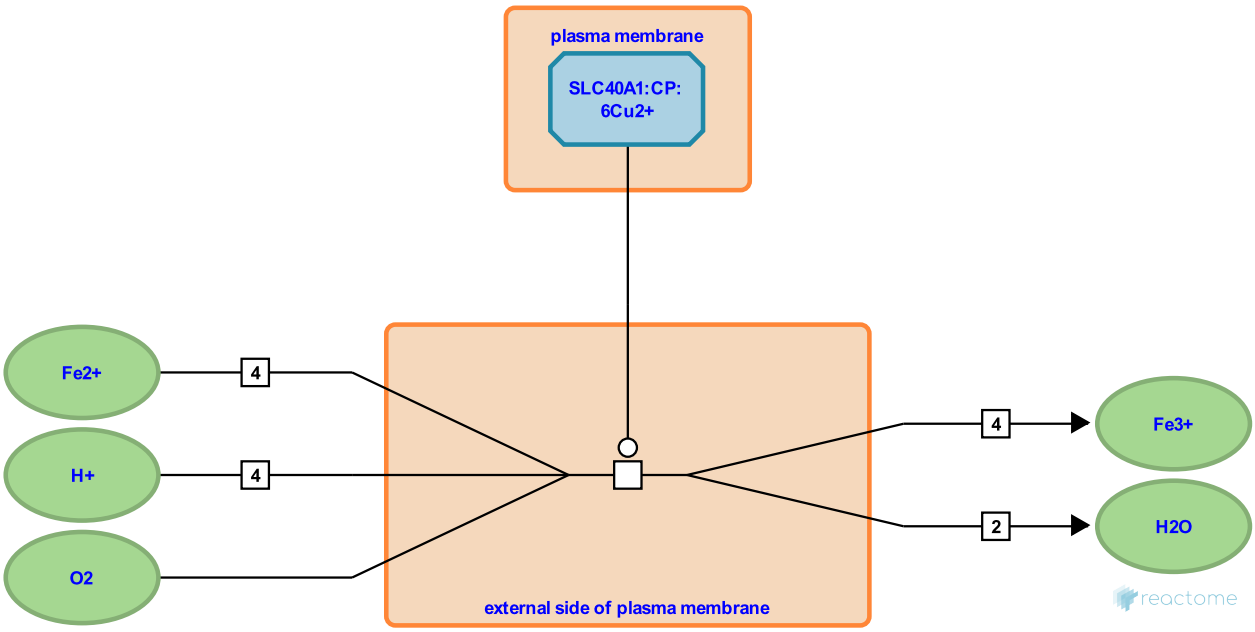
SLC40A1:CP:6Cu2+ oxidises Fe2+ to Fe3+ ↗

Location: Iron uptake and transport

Stable identifier: R-HSA-917891

Type: transition

Compartments: external side of plasma membrane



In tissues other than the duodenum, ceruloplasmin (CP), in complex with SLC40A1 and 6 copper ions, oxidises ferrous iron (Fe2+) to ferric iron (Fe3+) after it is exported from the cell (Sato et al. 1990).

Followed by: apoTF binds 2Fe3+ to form holoTF

Literature references

Sato, M., Morell, AG., Stockert, RJ., Schilsky, ML., Sternlieb, I. (1990). Detection of multiple forms of human ceruloplasmin. A novel Mr 200,000 form. *J Biol Chem, 265*, 2533-7. ↗

Editions

2010-07-04	Authored	Stephan, R.
2010-07-30	Edited	Jassal, B.
2010-11-05	Reviewed	D'Eustachio, P.
2014-08-29	Revised	Jassal, B.

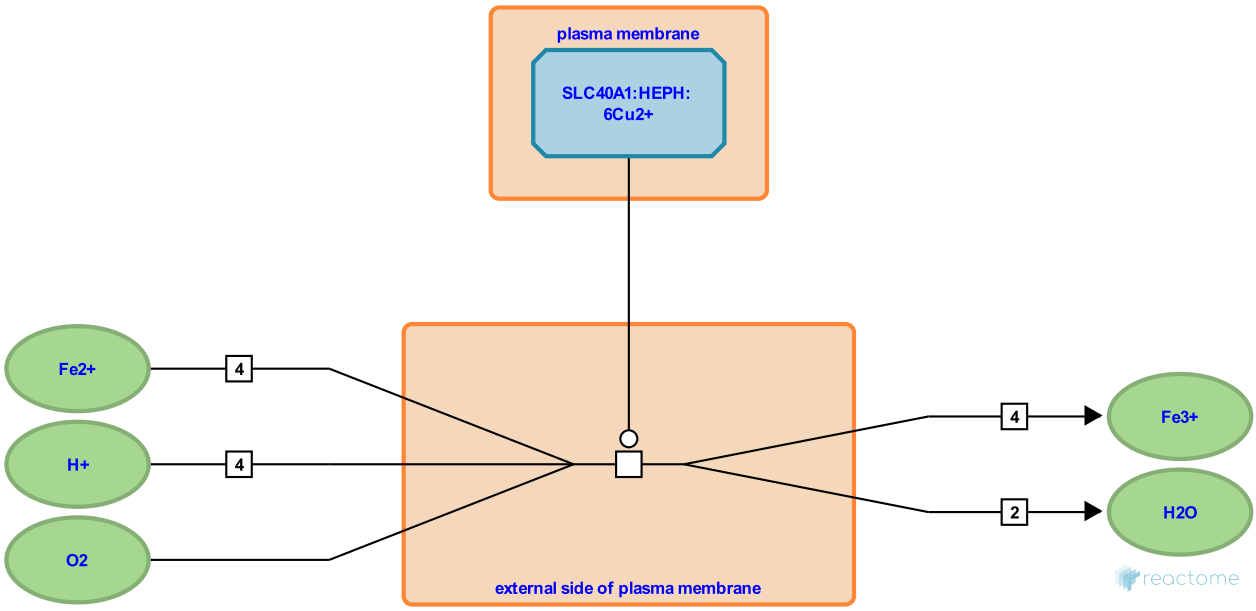
SLC40A1:HEPH:6Cu2+ oxidises 4Fe2+ to 4Fe3+ ↗

Location: Iron uptake and transport

Stable identifier: R-HSA-917933

Type: transition

Compartments: external side of plasma membrane



Hephaestin oxidizes ferrous iron (Fe2+) to ferric iron (Fe3+) after export from duodenal cells to enable its transport via transferrin (Griffiths et al, 2005).

Preceded by: SLC40A1:HEPH:6Cu2+ transports Fe2+ from cytosol to extracellular region

Followed by: apoTF binds 2Fe3+ to form holoTF

Literature references

Mauk, AG., MacGillivray, RT., Griffiths, TA. (2005). Recombinant expression and functional characterization of human hephaestin: a multicopper oxidase with ferroxidase activity. *Biochemistry, 44*, 14725-31. ↗

Editions

2010-07-04	Authored	Stephan, R.
2010-07-30	Edited	Jassal, B.
2010-11-05	Reviewed	D'Eustachio, P.

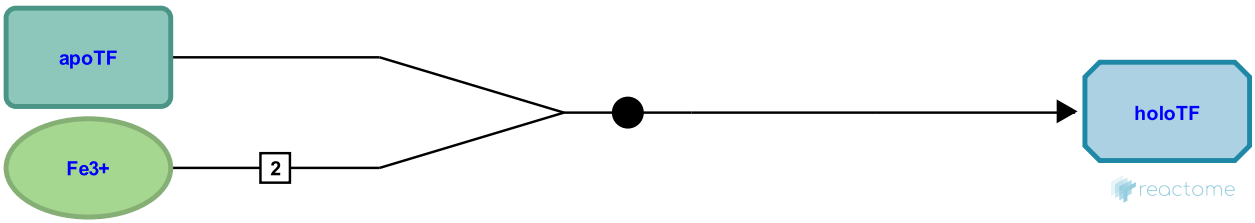
apoTF binds 2Fe3+ to form holoTF ↗

Location: Iron uptake and transport

Stable identifier: R-HSA-917888

Type: binding

Compartments: extracellular region



Transferrin (TF) is the main transporter of iron in the blood. The apo-form of TF can take up two ferric iron ions (Fe3+) to form holoTF (Wally et al. 2006).

Preceded by: SLC40A1:CP:6Cu2+ oxidises Fe2+ to Fe3+, SLC40A1:HEPH:6Cu2+ oxidises 4Fe2+ to 4Fe3+

Followed by: Transferrin endocytosis and recycling

Literature references

Mason, AB., Halbrooks, PJ., Wally, J., Everse, SJ., Vonrhein, C., Buchanan, SK. et al. (2006). The crystal structure of iron-free human serum transferrin provides insight into inter-lobe communication and receptor binding. *J Biol Chem, 281*, 24934-44. ↗

Editions

2010-07-07	Authored	Stephan, R.
2010-07-30	Edited	Jassal, B.
2010-11-05	Reviewed	D'Eustachio, P.

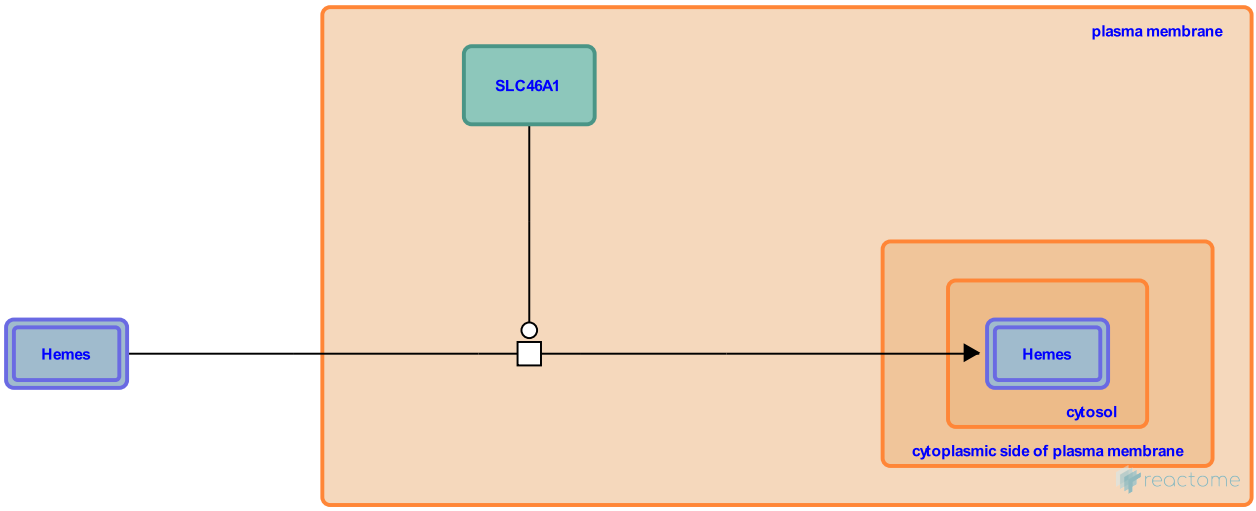
SLC46A1 transports hemes from extracellular region to cytosol ↗

Location: Iron uptake and transport

Stable identifier: R-HSA-917870

Type: transition

Compartments: plasma membrane



Uptake of iron from meat happens mostly in the form of ferriheme (FeHM), and via the same transporter that is used for folate. The process is more effective than taking up iron ions (Shayeghi M et al, 2005). In general, heme transporters do not differentiate between ferroheme and ferriheme.

Literature references

Simpson, RJ., McKie, AT., Shayeghi, M., Latunde-Dada, GO., Laftah, AH., Halliday, N. et al. (2005). Identification of an intestinal heme transporter. *Cell, 122*, 789-801. ↗

Editions

2010-07-01	Authored	Stephan, R.
2010-07-30	Edited	Jassal, B.
2010-11-05	Reviewed	D'Eustachio, P.
2021-01-23	Reviewed	Somers, J.

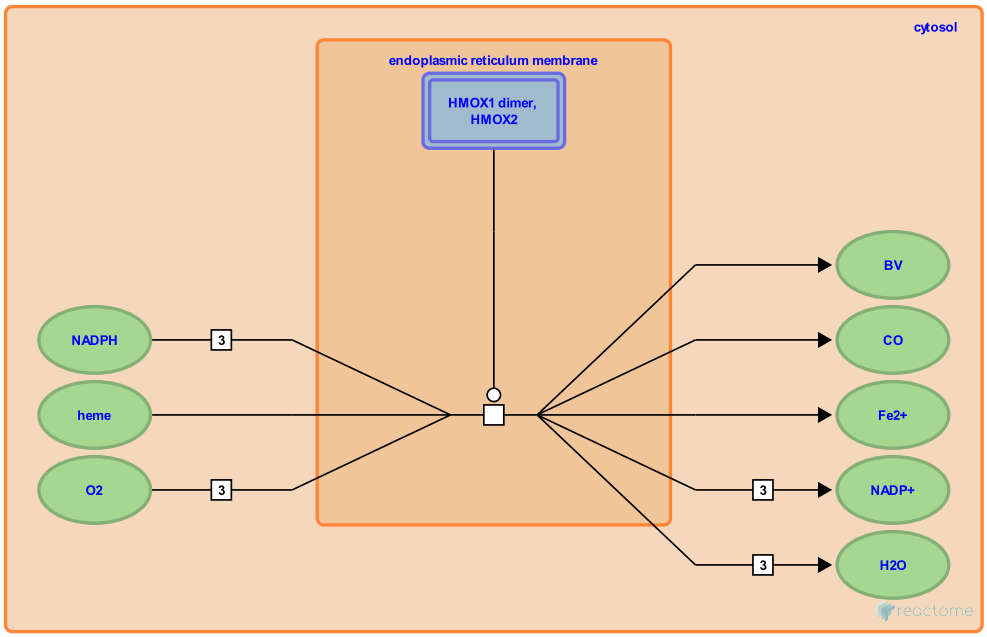
HMOX1 dimer, HMOX2 cleave heme ↗

Location: Iron uptake and transport

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.

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.

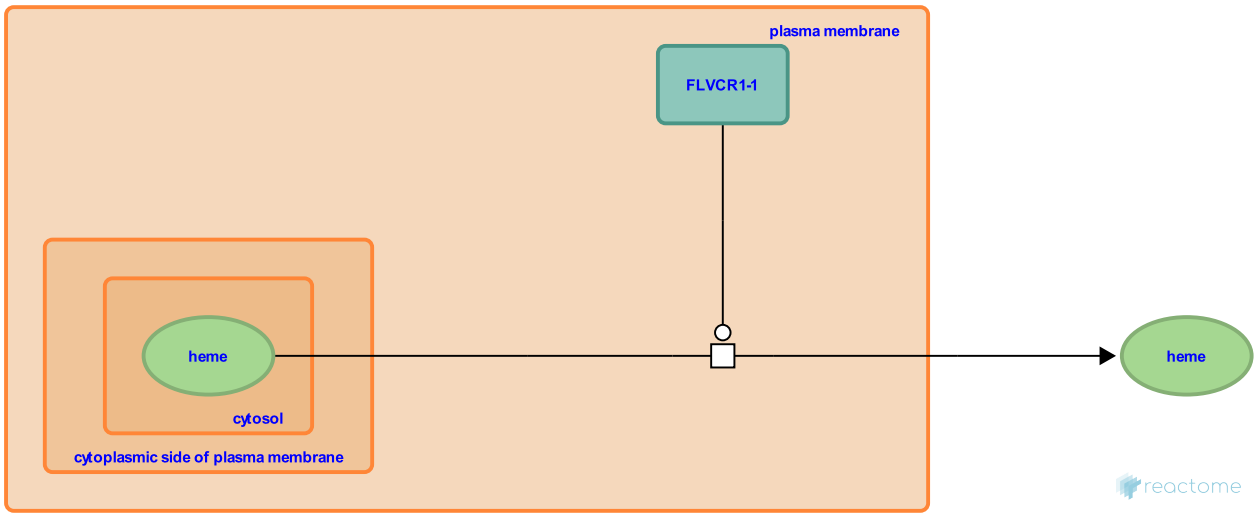
FLVCR1-1 transports heme from cytosol to extracellular region ↗

Location: Iron uptake and transport

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.

Literature references

Quigley, JG., Sassa, S., Sabo, KM., Berg, CL., Phillips, JD., Sabath, DE. et al. (2004). Identification of a human heme exporter that is essential for erythropoiesis. *Cell, 118*, 757-66. ↗

Dick, JE., Kennedy, JA., Brown, JK., Tailor, CS., Rey, MA., Duffy, SP. et al. (2008). Enhanced alternative splicing of the FLVCR1 gene in Diamond Blackfan anemia disrupts FLVCR1 expression and function that are critical for erythropoiesis. *Haematologica, 93*, 1617-26. ↗

Editions

2010-07-06	Authored	Stephan, R.
2010-07-30	Edited	Jassal, B.
2010-11-05	Reviewed	D'Eustachio, P.
2019-09-18	Revised	Jassal, B.
2023-11-22	Revised	D'Eustachio, P.

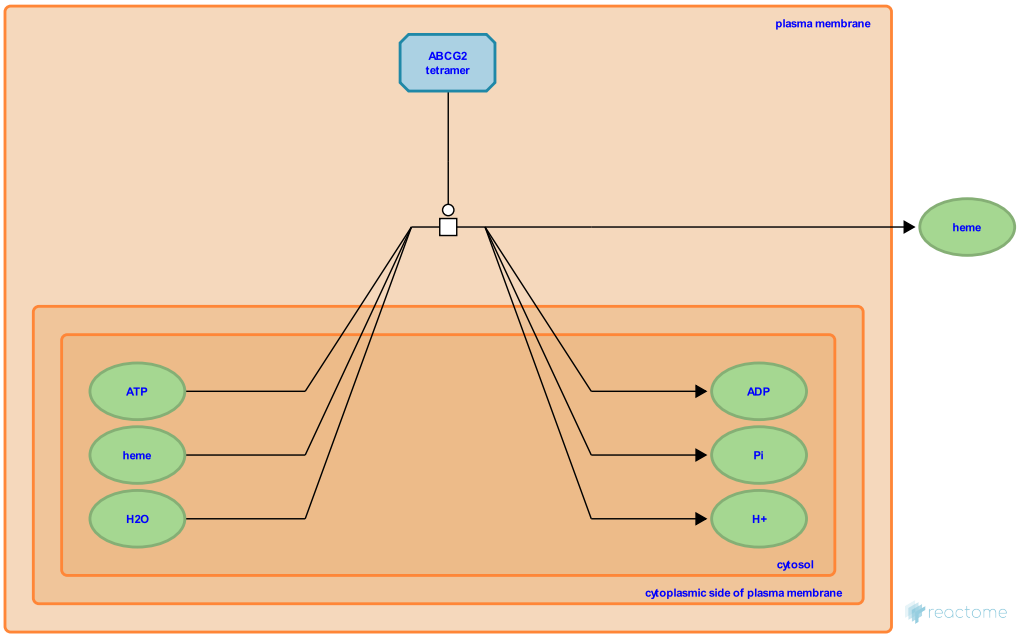
ABCG2 tetramer transports heme from cytosol to extracellular region ↗

Location: Iron uptake and transport

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).

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. ↗

Stanimirovic, DB., Zhang, H., Mojsilovic-Petrovic, J., Andrade, MF., Ball, M., Zhang, W. (2003). The expression and functional characterization of ABCG2 in brain endothelial cells and vessels. *FASEB J, 17*, 2085-7. ↗

Zhou, S., Sarkadi, B., Ross, DD., Sorrentino, BP., Nakanishi, T., Bailey-Dell, K. et al. (2004). The stem cell marker Bcrp/ABCG2 enhances hypoxic cell survival through interactions with heme. *J Biol Chem, 279*, 24218-25. ↗

Ross, DD., Doyle, LA. (2003). Multidrug resistance mediated by the breast cancer resistance protein BCRP (ABCG2). *Oncogene, 22*, 7340-58. ↗

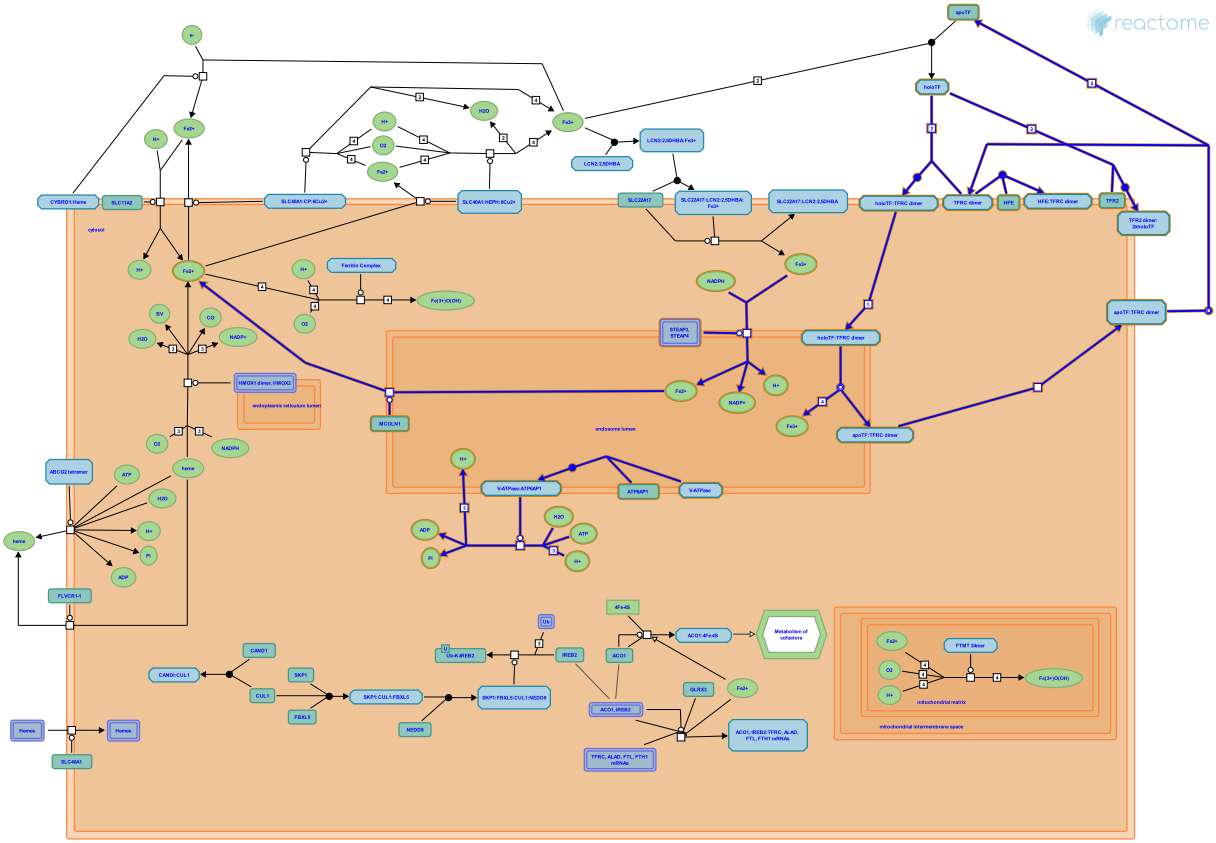
Editions

2010-07-07	Authored	Stephan, R.
2010-07-30	Edited	Jassal, B.
2010-11-05	Reviewed	D'Eustachio, P.
2019-09-18	Revised	Jassal, B.
2023-11-22	Revised	D'Eustachio, P.
2024-02-16	Reviewed	Hill, DP.

Transferrin endocytosis and recycling ↗

Location: Iron uptake and transport

Stable identifier: R-HSA-917977



Endocytosis of iron loaded transferrin/receptor complex leads, after acidification of the endosome, to the separation of iron and its diffusion out of the vesicle. The endosome is not fused with a lysosome but recycles its content back to the cell surface where soon transferrin dissociates from its receptor (Dautry-Varsat, 1986).

Literature references

Dautry-Varsat, A. (1986). Receptor-mediated endocytosis: the intracellular journey of transferrin and its receptor. *Biochimie, 68*, 375-81. ↗

Editions

2010-07-11	Authored	Stephan, R.
2010-07-30	Edited	Jassal, B.
2010-11-05	Reviewed	D'Eustachio, P.

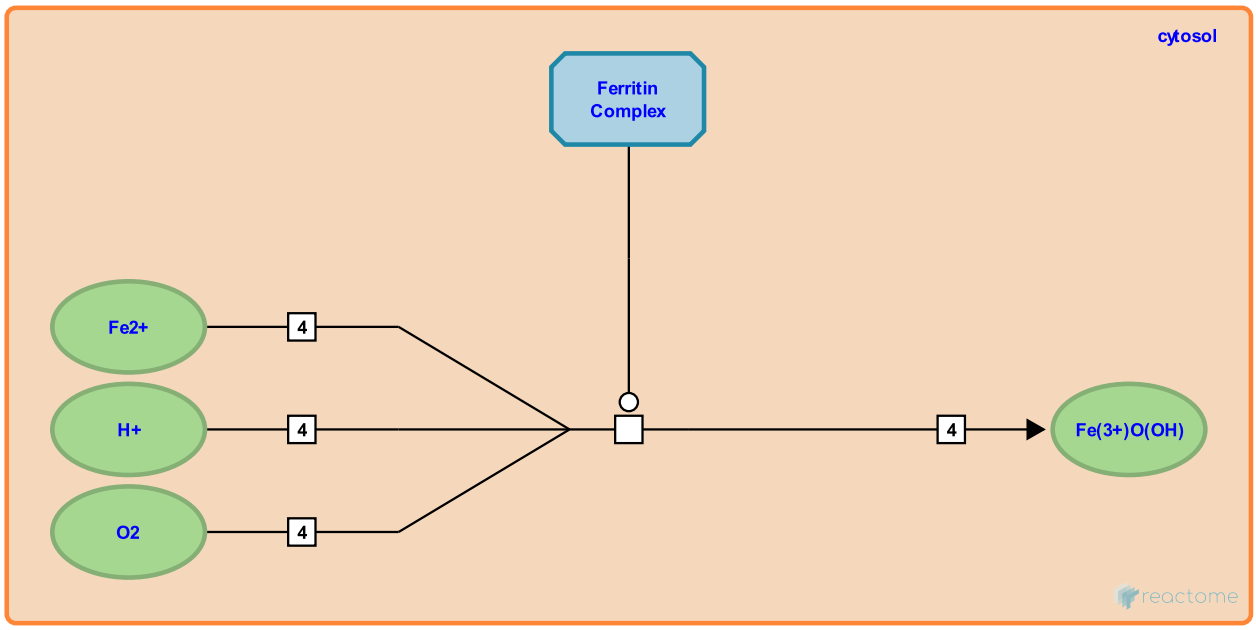
Ferritin Complex oxidises 4Fe2+ to Fe(3+)O(OH) ↗

Location: Iron uptake and transport

Stable identifier: R-HSA-1562626

Type: transition

Compartments: cytosol



Ferritin oxidises Fe(2+) ions to Fe(3+), migrates them to its centre, and collects thousands of them as ferric hydroxide (Fe(3+)O(OH)) in the central mineral core from which they can be later remobilised (Harrison & Arrosio 1996).

Literature references

Harrison, PM., Arosio, P. (1996). The ferritins: molecular properties, iron storage function and cellular regulation. *Biochim Biophys Acta, 1275*, 161-203. ↗

Editions

2011-01-10	Authored	Stephan, R.
2011-09-05	Edited	Jassal, B.
2011-10-26	Reviewed	D'Eustachio, P.

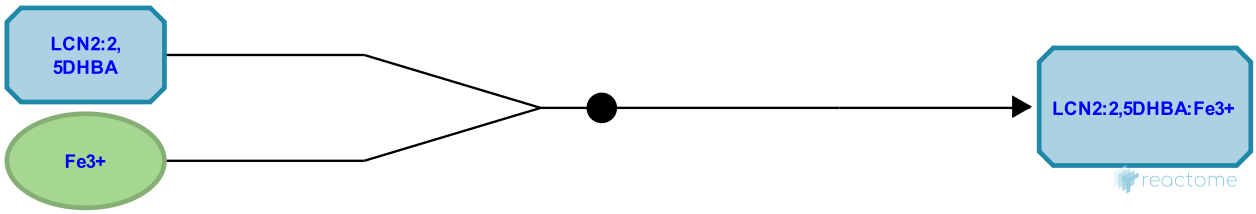
LCN2:2,5DHBA binds Fe3+ ↗

Location: Iron uptake and transport

Stable identifier: R-HSA-5229273

Type: binding

Compartments: extracellular region



Neutrophil gelatinase associated lipocalin (LCN2, NGAL) is a member of the lipocalin superfamily that is involved in iron trafficking both in and out of cells. LCN2 binds iron via an association with 2,5 dihydroxybenzoic acid (2,5DHBA), a siderophore that shares structural similarities with bacterial enterobactin, and delivers or removes iron from the cell via interacting with different receptors, depending on cellular requirement (Goetz et al. 2002, Devireddy et al. 2010). LCN2 is a potent bacteriostatic agent in iron limiting conditions therefore it is proposed that LCN2 participates in the antibacterial iron depletion strategy of the innate immune system (Flo et al. 2004).

Literature references

Goetz, DH., Hart, DO., Green, MR., Devireddy, LR. (2010). A mammalian siderophore synthesized by an enzyme with a bacterial homolog involved in enterobactin production. *Cell, 141*, 1006-17. ↗

Raymond, KN., Bluhm, ME., Goetz, DH., Strong, RK., Holmes, MA., Borregaard, N. (2002). The neutrophil lipocalin NGAL is a bacteriostatic agent that interferes with siderophore-mediated iron acquisition. *Mol. Cell, 10*, 1033-43. ↗

Aderem, A., Rodriguez, DJ., Flo, TH., Sato, S., Strong, RK., Akira, S. et al. (2004). Lipocalin 2 mediates an innate immune response to bacterial infection by sequestrating iron. *Nature, 432*, 917-21. ↗

Editions

2014-01-17	Authored, Edited	Jassal, B.
2014-06-09	Reviewed	Chen, C.

SLC22A17 binds LCN2:2,5DHBA:Fe3+ ↗

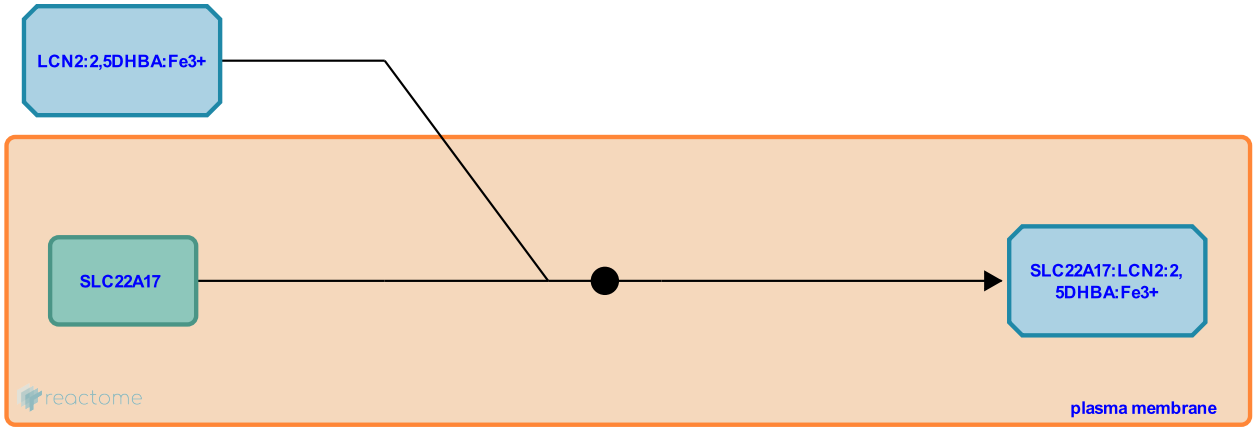
Location: Iron uptake and transport

Stable identifier: R-HSA-5246444

Type: binding

Compartments: plasma membrane, extracellular region, cytosol

Inferred from: Slc22a17 binds Lcn2, internalising it, releasing Fe3+ (Mus musculus)



Neutrophil gelatinase-associated lipocalin (LCN2, NGAL) is a member of the lipocalin superfamily that is involved in iron trafficking both in and out of cells (Goetz et al. 2002). LCN2 binds iron through association with 2,5-dihydroxybenzoic acid (2,5DHBA), a siderophore that shares structural similarities with bacterial enterobactin, and delivers or removes iron from the cell, depending on the context. The iron-bound form of LCN2 (holo-LCN2) is internalised following binding to the solute carrier family 22 member 17 (SLC22A17) receptor, leading to release of iron which increases intracellular iron concentration and subsequent inhibition of apoptosis. This step is inferred from experiments using the highly homologous 24p3 mouse lipocalin and 24p3R mouse cell surface receptor (Devireddy et al. 2005). During infection, bacteria scavenge iron from the host cell and transfer it to the pathogen cell. Upon encountering invading bacteria, Toll-like receptors on immune cells can stimulate the transcription, translation and secretion of LCN2. LCN2 can then limit bacterial growth by sequestrating the iron-laden siderophore so this event is pivotal in the innate immune response to bacterial infection (Flo et al. 2004).

Literature references

Raymond, KN., Bluhm, ME., Goetz, DH., Strong, RK., Holmes, MA., Borregaard, N. (2002). The neutrophil lipocalin NGAL is a bacteriostatic agent that interferes with siderophore-mediated iron acquisition. *Mol. Cell, 10*, 1033-43. ↗

Zhu, X., Gazin, C., Green, MR., Devireddy, LR. (2005). A cell-surface receptor for lipocalin 24p3 selectively mediates apoptosis and iron uptake. *Cell, 123*, 1293-305. ↗

Aderem, A., Rodriguez, DJ., Flo, TH., Sato, S., Strong, RK., Akira, S. et al. (2004). Lipocalin 2 mediates an innate immune response to bacterial infection by sequestrating iron. *Nature, 432*, 917-21. ↗

Editions

2014-01-21	Authored, Edited	Jassal, B.
2014-06-09	Reviewed	Chen, C.

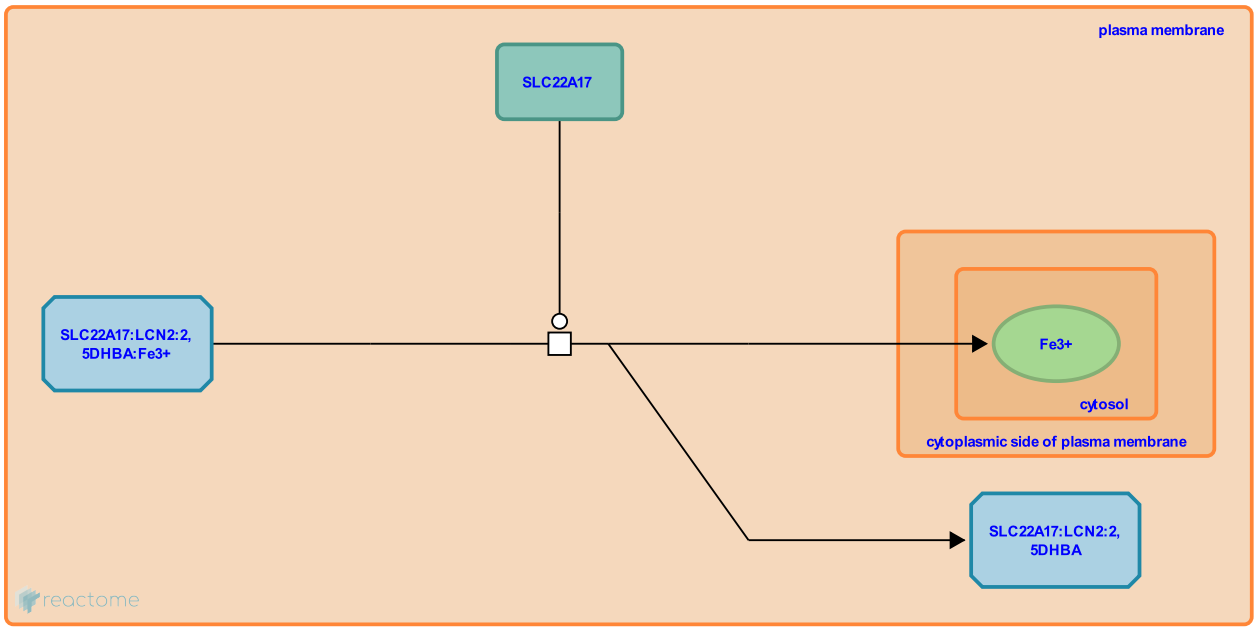
Fe3+ dissociates from SLC22A17:LCN2:2,5DHBA ↗

Location: Iron uptake and transport

Stable identifier: R-HSA-5671707

Type: transition

Compartments: plasma membrane, extracellular region, cytosol



Neutrophil gelatinase-associated lipocalin (LCN2, NGAL) is a member of the lipocalin superfamily that is involved in iron trafficking both in and out of cells (Goetz et al. 2002). LCN2 binds iron through association with 2,5-dihydroxybenzoic acid (2,5DHBA), a siderophore that shares structural similarities with bacterial enterobactin, and delivers or removes iron from the cell, depending on the context. The iron-bound form of LCN2 (holo-LCN2) is internalised following binding to the solute carrier family 22 member 17 (SLC22A17) receptor, leading to release of iron which increases intracellular iron concentration and subsequent inhibition of apoptosis. This step is inferred from experiments using the highly homologous 24p3 mouse lipocalin and 24p3R mouse cell surface receptor (Devireddy et al. 2005).

Literature references

Raymond, KN., Bluhm, ME., Goetz, DH., Strong, RK., Holmes, MA., Borregaard, N. (2002). The neutrophil lipocalin NGAL is a bacteriostatic agent that interferes with siderophore-mediated iron acquisition. *Mol. Cell, 10*, 1033-43. ↗

Zhu, X., Gazin, C., Green, MR., Devireddy, LR. (2005). A cell-surface receptor for lipocalin 24p3 selectively mediates apoptosis and iron uptake. *Cell, 123*, 1293-305. ↗

Aderem, A., Rodriguez, DJ., Flo, TH., Sato, S., Strong, RK., Akira, S. et al. (2004). Lipocalin 2 mediates an innate immune response to bacterial infection by sequestrating iron. *Nature, 432*, 917-21. ↗

Editions

2014-06-09	Reviewed	Chen, C.
2015-02-02	Authored, Edited	Jassal, B.

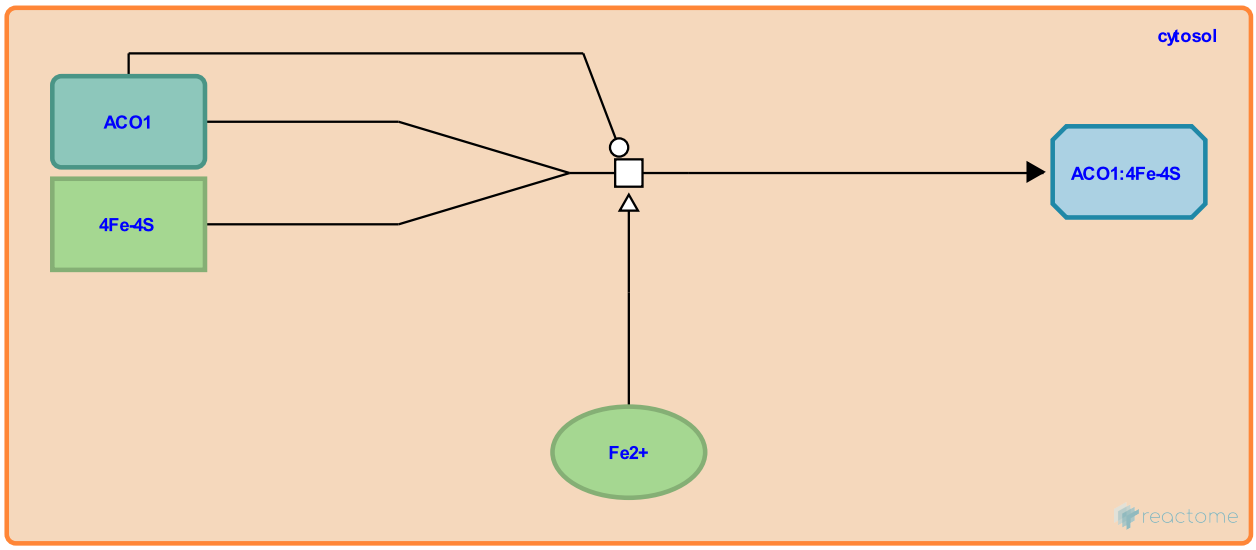
ACO1 binds 4Fe-4S ↗

Location: Iron uptake and transport

Stable identifier: R-HSA-5690873

Type: transition

Compartments: cytosol



Iron and citrate are essential for the metabolism of most organisms so their regulation is critical for normal physiology and survival. Depending on cellular conditions, cytoplasmic aconitate hydratase (ACO1 aka iron regulatory protein 1, IRP1) can assume two different functions. During iron scarcity or oxidative stress, ACO1 functions as IRP1, binding to iron responsive elements (IREs) to modulate the translation of iron metabolism genes. In iron-rich conditions, IRP1 binds an iron-sulfur cluster (4Fe-4S) to function as a cytosolic aconitase. This functional duality of IRP1 connects the translational control of iron metabolising proteins to cellular iron levels.

Under iron-replete conditions, ACO1 binds the cofactor 4Fe-4S cluster and acts as an aconitase, isomerising citrate (CIT) to isocitrate (ISCIT) (Kaptain et al. 1991, Philpott et al. 1994, Dupuy et al. 2006).

Literature references

Fontecilla-Camps, JC., Darnault, C., Carpentier, P., Volbeda, A., Dupuy, J., Moulis, JM. (2006). Crystal structure of human iron regulatory protein 1 as cytosolic aconitase. *Structure, 14*, 129-39. ↗

Haile, D., Downey, WE., Orloff, DG., Harford, JB., Philpott, C., Kaptain, S. et al. (1991). A regulated RNA binding protein also possesses aconitase activity. *Proc. Natl. Acad. Sci. U.S.A., 88*, 10109-13. ↗

Philpott, CC., Klausner, RD., Rouault, TA. (1994). The bifunctional iron-responsive element binding protein/cytosolic aconitase: the role of active-site residues in ligand binding and regulation. *Proc. Natl. Acad. Sci. U.S.A., 91*, 7321-5. ↗

Editions

2015-04-30	Authored, Edited	Jassal, B.
2017-01-06	Reviewed	D'Eustachio, P.
2024-02-16	Reviewed	Hill, DP.
2024-03-04	Reviewed	D'Eustachio, P.

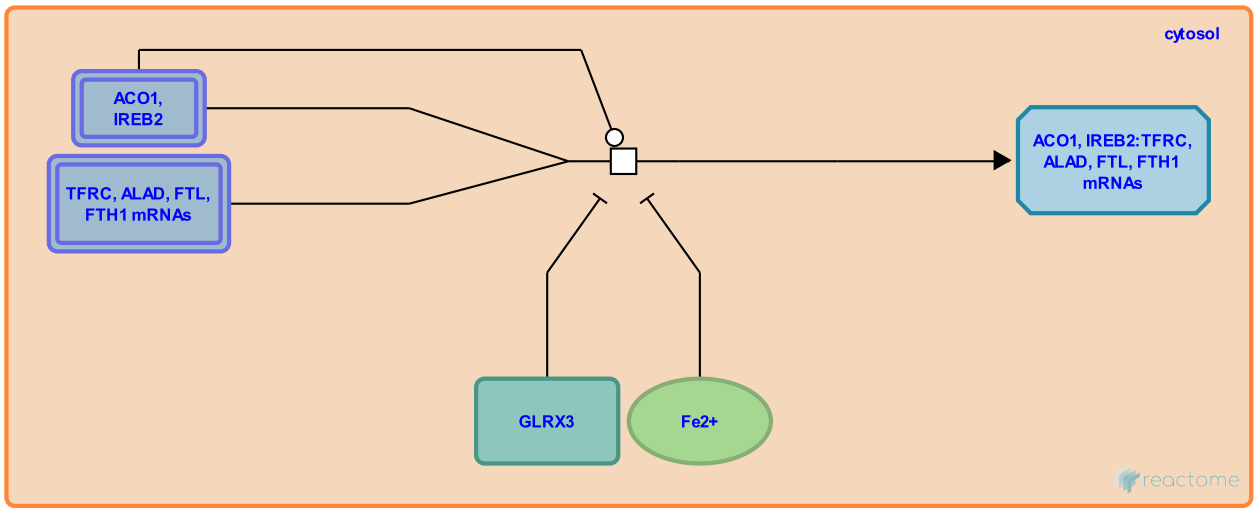
ACO1, IREB2 bind IREs in TFRC, ALAD, FTL, FTH1 mRNAs ↗

Location: Iron uptake and transport

Stable identifier: R-HSA-5690886

Type: transition

Compartments: cytosol



Iron and citrate are essential for the metabolism of most organisms so their regulation is critical for normal physiology and survival. Depending on cellular conditions, cytoplasmic aconitate hydratase (ACO1 aka iron regulatory protein 1, IRP1) can assume two different functions. During iron scarcity or oxidative stress, ACO1 functions as IRP1, binding to iron responsive elements (IREs) to modulate the translation of iron metabolism genes. In iron-rich conditions, IRP1 binds an iron-sulfur cluster (4Fe-4S) to function as a cytosolic aconitase. This functional duality of IRP1 connects the translational control of iron metabolising proteins to cellular iron levels.

During iron scarcity, ACO1 and iron-responsive element-binding protein 2 (IREB2) bind with high affinity to RNA stem-loops known as iron-responsive elements (IREs) present in the 5' untranslated region of the mRNAs of ferritin (composed of heavy and light subunits, FTH1 and FTL) and the erythroid form of aminolevulinic acid synthase (ALAD) and in the 3' untranslated region of the mRNA of the transferrin receptor (TFRC). Binding of ACO1 or IREB2 prevents translation of FTH1:FTL and ALAD and protects the mRNA of TFRC from degradation. ACO1 and IREB2 perform an important metabolic function in response to low intracellular iron levels by interacting with iron protein mRNAs to increase net iron uptake (via TFRC) and decrease sequestration (via FT) and utilisation (via ALAD) of iron (Kaptain et al. 1991, Philpott et al. 1994, Samaniego et al. 1994).

Glutaredoxin-3 (GLRX3) is essential for both transcriptional iron regulation and intracellular iron distribution. Silencing of human Grx3 expression in HeLa cells decreases the activities of several cytosolic Fe-S proteins, for example, iron-regulatory protein 1 (ACO1), a major component of posttranscriptional iron regulation. As a consequence, Grx3-depleted cells show decreased levels of ferritin and increased levels of transferrin receptor, features characteristic of cellular iron starvation (Haunhorst et al. 2013).

Literature references

Haile, D., Downey, WE., Orloff, DG., Harford, JB., Philpott, C., Kaptain, S. et al. (1991). A regulated RNA binding protein also possesses aconitase activity. *Proc. Natl. Acad. Sci. U.S.A., 88*, 10109-13. ↗

Chin, J., Iwai, K., Samaniego, F., Klausner, RD., Rouault, TA. (1994). Molecular characterization of a second iron-responsive element binding protein, iron regulatory protein 2. Structure, function, and post-translational regulation. *J. Biol. Chem., 269*, 30904-10. ↗

Lillig, CH., Lill, R., Hanschmann, EM., Haunhorst, P., Hoffmann, B., Stehling, O. et al. (2013). Crucial function of vertebrate glutaredoxin 3 (PICOT) in iron homeostasis and hemoglobin maturation. *Mol. Biol. Cell, 24*, 1895-903. ↗

Philpott, CC., Klausner, RD., Rouault, TA. (1994). The bifunctional iron-responsive element binding protein/cytosolic aconitase: the role of active-site residues in ligand binding and regulation. *Proc. Natl. Acad. Sci. U.S.A., 91*, 7321-5. ↗

Editions

2015-04-30	Authored, Edited	Jassal, B.
2017-01-06	Reviewed	D'Eustachio, P.
2024-02-16	Reviewed	Hill, DP.
2024-03-04	Reviewed	D'Eustachio, P.

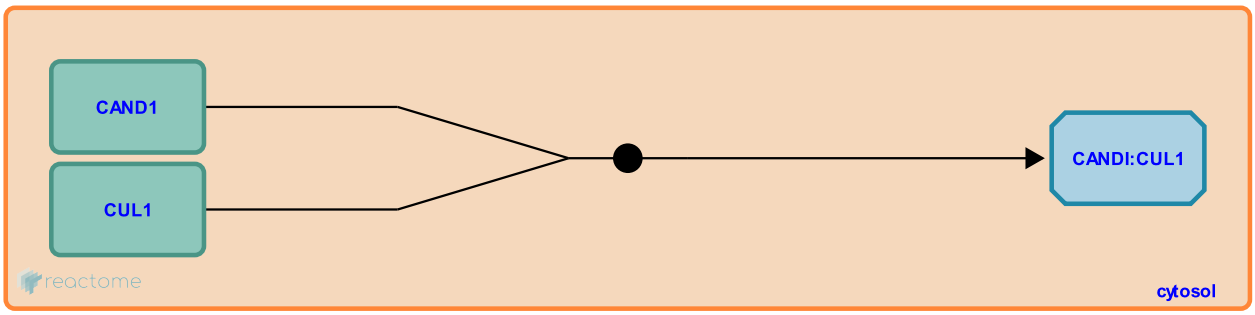
CANDI binds CUL1 ↗

Location: Iron uptake and transport

Stable identifier: R-HSA-5691131

Type: binding

Compartments: cytosol



Cullin-associated NEDD8-dissociated protein 1 (CANDI, TIP120) is a key assembly factor of SCF (SKP1-CUL1-F-box protein) E3 ubiquitin ligase complexes, acting as a F-box protein exchange factor. CANDI binds cullin-1 (CUL1), preventing its association with SKP1 thereby disrupting the formation of SCF complexes. Neddylated CUL1 prevents CANDI binding (Zheng et al. 2002, Goldenberg et al. 2004).

Literature references

Liu, J., Cascio, TC., Zheng, N., Xiong, Y., Shumway, SD., Garbutt, KC. et al. (2004). Structure of the Cand1-Cul1-Roc1 complex reveals regulatory mechanisms for the assembly of the multisubunit cullin-dependent ubiquitin ligases. *Cell, 119*, 517-28. ↗

Lykke-Andersen, K., Harrell, JM., Ryzhikov, S., Sun, H., Wei, N., Shim, EH. et al. (2002). CAND1 binds to unneddylated CUL1 and regulates the formation of SCF ubiquitin E3 ligase complex. *Mol. Cell, 10*, 1519-26. ↗

Editions

2015-05-05	Authored, Edited	Jassal, B.
2017-01-06	Reviewed	D'Eustachio, P.

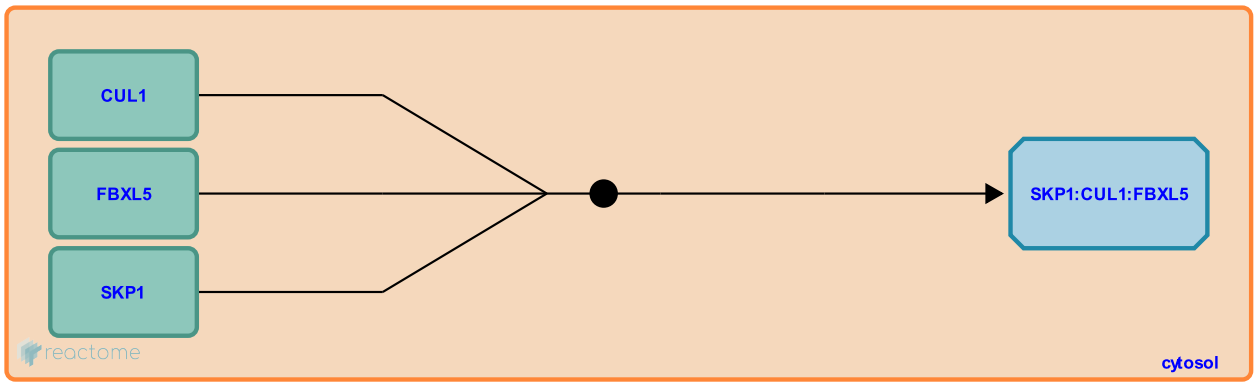
CUL1, SKP1, FBXL5 bind ↗

Location: Iron uptake and transport

Stable identifier: R-HSA-5691167

Type: binding

Compartments: cytosol



Cellular iron homeostasis is maintained by the coordinate posttranscriptional regulation of iron metabolism genes. The E3 ubiquitin ligase complex comprising the F-box/LRR-repeat protein 5 (FBXL5) protein, S-phase kinase-associated protein 1 (SKP1), cullin 1 (CUL1) and NEDD8. This complex targets iron-responsive element-binding protein 2 (IREB2) for proteasomal degradation in iron-replete cells (Vashisht et al. 2009, Salahudeen et al. 2009). Here, CUL1, FBXF5 and SKP1 bind.

Followed by: NEDD8 binds CUL1 (in SKP1:CUL1:FXBL5)

Literature references

Leibold, EA., Sun, D., Sangfelt, O., Bhaskaran, N., Powers, DN., Huang, X. et al. (2009). Control of iron homeostasis by an iron-regulated ubiquitin ligase. *Science, 326*, 718-21. ↗

Ma, HW., Salahudeen, AA., Kinch, LN., Ruiz, JC., Li, Q., Grishin, NV. et al. (2009). An E3 ligase possessing an iron-responsive hemerythrin domain is a regulator of iron homeostasis. *Science, 326*, 722-6. ↗

Editions

2015-05-05	Authored, Edited	Jassal, B.
2017-01-06	Reviewed	D'Eustachio, P.

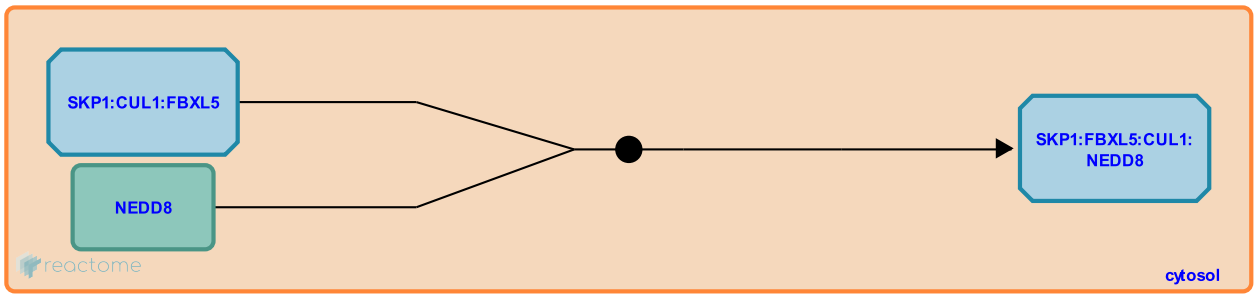
NEDD8 binds CUL1 (in SKP1:CUL1:FXBL5)

Location: Iron uptake and transport

Stable identifier: R-HSA-5691176

Type: binding

Compartments: cytosol



Cellular iron homeostasis is maintained by the coordinate posttranscriptional regulation of iron metabolism genes. The E3 ubiquitin ligase complex comprising the F-box/LRR-repeat protein 5 (FBXL5) protein, S-phase kinase-associated protein 1 (SKP1), cullin 1 (CUL1) and NEDD8. NEDD8 (Neddylin, Neural precursor cell expressed developmentally down-regulated protein 8) is a ubiquitin-like protein which plays an important role in cell cycle control and embryogenesis. NEDD8 covalently attachs to cullins (eg CUL1) and activates their associated E3-ubiquitin ligase activity thus promoting polyubiquitination and proteasomal degradation of cyclins and other regulatory proteins (Hori et al. 1999).

Preceded by: CUL1, SKP1, FBXL5 bind

Followed by: SKP1:FBXL5:CUL1:NEDD8 ubiquitinylates IREB2

Literature references

Kato, S., Shimbara, N., Miyamoto, C., Osaka, F., Okabayashi, K., Chiba, T. et al. (1999). Covalent modification of all members of human cullin family proteins by NEDD8. *Oncogene, 18*, 6829-34.

Editions

2015-05-05	Authored, Edited	Jassal, B.
2017-01-06	Reviewed	D'Eustachio, P.

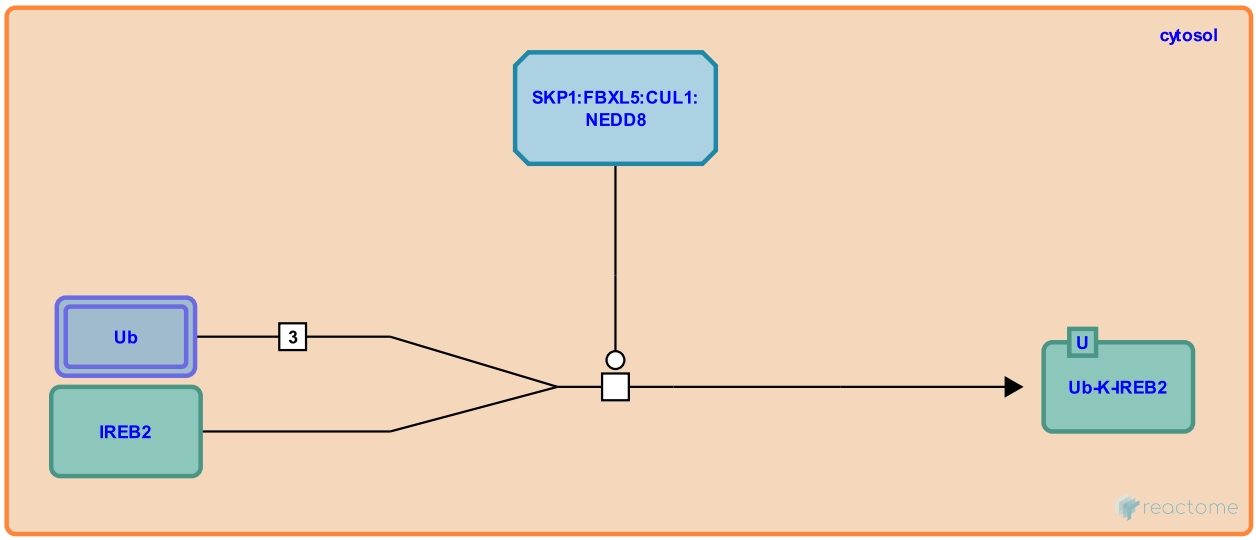
SKP1:FBXL5:CUL1:NEDD8 ubiquitinylates IREB2 ↗

Location: Iron uptake and transport

Stable identifier: R-HSA-5691108

Type: transition

Compartments: cytosol



Cellular iron homeostasis is maintained by the coordinate posttranscriptional regulation of iron metabolism genes. The E3 ubiquitin ligase complex containing the F-box/LRR-repeat protein 5 (FBXL5) protein (SKP1:FBXL5:CUL1:NEDD8) targets iron-responsive element-binding protein 2 (IREB2) for proteasomal degradation in iron-replete cells (Vashisht et al. 2009, Salahudeen et al. 2009). Cullin-1 (CUL1) is in neddylated form (NEDD8) which allows it to associate with this complex.

Preceded by: NEDD8 binds CUL1 (in SKP1:CUL1:FXBL5)

Literature references

Leibold, EA., Sun, D., Sangfelt, O., Bhaskaran, N., Powers, DN., Huang, X. et al. (2009). Control of iron homeostasis by an iron-regulated ubiquitin ligase. *Science, 326*, 718-21. ↗

Ma, HW., Salahudeen, AA., Kinch, LN., Ruiz, JC., Li, Q., Grishin, NV. et al. (2009). An E3 ligase possessing an iron-responsive hemerythrin domain is a regulator of iron homeostasis. *Science, 326*, 722-6. ↗

Editions

2015-05-05	Authored, Edited	Jassal, B.
2017-01-06	Reviewed	D'Eustachio, P.

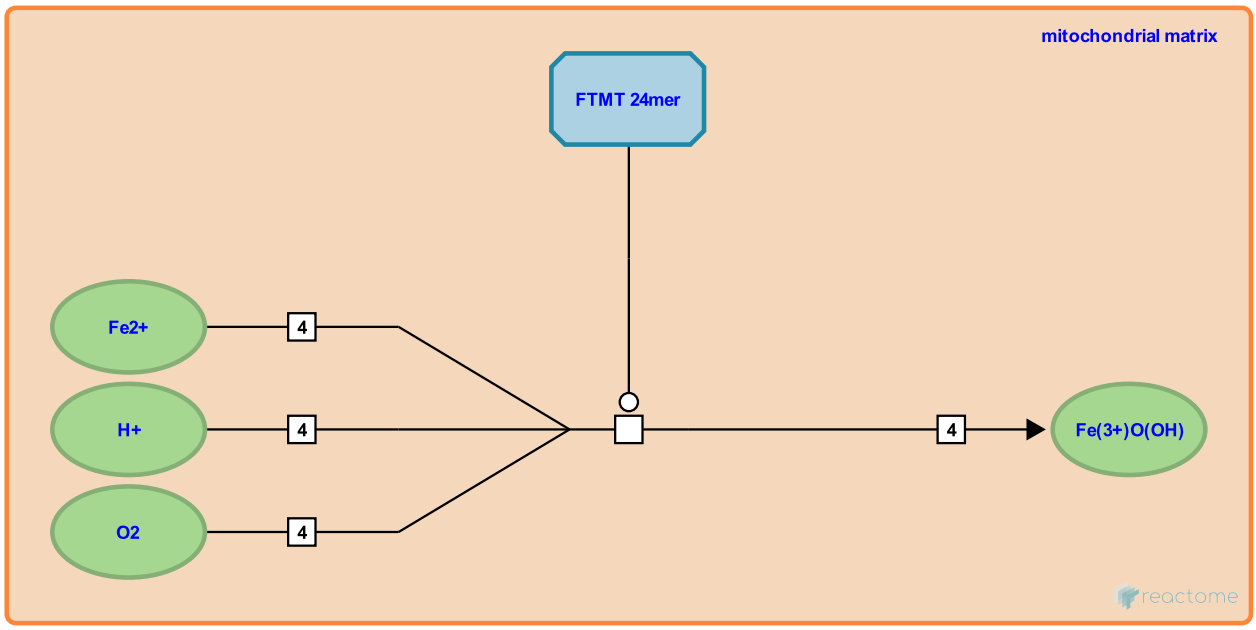
FTMT 24mer oxidises 4Fe2+ to 4Fe(3+)O(OH)

Location: Iron uptake and transport

Stable identifier: R-HSA-5691107

Type: transition

Compartments: mitochondrial matrix



Mitochondrial ferritin (FTMT) is specifically taken up by the mitochondria and processed to a mature protein that assembles into functional ferritin shells. It is a homooligomer of 24 subunits, is roughly spherical and contains a central cavity into which the mineral iron core is deposited. FTMT possesses ferroxidase activity. Iron is taken up in the ferrous form (Fe2+) and deposited as ferric hydroxide (Fe(3+)O(OH)) after oxidation. FTMT may play an important role in the regulation of iron homeostasis in the mitochondrion (Levi et al. 2001, Langlois d'Estaintot et al. 2004).

Literature references

Drysdale, J., Bosisio, M., Arosio, P., Levi, S., Sanford, D., Corsi, B. et al. (2001). A human mitochondrial ferritin encoded by an intronless gene. *J. Biol. Chem., 276*, 24437-40.

Santambrogio, P., Précigoux, G., Gallois, B., Arosio, P., Levi, S., Granier, T. et al. (2004). Crystal structure and biochemical properties of the human mitochondrial ferritin and its mutant Ser144Ala. *J. Mol. Biol., 340*, 277-93.

Editions

2015-05-05	Authored, Edited	Jassal, B.
2017-01-06	Reviewed	D'Eustachio, P.

Table of Contents