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Iron Metabolism in Humans: An Overview

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1. Introduction

Iron is the most abundant element on earth, yet only trace elements are present in living cells. The four major reasons leading to limited availability of iron in living cells despite environmental abundance would be:

1. When iron was available some 10 billion years ago, it was available as Fe (II), but Fe (II) is not a very strong Lewis acid. Thus, it does not bind strongly to most small molecules or activate them strongly toward reaction.
2. Today iron is not readily available from sea or water solutions due to oxidation and hydrolysis.
3. Iron in ferrous state is not easily retained by proteins since it does not bind very strongly to them.
4. Free Fe (II) is mutagenic, especially in the presence of dioxygen.

To overcome, the above problems with availability of iron, specific ligands have evolved for its transport and storage because of its limited solubility at near neutral pH under aerobic conditions [1].

Iron is involved in many enzymatic reactions of a cell; hence it is believed that the presence of iron was obligatory for the evolution of aerobic life on earth. Furthermore, the propensity of iron to catalyze the oxygen radicals in aerobic and facultative anaerobic species indicates that the intracellular concentration and chemical form of the element must be kept under tight control.

2. Overview of iron metabolism

2.1 Oxidation states

The common oxidation states are either ferrous (Fe^{2+}) or ferric (Fe^{3+}); higher oxidation levels occur as short-lived intermediates in certain redox processes. Iron has affinity for electronegative atoms such as oxygen, nitrogen and sulfur, which provide the electrons that form the bond with iron, hence these atoms are found at the heart of the iron-binding centers of macromolecules. When favorably oriented on the macromolecules, these anions can bind iron with high affinity. During formation of complexes, no bonding electrons are

derived from iron. The non bonding electrons in the outer shell of iron (the incompletely filled *3d* orbitals) can exist in two states. When bonding interactions with iron are weak, the outer non-bonding electrons will avoid pairing and distribute throughout the *3d* orbitals. When bonding electrons interact strongly with iron, there will be pairing of the outer non-bonding electrons, favoring lower energy *3d* orbitals. These two different distributions for each oxidation state of iron can be determined by electron spin resonance measurements. Dispersion of *3d* electrons to all orbitals leads to the high-spin state, whereas restriction of *3d* electrons to lower energy orbitals, because of electron pairing, leads to a low-spin state.

3. Distribution and function

The total body iron in an adult male is 3000 to 4000 mg. In contrast, the average adult woman has only 2000-3000 mg of iron in her body. This difference may be attributed to much smaller iron reserves in women, lower concentration of hemoglobin and a smaller vascular volume than men.

Iron is distributed in six compartments in the body.

i. Hemoglobin

Iron is a key functional component of this oxygen transporting molecule. About 65% to 70% total body iron is found in heme group of hemoglobin. A heme group consists of iron (Fe^{2+}) ion held in a heterocyclic ring, known as aporphyrin. This porphyrin ring consists of four pyrrole molecules cyclically linked together (by methene bridges) with the iron ion bound in the center [Figure 1] [2]. The nitrogen atoms of the pyrrole molecules form coordinate covalent bonds with four of the iron's six available positions which all lie in one plane. The iron is bound strongly (covalently) to the globular protein via the imidazole ring of the F8 histidine residue (also known as the proximal histidine) below the porphyrin ring. A sixth position can reversibly bind oxygen by a coordinate covalent bond, completing the

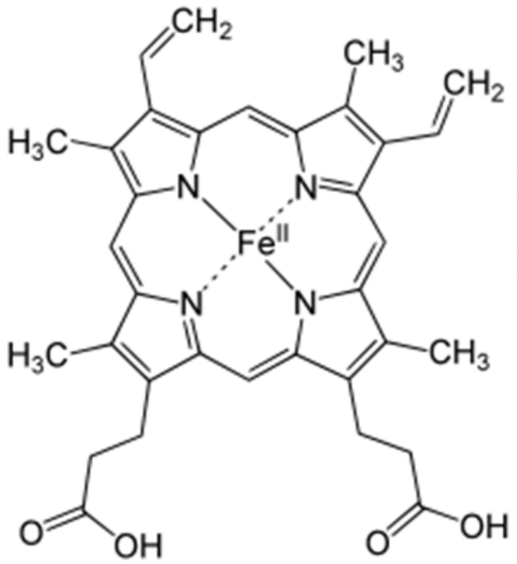


Fig. 1. Structure of heme showing the four coordinate bonds between ferrous ion and four nitrogen bases of the porphyrin rings.

octahedral group of six ligands [Figure 2]. This site is empty in the nonoxygenated forms of hemoglobin and myoglobin. Oxygen binds in an "end-on bent" geometry where one oxygen atom binds Fe and the other protrudes at an angle. When oxygen is not bound, a very weakly bonded water molecule fills the site, forming a distorted octahedron**.**

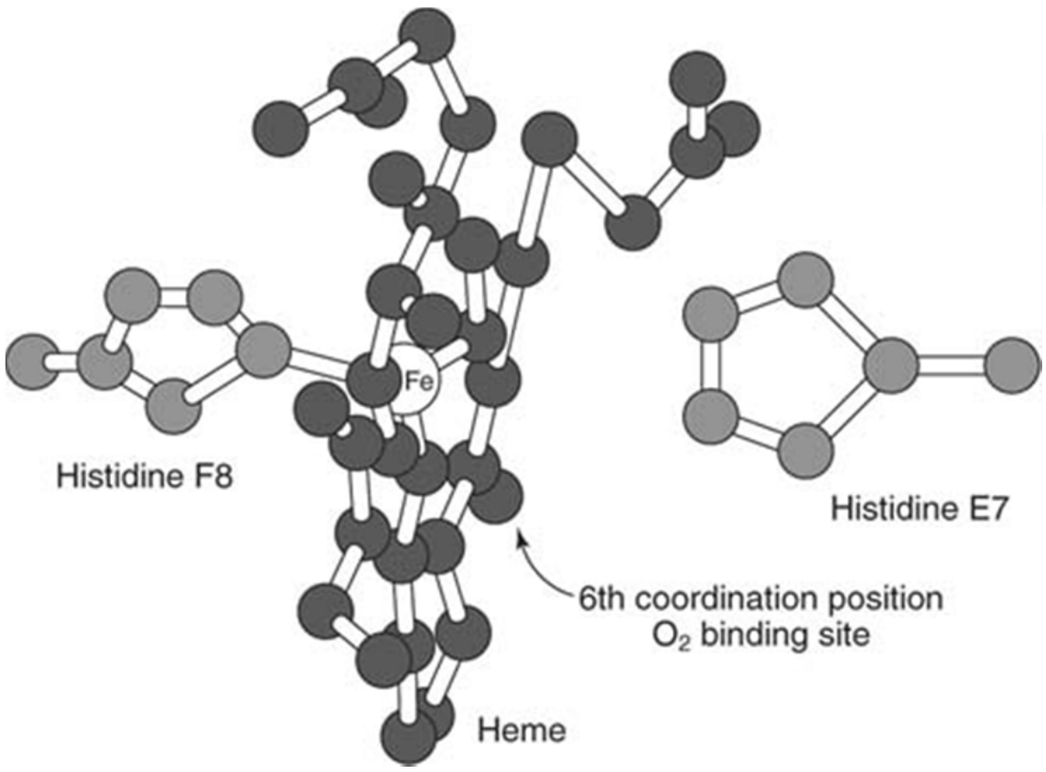


Fig. 2. Structure of heme showing the square planar tetrapyrrole along with the proximal and the distal histidine.

Even though carbon dioxide is also carried by hemoglobin, it does not compete with oxygen for the iron-binding positions, but is actually bound to the protein chains of the structure. The iron ion may be either in the Fe^{2+} or in the Fe^{3+} state, but ferrihemoglobin also called methemoglobin (Fe^{3+}) cannot bind oxygen [3]. In binding, oxygen temporarily and reversibly oxidizes (Fe^{2+}) to (Fe^{3+}) while oxygen temporarily turns into superoxide, thus iron must exist in the +2 oxidation state to bind oxygen. If superoxide ion associated to Fe^{3+} is protonated the hemoglobin iron will remain oxidized and incapable to bind oxygen. In such cases, the enzyme methemoglobin reductase will be able to eventually reactivate methemoglobin by reducing the iron center.

ii. Storage Iron- Ferritin and Hemosiderin

Ferritin is the major protein involved in the storage of iron. The protein consists of an outer polypeptide shell (also termed apoferritin) composed of 24 symmetrically placed protein chains (subunits), the average outside diameter is approximately 12.0 nm in hydrated state. The inner core (approximately 6.0 nm) contains an electron-dense and chemically inert inorganic ferric "iron-core" made of ferric oxyhydroxyhydroxide phosphate $[(FeOOH)_8(FeO\text{-}OPO_3H_2)]$. [Figure 3]. The ferritins are extremely large proteins (450kDa)

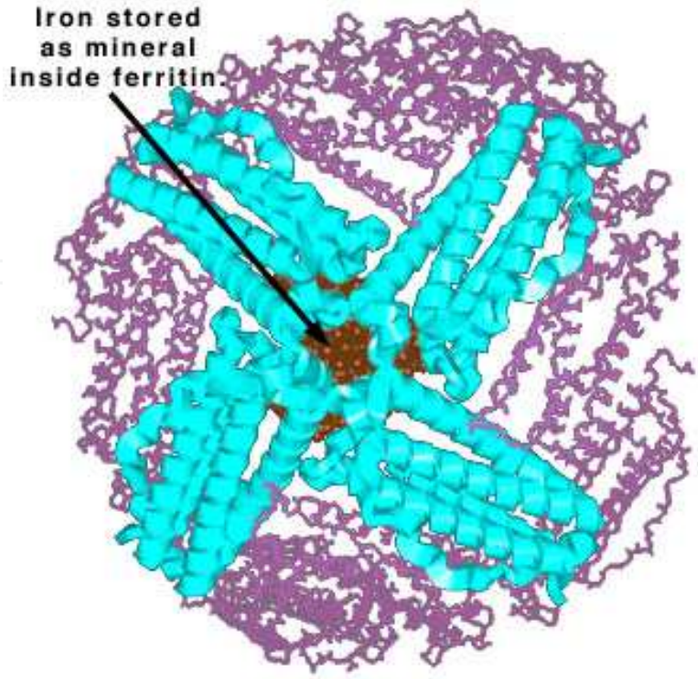


Fig. 3. Structure of ferritin showing the outer polypeptide shell with inner iron-core containing iron stored as mineral –ferric oxyhydroxyhydroxide phosphate $[(FeOOH)_8\ (FeO\text{-}OPO_3H_2)]$.

which can store upto 4500 iron atoms as hydrous ferric oxide. The ratio of iron to polypeptide is not constant, since the protein has the ability to gain and release iron according to physiological needs. Channels from the surface permit the accumulation and release of iron. All iron-containing organisms including bacteria, plants, vertebrates and invertebrates have ferritin [4,5].

Ferritin from humans, horses, pigs and rats and mice consists of two different types of subunits- H subunit (*heavy; 178 amino acids)* and L *(Light, 171 amino acids)* that provide various isoprotein forms. H subunits predominate in nucleated blood cells and heart. L –subunits in liver and spleen. H-rich ferritins take up iron faster than L-rich *in –vitro* and may function more in iron detoxification than in storage [6]. Synthesis of the subunits is regulated mainly by the concentration of free intracellular iron. The bulk of the iron storage occurs in hepatocytes, reticuloendothelial cells and skeletal muscle. When iron is in excess, the storage capacity of newly synthesized apoferritin may be exceeded. This leads to iron deposition adjacent to ferritin spheres. This amorphous deposition of iron is called **hemosiderin** and the clinical condition is termed as hemosiderosis.

Multiple genes encode the ferritin proteins, at least in animals, which are expressed in a cell-specific manner. All cells synthesize ferritin at some point in the cell cycle, though the amount may vary depending on the role of the cell in iron storage, i.e housekeeping for intracellular use or specialized for use by other cells.

Expression of ferroportin (FPN) results in export of cytosolic iron and ferritin degradation. FPN-mediated iron loss from ferritin occurs in the cytosol and precedes ferritin degradation

by the proteasome. Depletion of ferritin iron induces the monoubiquitination of ferritin subunits. Ubiquitination is not required for iron release but is required for disassembly of ferritin nanocages, which is followed by degradation of ferritin by the proteasome [7].

iii. Myoglobin

Myoglobin is an iron- and oxygen-binding protein found in the muscle tissue of vertebrates in general and in almost all mammals. It is a single-chain globular protein of 153 or 154 amino acids [8,9], containing a heme prosthetic group in the center around which the remaining apoprotein folds. It has eight alpha helices and a hydrophobic core. It has a molecular weight of 17,699 daltons (with heme), and is the primary oxygen-carrying pigment of muscle tissues [9]. Unlike the blood-borne hemoglobin, to which it is structurally related [10], this protein does not exhibit cooperative binding of oxygen, since positive cooperativity is a property of multimeric /oligomeric proteins only. Instead, the binding of oxygen by myoglobin is unaffected by the oxygen pressure in the surrounding tissue. Myoglobin is often cited as having an "instant binding tenacity" to oxygen given its hyperbolic oxygen dissociation curve [Figure 4].

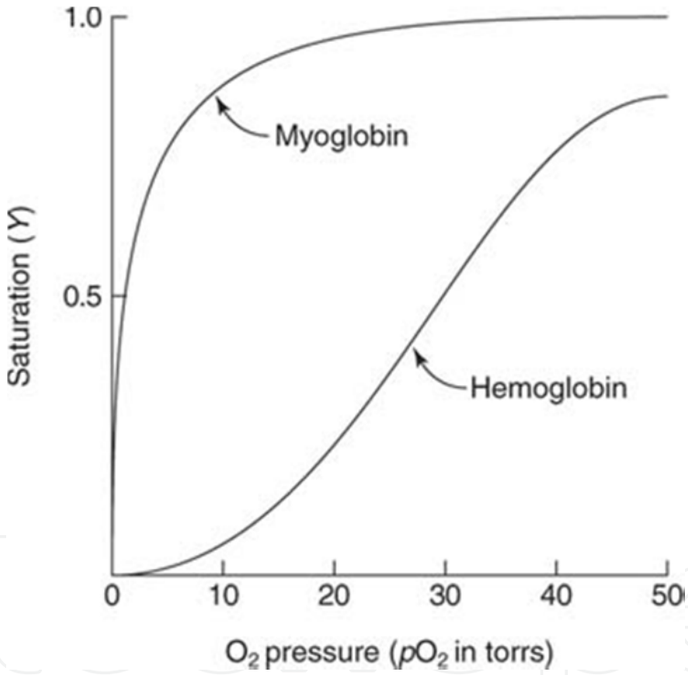


Fig. 4. Iron dissociation curve of hemoglobin and myoglobin.

iv. Transport Iron- Transferrin

Transferrin is a protein involved in the transport of iron. The transferrins are glycoproteins with molecular weight of approximately 80, 000 Da, consisting of a single polypeptide chain of 680 to 700 amino acids and no subunits. The transferrins consist of two non cooperative iron- binding lobes of approximately equal size. Each lobe is an ellipsoid of approximate dimensions 55 x35 x 35A^{o} and contains a metal binding site buried below the surface of the protein in a hydrophilic environment [Figure 5]. The two binding sites are separated by 42 A^{o} [11]. There is approximately 40% identity in the amino acid sequence between the two

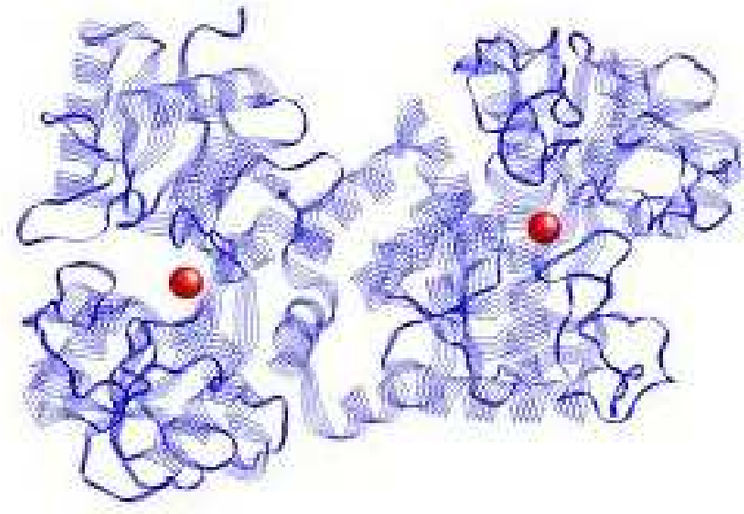


Fig. 5. Bilobar structure of Human transferrin

lobes [12, 13]. The protein is a product of gene duplication derived from a putative ancestral gene coding for a protein binding only one atom of iron.

The transferrins are highly cross-linked proteins, the number of disulfide bridges varying between proteins and between domains within each protein. There are six disulfide bonds conserved in each of the two-domains of all the transferrins, plus additional ones for the individual proteins. Human serum transferrin is the most cross- linked, having 8 and 11 disulfide bridges in the N- and C- terminal metal-binding lobes. The transferrins, with the exception of lactoferrin, are acidic proteins, having an isoelectric point (pI) value around 5.6 to 5.8.

Several metals bind to transferrin; the highest affinity is for Fe^{3+}; Fe^{2+} ion is not bound. Various spectroscopic and chemical modification studies have implicated histidine, tyrosine, water (or hydroxide) and (bi) carbonate as ligands to the Fe^{3+} in the metal-protein complex.

The transferrins are unique among proteins in their requirement of coordinate binding of an anion (bicarbonate) for iron binding [14,15]. Several studies suggest that the bicarbonate is directly coordinated to the iron, presumably forming a bridge between the metal and a cationic group on the protein. In the normal physiological state, approximately one-ninth of all the transferrin molecules are saturated with iron at both sides; four-ninths of transferrin molecules have iron at either site; and four-ninth of transferrin molecules are free of iron.

Transferrin delivers iron to cells by binding to specific cell surface receptors (TfR) that mediate the internalization of the protein. The TfR is a transmembrane protein consisting of two subunits of 90,000 Da each, joined by a disulfide bond. Each subunit contains one transmembrane segment and about 670 residues that are extracellular and bind a transferrin molecule, favoring the diferric form. Internalization of the receptor- transferrin complex is dependent on receptor phosphorylation by a Ca^{2+}- Calmodulin- protein kinase C complex. Release of the iron atoms occurs within the acidic milieu of the lysososme after which the receptor- apotransferrin complex returns to the cell surface where the apotransferrin is released to be reutilized in the plasma [Figure 6]. Inside the cell, iron is used for heme synthesis within the mitochondria, or is stored as ferritin.

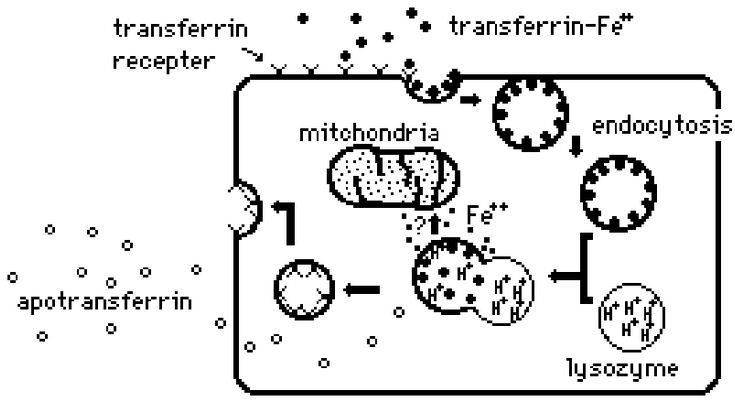


Fig. 6. Cellular uptake of iron by transferrin receptor

v. Labile iron Pool

The uptake and storage of iron is carried out by different proteins, hence a pool of accessible iron ions, called labile iron pool (LIP) exists, that constitutes crossroads of the metabolic pathways of iron containing compounds [16]. The LIP is localized primarily but not exclusively, within the cytoplasm of the cells. It is bound to low-affinity ligands [17] and is accessible to permeant chelators and contains the cells' metabolically and catalytically reactive iron. LIP is maintained by a balanced movement of iron from extra- and intracellular sources [18].

The trace amounts of "free" iron can catalyse production of a highly toxic hydroxyl radical via Fenton/Haber-Weiss reaction cycle. The critical factor appears to be the availability and abundance of cellular labile iron pool (LIP) that constitutes a crossroad of metabolic pathways of iron-containing compounds and is midway between the cellular need of iron, its uptake and storage. To avoid an excess of harmful "free" iron, the LIP is kept at the lowest sufficient level by transcriptional and posttranscriptional control of the expression of principal proteins involved in iron homeostasis [19].

vi. Other heme proteins and flavoproteins

Certain enzymes also contain heme as part of their prosthetic group (e.g. catalase, peroxidases, tryptophan pyrrolase, guanylate cyclase, Nitric oxide synthase and mitochondrial cytochromes).

Iron readily forms clusters linked to the polypeptide chain by thiol groups of cysteine residues or to non-proteins by inorganic sulphide and cysteine thiols leading to generation of iron- sulphur clusters. Examples of iron-sulphur proteins are the ferredoxins, hydrogenases, nitrogenases, NADH dehydrogenases and aconitases. Structure of most of these proteins dictates their function.

4. Physiological turnover of iron in the body

Daily requirements for iron vary depending on the person's age, sex and physiological status. Although iron is not excreted in the conventional sense, about 1 mg is lost daily

through the normal shedding of skin epithelial cells and cells that line the gastrointestinal and urinary tracts. Small numbers of erythrocytes are lost in urine and feces as well. Humans and other vertebrates strictly conserve iron by recycling it from senescent erythrocytes and from other sources. The loss of iron in a typical adult male is so small that it can be met by absorbing approximately 1 mg of iron per day [20] [Figure 7]. In comparison, the daily iron requirement for erythropoiesis is about 20 mg. Such conservation of iron is essential because many human diets contain just enough iron to replace the small losses. However, the blood lost in each menstrual cycle drains 20 to 40 mg of iron, so women in their reproductive years need to absorb approximately 2 mg of iron per day. However, when dietary iron is more abundant, absorption is appropriately attenuated.

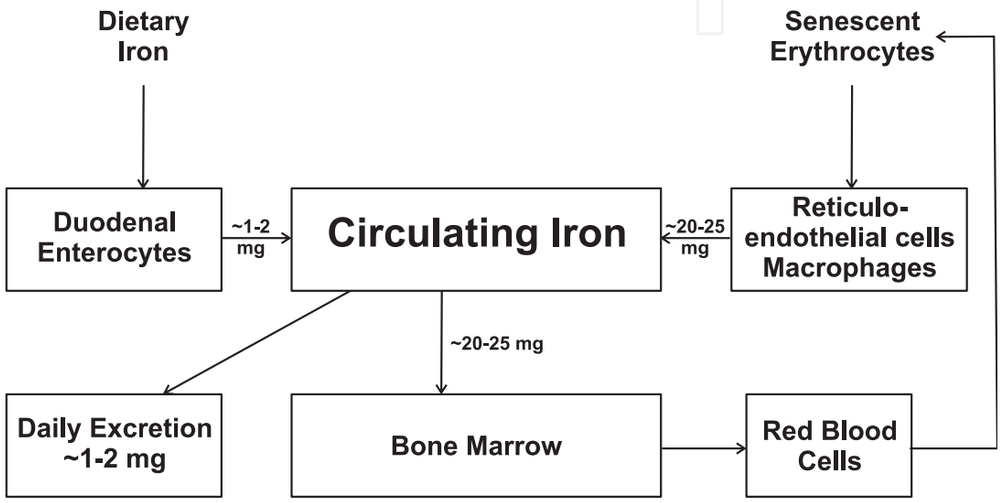


Fig. 7. Diagram showing the physiological turnover of iron in the body

5. Mechanisms regulating Iron absorption

The iron stores in the body are regulated by intestinal absorption. Intestinal absorption of iron is itself a regulated process and the efficacy of absorption increases or decreases depending on the body requirements of iron.

The dietary iron, which exists mostly in the ferric form, is converted to the more soluble ferrous form, which is readily absorbed. The ferric form is reduced to ferrous by the action of acids in stomach, reducing agents such as ascorbic acid, cysteine and –SH groups of proteins. Entry of Fe^{3+} into the mucosal cells may be aided by an enzyme on the brush-border of the enterocyte (the enzyme possesses ferric reductase activity also). The ferrous ion is then transported in the cell by a divalent metal transporter (DMT1) [Figure 8].

In the intestinal cell, the iron may be (a) stored by incorporation into ferritin in those individuals who have adequate plasma iron concentration. A ferroxidase converts the absorbed ferrous iron to the ferric form, which then combines with apoferritin to form ferritin, or (b) transported to a transport protein at the basolateral cell membrane and released into the circulation. However, the basolateral-transport protein has not yet been identified, It is believed to work in combination with hephaestin, a copper-containing protein, which oxidizes Fe^{2+} back to Fe^{3+} .

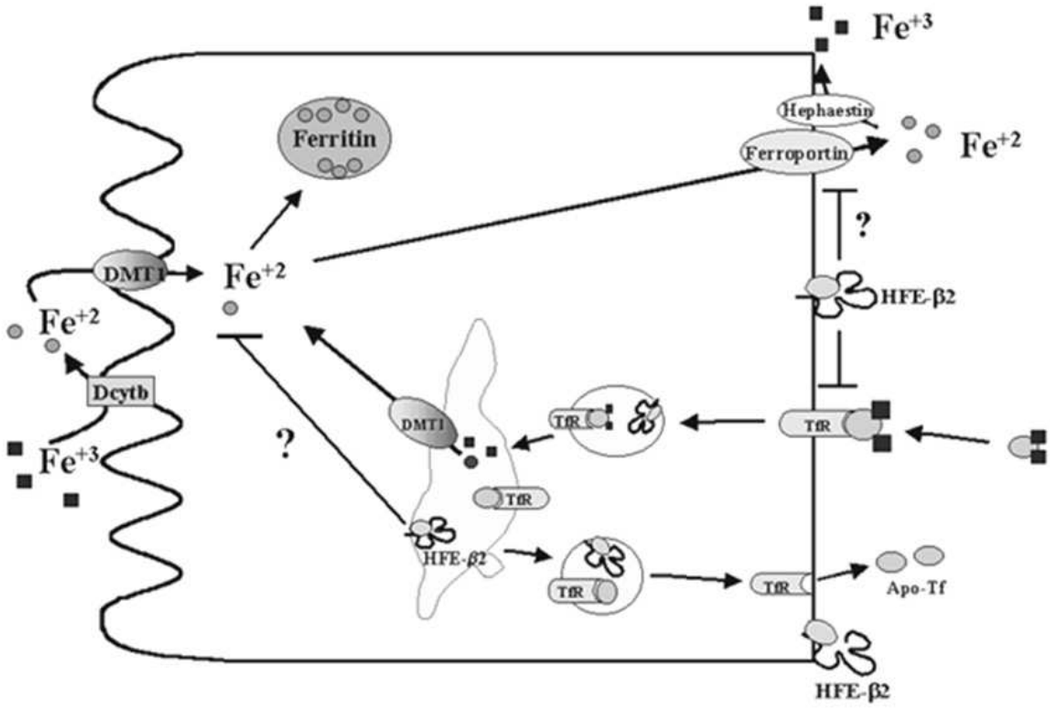


Fig. 8. Mechanism of intestinal Iron absorption

The intestinal cells internalize more iron than the amount that will eventually enter the circulation. The surplus, incorporated into ferritin for storage, is subsequently mobilized, if necessary. The ferritin stores are gradually built up, but most are lost when the mucosal cells are shed.

Thus during the dietary iron absorption, iron needs to traverse both the apical and basolateral membranes of absorptive epithelial cells in the duodenum to reach the blood, where it is incorporated into transferrin. The transport of non-heme iron across the apical membrane occurs via the divalent metal transporter 1 (DMT1), the only known intestinal iron importer. Dietary non-heme iron exists mainly in ferric form (Fe^{+3}) and must be reduced prior to transport. Duodenal cytochrome B (DcytB) is one of the major reductases localized in the apical membrane of intestinal enterocytes [21]. A heme protein, Dcytb, is upregulated by conditions that stimulate iron absorption, including iron deficiency, chronic anaemia and hypoxia. The mechanism by which its expression is upregulated in these conditions is unclear, as there are no obvious IREs in the mRNA of Dcytb. Nevertheless, the localization of Dcytb on the brush border of duodenal enterocytes closely mirrors that of DMT1, supporting the concept that Dcytb supplies ferrous iron to DMT1.

In addition, iron is also absorbed as heme. The transporter responsible for heme uptake at the apical membrane has not yet been conclusively identified. Cytosolic iron in intestinal enterocytes can be either stored in ferritin or exported into plasma by the basolateral iron exporter ferroportin (FPN). FPN is most likely the only cellular iron exporter in the duodenal mucosa as well as in macrophages, hepatocytes and the syncytial trophoblasts of the placenta. The export of iron by FPN depends on two multicopper oxidases, ceruloplasmin (Cp) in the circulation and hephaestin on the basolateral membrane of enterocytes, which convert Fe^{+2} to Fe^{+3} for incorporation of iron into transferrin (Tf).

Intestinal iron absorption is dependent on the body iron needs and is a tightly controlled process. Recent studies indicate that this process is accomplished by modulating the expression levels of DMT1, DcytB and FPN by multiple pathways.

Iron regulatory proteins (IRPs) are essential for intestinal iron absorption. DMT1 mRNA has an iron responsive element (IRE) at the 3'UTR and is stabilized upon IRP binding. In contrast, FPN mRNA has IRE at the 5'UTR and IRP binding inhibits translation. Specific intestinal depletion of both IRP1 and IRP2 in mice markedly decreases the DMT1 and increases FPN, resulting in the death of the intestinal epithelial cells [22]. The mice die of malnutrition within two weeks of birth, underscoring the importance of these proteins. These results demonstrate the critical role of IRPs in the control of DMT1 and FPN expression. A novel isoform of FPN lacking an IRE was recently identified in enterocytes [23]. This FPN isoform is hypothesized to allow intestinal cells to export iron into the body under low iron conditions. DMT1 also expresses multiple isoforms with and without 3'IRE. The IRP/IRE regulatory network is described in detail in the subsequent chapters.

Secondly, the hypoxia-inducible factor (HIF)-mediated signaling plays a critical role in regulating iron absorption. Two studies [24,25] show that acute iron deficiency induces HIF signaling via HIF-2α in the duodenum, which upregulates DcytB and DMT1 expression and increases iron absorption. A conditional knockdown of intestinal HIF-2α in mice abolishes this response. In addition to DMT1 and FPN, both HIF signaling and IRP1 activation are associated with the regulation of iron absorption [26, 27]. HIF-2α mRNA contains an IRE within its 5'-UTR [26]. Under conditions of cellular hypoxia, HIF-2α is derepressed through the inhibition of IRP-1–dependent translational repression [27].

Thirdly, FPN protein is negatively regulated by hepcidin, a critical and one of the most important iron regulatory hormones, predominantly secreted by liver hepatocytes. Thus, intestinal iron absorption is coordinately regulated by several signaling pathways and is sensitive to hypoxia by HIF-2α, enterocyte iron levels by IRP/IRE and bodily iron levels by hepcidin.

Although iron uptake into the body is tightly controlled, iron loss does not appear to be regulated. Under normal conditions iron is excreted through blood loss, sweat, and the sloughing of epithelial cells. These losses amount to approximately 1 to 2 mg of iron per day. Under certain pathological states, Tf, and therefore iron, can be lost when the kidney fails to reabsorb proteins from the urinary filtrate. These proteinurea syndromes result from the lack of functional cubulin, megalin, or ClC-5 [28]. Cubulin and megalin are protein scavenging receptors, whose function in the proximal renal tubule is the reuptake of nutrients from the urinary filtrate. ClC-5, a voltage-gated chloride channel, is required for the acidification of endocytic vesicles and the release of iron from Tf.

6. Mechanisms of cellular iron transport and uptake

(This section is only briefly described here. The topic is discussed in detail in subsequent chapter by Dr Sanchez etal).

The abundance and availability of transferrin receptor for cellular iron uptake is regulated by cellular iron status. Cellular iron content determines the composition of a cytosolic protein termed iron regulatory protein 1 (IRP1). Under iron-replete conditions, IRP1

contains a 4Fe–4S cluster that is unable to bind to iron-responsive elements (IRE) in the mRNAs of TfR1 and ferritin. When cellular iron content is low, the iron–sulphur cluster is disassembled, liberating an apo-IRP that binds to specific stem–loop structures in the 3′ or 5′ untranslated regions (UTRs) of the mRNAs encoding these proteins. In the case of TfR1, the IREs are located in the 3′ UTR, and binding of IRP1 increases the stability of the message and enhances the synthesis of TfR1.

Conversely, binding of IRP1 to the IREs in the 5′ UTR of ferritin mRNA mediates translation repression. Thus, under iron replete conditions, there is more rapid turnover of TfR1 mRNA, leading to diminished translation and cell-surface expression of TfR1, reduced uptake of transferrin-bound iron and an expanded capacity for iron storage through increased synthesis of ferritin. Hepatic transferrin receptor (TfR2) expression is not downregulated by iron overload [29]. Given that the liver is a major site for iron storage, the high level of expression of TfR2 and its lack of responsiveness to iron status might be viewed as a protective mechanism, selectively diverting iron to hepatocytes under conditions in which circulating levels of transferrin bound iron are high and peripheral iron stores are replete.

In normal individuals, nearly all cellular acquisition of iron from blood occurs via transferrin receptor-mediated uptake, since most of the iron in circulation is bound to transferrin. In circumstances in which the binding capacity of transferrin becomes saturated, as in case of iron loading disorders, iron forms low-molecular-weight complexes, the most abundant being iron citrate. It has been known for years that hepatic clearance of this non-transferrin-bound iron (NTBI) is rapid and highly efficient. Furthermore, studies in isolated perfused rat livers and cultured hepatocytes indicated that hepatic uptake of NTBI involves a membrane carrier protein whose iron transport function is subject to competition by other divalent metal ions. Based on these characteristics, it appears that the recently discovered divalent metal transporter 1 (DMT1; also known as DCT1 and Nramp-2) is the major transporter accounting for hepatic uptake of NTBI. Using a cDNA library prepared from iron-deficient rat intestine, the DMT1 transcript was identified by its ability to increase iron uptake in *Xenopu*s oocytes [30]. DMT1 has subsequently been shown to transport various divalent metal ions in a manner that is coupled to the transport of protons. Although DMT1 mRNA is broadly expressed in mammalian tissues including liver, its highest level of expression is found in the proximal intestine, consistent with its role in the absorption of dietary non-heme iron. Two isoforms of DMT1 have been described. The form of DMT1 that predominates in the intestine has an IRE in its 3′ UTR, indicating that the stability of this transcript is regulated by cellular iron status in a manner similar to that of TfR1. Reciprocal changes in duodenal DMT1 expression *vis-àvis* iron status have been demonstrated in iron-deficient rats and in humans with iron deficiency and iron overload [31].

Collectively, these data provide evidence for a negative feedback loop in which iron status regulates intestinal DMT1 expression, which in turn controls iron uptake.

7. Mechanism of iron mobilization and export from storage sites

Liver is the main site of iron storage under physiological conditions, hence various mechanisms regulate the mobilization and export of stored iron from liver to extrahepatic tissues. Under normal physiological circumstances, Kupffer cells play a prominent role in

inter organ iron trafficking. One of the primary sites of erythrocyte turnover, Kupffer cells, along with the reticuloendothelial cells of the spleen and bone marrow, ingest senescent or damaged red blood cells, catabolize the haemoglobin and release the iron. Collectively, the quantity of iron that is recycled from erythrocytes through the macrophage compartment on a daily basis is several fold greater than that taken up through the intestine. Hence, the contribution of Kupffer cells to total body iron economy is both qualitatively and quantitatively important. It is therefore not surprising that Kupffer cells are the major type of liver cell that express a recently described iron exporter, FPN (also known as Ireg1 and MTP1) [32-34]. Consistent with its role in iron absorption, FPN is expressed at high levels along the basolateral membrane in mature enterocytes of the duodenal villi. In the intestine, FPN expression is upregulated by iron deficiency and anaemia. In addition, FPN transcripts are also detected in liver, spleen, kidney and placenta. In murine liver, hepatocytes as well as Kupffer cells show immunoreactivity for FPN, albeit less intense. The quantitative PCR study on isolated cells from rat livers discussed above reported similar levels of FPN transcripts in hepatocytes, Kupffer cells and stellate cells, and lower levels in sinusoidal endothelial cells [35]; however, FPN protein has not been demonstrated in the last two cell types. Interestingly, the subcellular localization of FPN appears to differ between hepatocytes and Kupffer cells, being localized to the plasma membrane along the sinusoidal border in the former and cytoplasmic in the latter [34]. It has been proposed that the intracellular localization of FPN in Kupffer cells (which is also observed in RAW267.4 cells, a murine macrophage cell line) indicates that FPN does not directly export iron across the plasma membrane in these cells but, rather, that it may participate in intracellular trafficking of iron, perhaps through the secretory pathway. Further studies are needed to determine whether FPN is involved in multiple pathways of iron export.

Like cellular uptake of iron, efflux of iron from cells requires ferroxidase activity. It has been known for some time that ceruloplasmin, a copper-containing plasma ferroxidase synthesized by hepatocytes, plays an important role in iron homeostasis. Aceruloplasminaemia results in a form of iron overload that is recapitulated in mice with a targeted disruption of the ceruloplasmin gene [36]. Interestingly, although the ceruloplasmin knockout mice accumulate iron in both hepatocytes and Kupffer cells, intestinal iron absorption is unaffected by ceruloplasmin deficiency. This observation could probably be explained by the recent demonstration of ceruloplasmin homologue, termed hephaestin in the intestinal villi. Despite their similarities, the function of hephaestin is distinct from that of ceruloplasmin,as mutations in hephaestin lead to iron deficiency rather than iron overload.

In this context, it is interesting to contrast hepatocytes, which have low levels of FPN protein and lack detectable hephaestin transcripts, with Kupffer cells, which have higher levels of FPN and express hephaestin transcripts, at levels that are considerably lower than the intestine [35]. Taken together, these observations suggest that the ferroxidase activity of ceruloplasmin can indeed substitute for hephaestin in FPN-expressing cells in the liver (but not in the intestine). Another possibility is that hepatocytes and Kupffer cells may employ additional means to promote iron export, such as upregulation of hephaestin in response to iron loading and/or the expression of alternative exporters or ferroxidases.

A major advance in the understanding of iron metabolism was the discovery of the iron regulatory hormone hepcidin nearly 10 years ago. Hepcidin was originally identified as an

antimicrobial peptide isolated from human urine [37]. The liver is the predominant source of hepcidin, where the 84-amino-acid prepropeptide is synthesized and cleaved to yield 20- and 25-amino-acid peptides that are released into the circulation and filtered by the kidney. Consistent with release into the blood from hepatocytes, hepcidin immunoreactivity is observed along the sinusoidal borders of hepatocyte membranes, with accentuated staining of periportal (zone 1) hepatocytes which decreases towards the central vein and sinusoids [38].

Hepcidin acts as a systemic iron-regulatory hormone as it controls iron transport from iron-exporting tissues into plasma [39]. [Figure 9] Studies have demonstrated that hepcidin knockout mice develop a form of iron overload reminiscent of hereditary haemochromatosis [40], while mice with over expression of hepcidin have severe iron-deficiency anaemia [41]. Hepcidin inhibits the intestinal absorption [37,41], macrophage release [42,43] and placental passage [41] of iron. A pharmacodynamic study of the effects of a radiolabelled hepcidin injection in mice, showed that a single 50 μg dose resulted in 80% drop in serum iron within 1 h which did not return to normal until 96 hours [44]. This time course is consistent with the blockage of recycled iron from macrophages and previous reports of the rapid hepcidin response to IL-6 administration [45]. The rapid disappearance of plasma iron was followed by a delayed recovery, possibly due to the slow resynthesis of membrane FPN. Tissue concentrations revealed that hepcidin preferentially accumulates in the proximal duodenum and spleen, reflecting the high expression of FPN in these areas.

Hepatocytes evaluate body iron status and release or downregulate hepcidin according to the iron status of the body [Figure 9]. An oral load of 65 mg of iron in healthy volunteers caused > 5-fold increase in hepcidin within 1 day [45]. Hepcidin mRNA moves with the

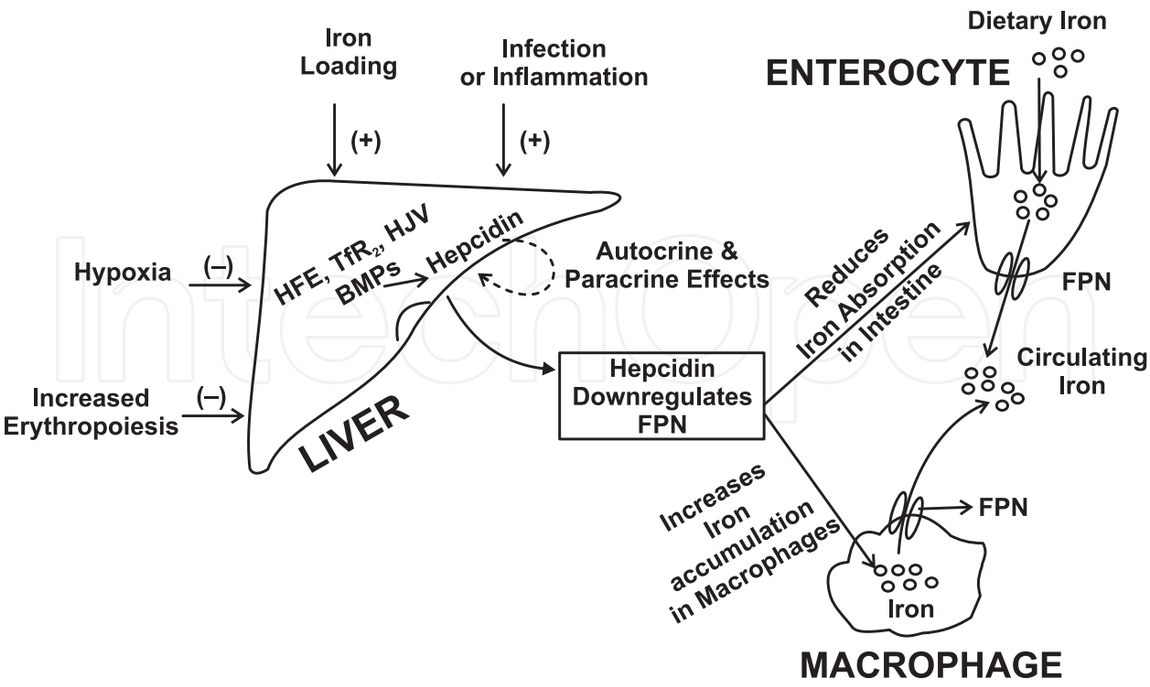


Fig. 9. Schematic Diagram showing the regulation of circulating iron levels by Hepcidin

body's iron levels, increasing as they increase and decreasing as they decrease [46]. Hepcidin regulates iron uptake constantly on a daily basis, to maintain sufficient iron stores for erythropoiesis [47], as well as its feedback mechanism to prevent iron overload. Hepcidin negatively regulates the uptake of iron by Tf, the major iron transport protein in the blood. Since Tf is the major source of iron for hemoglobin synthesis by red blood cell precursors, increased hepcidin limits erythropoiesis and is a major contributor to the anemia of chronic disease [48]. In humans, patients with large hepatic adenomas found to overexpress hepcidin, had a severe iron refractory microcytic anaemia, which was corrected by removal of the adenoma [49].

Recent studies have provided insight into the mechanisms by which hepcidin modulates iron absorption. Within a week of being placed on a low-iron diet, rats show a twofold increase in intestinal iron absorption that is temporally associated with a significant drop in hepatic hepcidin expression, and increases in duodenal mRNAs for Dcytb, DMT1 and FPN [50]. Although the increase in FPN mRNA under these circumstances is of relatively small magnitude, the increase in FPN protein is more substantial. A similar pattern is seen in the intestine of hepcidin knockout mice, providing additional evidence that hepcidin suppresses the expression of these iron transporters. While the role of hepcidin in the regulation of Dcytb and DMT1 has not been characterized, several reports have established that FPN is a major target of hepcidin's action. As suggested by the observations discussed above, hepcidin appears to regulate FPN expression by two distinct mechanisms. The first is at the level of FPN transcripts, which are decreased following stimulation of endogenous hepcidin production or administration of recombinant hepcidin [51]. The second involves binding of hepcidin to FPN at the cell membrane, causing internalization and degradation of FPN, thus diminishing iron transfer [39, 52,53]. These mechanisms are clearly not mutually exclusive and, either or both may probably contribute to the decrease in intestinal iron absorption in response to hepcidin. However, it is unclear at present whether FPN expression in liver cells is regulated in the same manner. In mice treated with iron, intestinal FPN expression is low, consistent with the known effects of hepcidin. In the liver, however, FPN is increased, particularly in Kupffer cells [34]. This may result from enhanced translation due to the presence of the IRE in the 5′ UTR of FPN mRNA. If so, this effect must predominate over the hepcidin-induced increase in FPN turnover. Alternatively, the distinctive intracellular pattern of FPN in Kupffer cells implies that FPN may not physically interact with hepcidin in macrophages, again raising the possibility of differential regulation of FPN in liver vs. intestine.

Hepcidin inhibits the release of iron by macrophages and lessens the iron uptake in the gut by diminishing the effective number of iron exporters on the membrane of enterocytes or macrophages. In FPN mutations it has been observed that iron accumulates mainly in macrophages and is often combined with anemia [54].

The development of iron overload in hepcidin knockout mice [40] and humans with mutations in the hepcidin gene [55] is clearly explicable by the effects of hepcidin on intestinal iron absorption. Since the discovery of hepcidin, several authors have reported that hepcidin expression fails to increase in response to increased iron stores in other disease states characterized by iron loading. For example, hepcidin expression is inappropriately low in iron-loaded subjects with hereditary haemochromatosis [56] and haemojuvelin (HJV) mutations [57]. Similar findings are reported in a variety of iron-loading anaemias [58]. Under physiological conditions, hepatic hepcidin expression is regulated by a cohort of

proteins that are expressed in hepatocytes, including the hereditary hemochromatosis (HH) protein called HFE, transferrin receptor 2 (TfR2), hemojuvelin (HJV), bone morphogenetic protein 6 (BMP6), matriptase-2 and Tf. Hepcidin expression can also be robustly regulated by erythroid factors, hypoxia, and inflammation, regardless of body iron levels. The inappropriately low levels of hepcidin production in HFE-associated Hereditary Hemochromatosis (HH) suggest that HFE is upstream of hepcidin in the molecular regulation of hepcidin production [59]. Similarly, the HJV gene, which is mutated in Juvenile Hemochromatosis [JH] , is associated with low hepcidin levels [60], suggesting regulation proximal to hepcidin. Type 3 haemochromatosis is due to homozygous mutations in TfR2, a membrane glycoprotein that mediates cellular iron uptake from transferrin. TfR2 mutant mice have low levels of hepcidin mRNA expression, even after massive intraperitoneal iron loading also suggestive of iron modulation proximal to hepcidin [61]

It is possible that hepcidin is the common pathway modulating iron absorption via HFE, TfR2 and HJV, mutations of which all result in an iron overload phenotype. Mutations in these proteins, or their genetic ablation, result in diminished hepcidin expression, indicating that they positively regulate hepcidin production. Signaling through the BMP pathway has been shown to be a central axis for hepcidin regulation. BMPs (such as BMP2, 4, 6, or 9) are secreted soluble factors that interact with cell-surface BMP receptors, initiating an intracellular signaling cascade that activates hepcidin transcription [62].

In vivo, BMP6 seems especially important for iron homeostasis; because Bmp6-null mice display reduced hepcidin expression and iron overload [63]. Efficient BMP signaling through BMP receptor requires HJV, a 50-kDa protein with a glycosylphosphatidylinositol (GPI) anchor that tethers the protein to the extracellular surface of the plasma membrane. This membrane-bound hemojuvelin (m-HJV) is capable of binding BMPs, facilitating their association with the BMP receptor [64]. As such, m-HJV is often referred to as a BMP co-receptor. The potent contribution of m-HJV to BMP-mediated hepcidin activation is illustrated by mutations in HJV that abrogate cell surface expression. Individuals with such mutations develop juvenile hemochromatosis, characterized by exceedingly low serum hepcidin concentrations (<5 ng/mL) [65] and severe hepatic iron overload.

Several studies have proved that there is local production of hepcidin by macrophages [74], cardiomyocytes [66] and fat cells [67], suggesting that hepcidin is involved in different regulatory mechanisms to control iron imbalance. Apart from this, few studies have proposed that hepcidin might also directly inhibit erythroid-progenitor proliferation and survival [68]. At the same time hepcidin synthesis is increased by iron loading and decreased by anemia and hypoxia [69]. Anemia and hypoxia are associated with a dramatic decrease in liver hepcidin gene expression, which may account for the increase in iron release from reticuloendothelial cells and increase in iron absorption frequently observed in these situations [47].

HFE is highly expressed in the liver as well as the intestine and is involved in regulation of iron metabolism. Originally identified on the basis of a high frequency of HFE mutations in patients with genetic haemochromatosis, wild-type HFE protein forms a complex at the plasma membrane with TfR1 and β2-microglobulin [Figure 8]. Studies in transfected cells indicate that the stoichiometry of these components influences the rate of recycling of TfR1, thus modulating iron uptake [70]. Nonetheless, the precise mechanism whereby HFE mutations lead to iron loading remains speculative. While immunohistochemistry for HFE

demonstrates a distinctive pattern of intracellular perinuclear staining in the epithelial cells of the small intestine [71], immunoreactivity for HFE in liver has been variously ascribed to bile ducts, sinusoidal lining cells, Kupffer cells and endothelial cells. Furthermore, these studies are at variance with results of PCR and Western blot analysis of isolated liver cells demonstrating that hepatocytes are the major source of HFE in rat liver, with a minor contribution from Kupffer cells [35]. Additional studies are needed to resolve this discrepancy and provide further insight into the function of HFE.

While the function of HJV is unknown, it has been proposed that HJV is 'upstream' of hepcidin in the pathways controlling iron metabolism, as both patients with iron overload resulting from HJV mutations and HJV knockout mice fail to respond to their iron burden with an appropriate increase in hepcidin. On treatment with parenteral iron in mice, hepatic expression of HJV is not altered despite an increase in hepcidin mRNA indicating that a direct interaction between these two proteins is unlikely. Thus, currently available studies demonstrate lack of responsiveness of HJV to iron as well as divergent regulation of HJV and hepcidin in normal animals treated with iron.

8. Conclusion

Iron is an essential element in the body but its effect in the body is like a two-edged sword. At one end it is essential for maintaining most of the body functions and at the other end it becomes potentially toxic if in excess. Thus, elaborate physiological mechanisms have evolved for regulation of uptake and disposition of iron. The earlier concept of regulation of iron levels by absorption could not explain several clinical conditions like hemochromatosis and severe anemias associated with chronic diseases and malignancies. However, a newer insight into the understanding of iron metabolism has been provided in the past few years, mainly as a result of the discovery of hepcidin, a key regulator of whole-body iron homeostasis.

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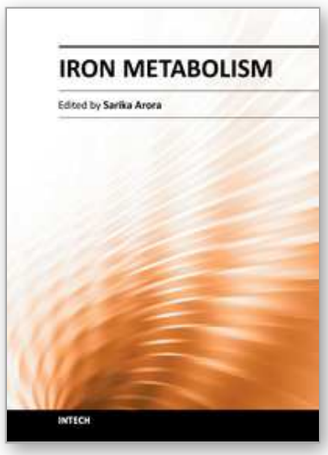
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Iron has various functions in the body, including the metabolism of oxygen in a variety of biochemical processes. Iron, as either heme or in its "nonheme" form, plays an important role in key reactions of DNA synthesis and energy production. However, low solubility of iron in body fluids and the ability to form toxic hydroxyl radicals in presence of oxygen make iron uptake, use and storage a serious challenge. The discovery of new metal transporters, receptors and peptides and as well as the discovery of new cross-interactions between known proteins are now leading to a breakthrough in the understanding of systemic iron metabolism. The objective of this book is to review and summarize recent developments in our understanding of iron transport and storage in living systems.

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