### Iron Hemostasis Pathway (PW:0000590)

**Description**

Iron (Fe) is essential for a wide range of important and vital processes as a component of heme- and iron-sulfur cluster (ISC)-containing proteins and as cofactor for non-heme iron-dependent enzymes. Very few life forms can survive in the absence of iron. Iron can be in its reduced, ferrous Fe(II)/Fe2+ form or in the oxidized, ferric Fe(III)/Fe3+ form. The redox cycling of iron underlies the chemistry of its biological functions. It also makes it potentially toxic, as it can lead to the producti

on of reactive oxygen species (ROS), in particular the highly reactive hydroxyl radical via Fenton reaction. Iron deficiency or iron overload contribute to the development of numerous conditions, from anemia to inflammation, cancer, cardiovascular, infectious and neurodegenerative diseases. The proper maintenance of cellular and systemic iron homeostasis is crucial for the well-being of cells, tissues and organs. A finely- orchestrated machinery controls the translation of genes important for iron metabolism and coordinates the uptake and trafficking, distribution and utilization, and storage of iron.

A major function of iron is oxygen transport: of the 3 to 5 grams of iron in adult humans, ~80% is in the hemoglobin of erythrocytes. Iron is important for the proper function of organelles and tissues. Mitochondria are the sites for the biogenesis of heme and of ISC, and also of important metabolic pathways, components of which need the prosthetic group or the cofactor. The brain's high energy requirement relies on mitochondrial ATP production and proper mitochondria homeostasis. The synthesis of many neurotransmitters is carried out by iron-dependent enzymes and iron also impacts on other aspects of their metabolism. The synthesis of lipid components of myelin requires iron as a cofactor. Cardiomyocytes rely on mitochondrial abundance and proper function for their high energy demand. Much of the iron demand is met by its recycling; ~90% in humans. Macrophages take up and digest senescent red blood cells; iron derived from heme catabolism is released into the plasma or stored in macrophages and hepatocytes. The remaining iron is derived from diet. Duodenal enterocytes capture iron through the apical membrane and export it into the plasma through the basolateral membrane. Various aspects of iron metabolism and homeostasis are presented in more detail.

**Iron transport pathway   
Iron uptake pathway**   
Circulating iron is bound by transferrin (Tf), iron-loaded Tf binds transferrin receptor 1 (Tfrc) and the complex is endocytosed and delivered to endosomes. Tf is a glycoprotein; it can bind up to 2 iron ions. Tfrc is an integral membrane glycoprotein that functions as a homodimer formed via disulfide bonds. In the acidic endosomal compartment, iron dissociates from Tf and the apo-Tf/Tfr1 complex is recycled back to the plasma membrane. When Tf is saturated, a non-Tf-bound iron (NTBI) species is taken up by the cell. Uptake of NTBI, and also of dietary non-heme iron, is mediated by divalent metal transporter Slc11a2, known as Dmt1, and the solute carrier Slc39 family members Slc39a14 and Slc39a8, known as Zip14 and 8, respectively. The Slc39 family is known for its role in zinc transport and homeostasis. Enterocytes employ Slc11a2, also used to deliver iron from the endosomal compartment into the cell, while Slc39a14 is the preferred uptake system for hepatocytes. Importantly, the iron that crosses the membrane must be in the soluble ferrous form, and the circulating ferric iron has to be reduced. Cybrd1, known as Dcytb, is the ferric reductase for Slc11a2 in enterocytes whereas the endosomal enzyme is Steap3. Evidence indicates that the prion protein (Prnp) acts as a ferric reductase for the Slc39a14 transporter. Uptake of iron into the mitochondria is better understood for the import across the inner mitochondrial membrane (IMM), and is mediated by Slc25a37 and Slc25a28 transporters, known as mitoferrin 1 and 2, respectively. Iron import into the mitochondria is important, as the organelles are the major site of iron utilization in heme and ISC biogenesis. A transient cytosolic pool of iron, termed the 'labile iron pool' (LIP) is thought to offer easy access to the iron taken up by the cells; the exact composition of the LIP is not known, except for the presence of ferrous Fe (II). The chelatable, 'labile' iron can then be used, stored, or exported. However, much of cytosolic iron trafficking is mediated by interacting proteins delivering the metal, as will be described.

**Iron efflux pathway**   
Regardless of which cell type delivers iron to circulation, a single system mediates the efflux. While there can be some iron loss, there is no dedicated iron excretion system. Slc40a1, known as ferroportin (Fpn1) mediates the efflux of iron into the plasma, where it will be linked to its carrier, transferrin. Transported iron is in its reduced iron (II) state and must be oxidized to be taken up by transferrin. The multi-copper oxidases (MCOs) carry out the reaction with ceruloplasmin (Cp) for macrophages and hepatocytes, and hephaestin (Heph) for enterocytes. A third MCO, Hehl1 known as zyklopen, facilitates iron efflux from placental cells (not shown). In addition to its soluble form, Cp can be found as a GPI-anchored protein, in certain cell types. Slc40a1 is regulated at many levels. Hepcidin (Hamp) binds to Slc40a1, resulting in its endocytosis and proteolysis. As such, it controls iron entry into the plasma from erythrocytes recycling macrophages, storage hepatocytes or dietary enterocytes, mediating the systemic regulation of iron homeostasis. Hamp is a preprotein whose post-translational cleavage gives rise to the 25 amino acid peptide secreted into the plasma, primarily by hepatocytes. Slc40a1 is also controlled at the transcriptional and post-transcriptional levels in a cell-specific manner. Slc40a1 mRNA contains a 5'UTR IRE (see the section on 'post-transcriptional control of iron homeostasis'); a number of other response elements are found in the promoter of the gene and appear to be isoform- specific. The Pcbp2 member of 'iron chaperones', (see the section on 'intracellular iron trafficking'), might deliver iron to Slc40a1.

**Iron storage pathway**   
The main iron storage protein is ferritin as a spherical cage-like multimeric complex comprising 24 units consisting of two types: heavy and light chains. Heavy (H, Fth1) and light chain (L, Ftl) ferritin subunits assemble in several isoferritin complexes with specific tissue distribution. For instance, L-rich ferritin in tissues with storage function (liver) or H-rich ferritin in tissue with elevated oxidative iron function (heart, brain). Mammalian ferritin is a hollow symmetrical complex whose cavity can store up to 4,500 iron atoms. The cage arranges with 2-, 3- and 4-fold symmetries. The iron entering ferritin is the ferrous form; it is oxidized to the ferric form required for deposition, by the oxidase activity of Fth1 ([click to see the structure of wild-type human FTH1](http://www.rcsb.org/pdb/explore/explore.do?structureId=3AJO)). Ftl binds ferric iron and promotes the later steps of core ferritin complex formation ([click to access an entry to the human FTL structure](http://www.rcsb.org/pdb/explore/explore.do?structureId=2FG8)). The oxidized iron moves inside the cavity and hydrolyzes to a mineral form. Three crystalline phases - ferrihydrite, magnetite, and hematite, are present inside the cavity of the complex. Delivery of iron to ferritin is facilitated by members of the poly(rC) family (Pcbp1-4), particularly Pcbp1 and 2 (see 'intracellular iron trafficking' section). Ferritin iron is made available upon lysosomal degradation of ferritin subsequent to its recruitment to the autophagosome. Ncoa4, better known as a nuclear receptor coactivator, is greatly enriched in the autophagosome, binds ferritin and mediates its delivery to the autophagosome. In certain tissues, a mitochondrial ferritin (Ftmt) is expressed with sequence and structure, and ferroxidase center reminiscent of cytosolic ferritin. Neuromelanin (NM), a product of dopamine oxidation, can chelate various transition metals - iron, copper and zinc in particular. Iron is the most abundant amongst them and in the dopaminergic neurons of the substantia nigra, NM acts as a main iron storage.

**Iron utilization pathway**   
The heme biosynthetic pathway and the pathways of iron-sulfur cluster (ISC) formation are the main routes of iron utilization; ~75% of bulk iron is directed towards them. These multi-component systems are separately described and presented (click on the pathway icon(s)). Both systems are dependent upon mitochondria. Heme biosynthesis is initiated and finalized in the mitochondria, with several intermediate steps taking place in the cytosol. The subsequent delivery of heme to various compartments for association with apoproteins is not well understood. The steps involved in the assembly of iron-sulfur (Fe-S) clusters (ISC) and delivery to Fe-S proteins are part of mitochondrial ISC biogenesis and the connected cytosolic assembly (CIA) pathways; ISCs provide for the maturation all Fe-S proteins. A subset of mitochondrial ISC pathway, termed 'core' and the mitochondrial ISC transport are essential for the function of the CIA pathway.

**Other important aspects   
Post-transcriptional control of iron homeostasis**   
Genes important for iron metabolism and homeostasis contain 'iron response elements' (IRE) in their 5'- and 3'-UTR mRNA, forming stem-loop structures to which the iron regulatory proteins can bind. There are two such proteins: ACO1 (known as IRP1) and Ireb2 (known as IRP2). Under low iron conditions binding of IRPs to the IREs in the 5'-UTR inhibits translation, whereas binding to IREs in the 3'-UTR protects the transcripts from nuclease attack and degradation. Under high iron conditions, IRPs' binding capacity for IREs is decreased. mRNAs with 5'-UTR IREs can now be translated whereas those with 3'-UTR IREs are now subject to nuclease attack. In high iron conditions, Aco1 acquires an ISC (Aco1-ISC), which converts it to an aconitase incapable of binding IREs; Ireb2 is targeted to proteasomal degradation by the Fbxl5 E3 ligase system (Ireb2-deg). Examples of genes with 5'-UTR IREs include Fth1, Ftl, Slc40a1 (Fpn1) and Alas2 (involved in heme synthesis in erythrocytes); examples of genes with 3'-UTR IREs include Tfr1 and Slc11a2 (Dmt1). Some of these genes and others are also regulated at the transcriptional level by the hypoxia inducible factor.

**Intracellular iron trafficking**   
It has been shown that poly(rC) family members (Pcbp1-4) can act as chaperones for the intracellular trafficking of iron, in particular Pcbp1 and 2. They contain three highly conserved K homology ([KH](http://pfam.xfam.org/family/PF00013)) domains. The ~70 amino acid domain is found in many and diverse nucleic acid binding proteins. The expression of Pcbp3 and 4 is much lower than that of Pcbp1 and 2, and their tissue distribution more limited. Pcbp1 and 2 form a ternary complex with ferritin, the main storage system of iron; both chaperones are required for the formation of a stable complex. Pcbp1-3 can directly interact with ferritin; Pcpb4 may do so indirectly. Apo-Pcbp2 iron loading is mediated by its interaction with the Slc11a2 transporter; the second K domain binds the cytoplasmic N-terminal domain of the transporter. Pcbp2 might also deliver iron to the efflux Slc40a1 transporter. The iron loading mode of Pcbp1 remains to be established. Pcbp1 and 2 bind ferrous iron and can also interact with one another. Pcbp chaperones also deliver iron to non-heme iron-dependent proteins, such as the hydrolases regulating the hypoxia-inducible alpha levels (Egln1 known as PHD2 and Hif1an), or the deoxyhypusine hydrolase which modifies an eukaryotic initiation factor, thus allowing for the translation of polyproline-containing peptides.

### Source: RGD Molecular Pathway Database