

Physiology of Iron Metabolism

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Summary

A revolution occurred during the last decade in the comprehension of the physiology as well as in the physiopathology of iron metabolism. The purpose of this review is to summarize the recent knowledge that has accumulated, allowing a better comprehension of the mechanisms implicated in iron homeostasis. Iron metabolism is very fine tuned. The free molecule is very toxic; therefore, complex regulatory mechanisms have been developed in mammalian to insure adequate intestinal absorption, transportation, utilization, and elimination. ‘Ironomics’ certainly will be the future of the understanding of genes as well as of the protein-protein interactions involved in iron metabolism.

Introduction

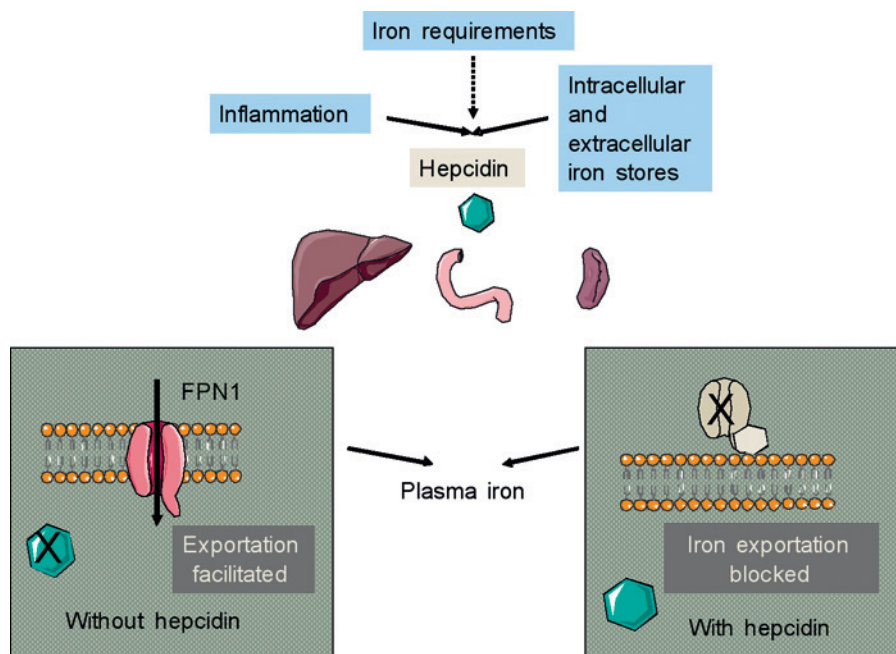
Various tests have been developed to evaluate iron metabolism and iron stores, and nowadays bone marrow examination has been replaced by the measurement of blood ferritin [1]. However, more sophisticated tests are available, notably measurements of transferrin (Tf), of soluble transferrin receptor (sTfR) or of hepcidin, reflecting dynamics of iron metabolism. In addition, many genetic variations of proteins, directly or indirectly involved in iron metabolism have been described, and their identification proved useful for the diagnosis of iron metabolic disorders [2–9].

Several papers addressed the question of genomics or of proteomics of iron metabolism in various organisms such as tomato [10] or *Arabidopsis* [11], but not in human. In vegetal biology, the term ‘ferromics’ has been coined; it covers all aspects of research unraveling the mysteries behind the perception and response to iron deficiency in plants [12]. It is a global approach, facilitated by the development of analytical and computational tools, that has allowed to decipher the biological processes assuring iron homeostasis in plants at the genomic, transcriptomic, and proteomic levels as well as to propose an integrative view on how plants respond to a varying supply of iron. The expression ‘ironomics’ has been used by investigators analyzing the role of iron transporters among *Yersinia pestis* biotypes and its nearest neighbor, *Yersinia pseudotuberculosis* [13], whereas the term ‘ironome’ was used by authors to describe iron metabolism and trafficking within cells and organelles [14, 15]. This review addresses some important physiologic pathways involved in iron metabolism of human that have relevance to transfusion medicine specialists in charge of donor management.

Iron Metabolism and Proteins

The physiology of iron trafficking and metabolism has been well evaluated over the last 20 years, and several comprehensive reviews have been published on the subject [16–22]. Many proteins have been identified playing roles in iron metabolism. Some proteins such as ferritin or Tf are the main cargos of blood iron, whereas peptides such as iron regulatory proteins (IRPs), hepcidin, and matriptase (Mt2) are key determinants of iron regulation at different physiological levels. A set of different proteins, notably divalent metal trans-

Fig. 1. Many mechanisms are involved in the regulation of hepcidin synthesis. The peptide is mainly produced by the liver, in responses to many different mechanisms. In presence of inflammation as well as in situations with increased intracellular and extracellular iron stores, the concentration of hepcidin is increased. Inversely, when iron requirements are high, such as in increased erythropoiesis, hepcidin levels are low. Hepcidin blocks the exportation of iron from hepatocytes, macrophages as well as from the enterocytes, by binding to ferroportin (FPN1) allowing its internalization and degradation (illustrations used elements from Servier Medical Art: www.servier.fr/servier-medical-art).



porter-1 (DMT1), ferroportin (FPN1), and transferrin receptors (TfRs) in association with ferroxidases such as duodenal cytochrome B, ceruloplasmin (Cp) and heme carrier protein (HCP1), are involved in the cellular membrane transportation of iron [23]. Others proteins such as myoglobin (Mb), Hb, and many different enzymes are the ‘end’ products of iron metabolism, because they require iron for their functions.

Hepcidin; the Queen of ‘Ironomics’

It is impossible to present a review dealing with iron metabolism without mentioning the central role of hepcidin as well as the pioneering works of Tomas Ganz and Elisabeta Nemeth. These two investigators, in collaboration with numerous other scientists, published about 100 scientific papers between 2003 and 2013, and more than a half of them contained the key word hepcidin. Hepcidin, is the biological equivalent of the Queen of the Night of the Mozart’s opera ‘The Magic Flute’; it is a 25 amino acid peptide hormone, mainly produced by hepatocytes (fig. 1). The peptide is encoded by the *HAMP* gene [24] which codes for the precursor protein pro-hepcidin which then is cleaved into the active hepcidin. Many mechanisms involved in the regulation of hepcidin synthesis in relation to iron have been elucidated [25–27]. Physiological and pathological conditions such as release of bone morphogenetic protein (BMP) [28], hypoxia [29, 30] as well as endocrine [31–34], metabolic [35, 36], and inflammatory [17, 37, 38] processes modulate hepcidin biosynthesis and may therefore regulate availability of iron to erythropoiesis by adaptation of iron absorption and recirculation.

A JAK-STAT3 pathway, triggered by IL-6 receptor dimerization with gp130 upon binding of the cognate ligand IL-6 is the primary pathway for hepcidin regulation in inflammation [39]. Iron sensing is dependent on an external pathway implicating the interactions of Tf on TfR1 and TfR2 and aid by the protein HFE. The binding of iron-loaded Tf to TfR1 followed by the binding of TfR2 depends on iron saturation of Tf; if iron-Tf is high, the TfR2-mediated signaling by theBMP6 receptor complex is increased.[40]. After activation of the BMP receptor, the SMAD pathway is activated leading to over-expression of hepcidin. In contrast, hepcidin mRNA is suppressed in anemia [59], but this effect is probably indirect, depending on the erythropoietin production [60]. Furthermore, at least 3 other proteins play roles by interacting between BMPs and the BMP receptor. The first protein is hemojuvelin (HJV) a glycosylphosphatidylinositol-linked membrane protein [41], the second is Mt2 [42], which regulates the levels of membrane-bound HJV, and the third is neogenin, a ubiquitously expressed transmembrane protein with multiple functions [43–48]. The gene of Mt2 carries several polymorphisms that have been linked to iron metabolic parameters, notably in patients presenting with iron-refractory iron-deficient anemia [49–58].

In blood, hepcidin exists in mature- and pro-hormone form (prohepcidin). Prohepcidin was found to specifically bind to the STAT3 site in the promoter of the *HAMP* gene, thus suggesting that prohepcidin affects the expression of its own gene, indicating an autoregulatory loop of hepcidin gene expression [24]. Using liquid chromatography in combination with high-resolution mass spectrometry, we and others were able to identify new forms of hepcidin in human plasma or serum samples [59, 60].

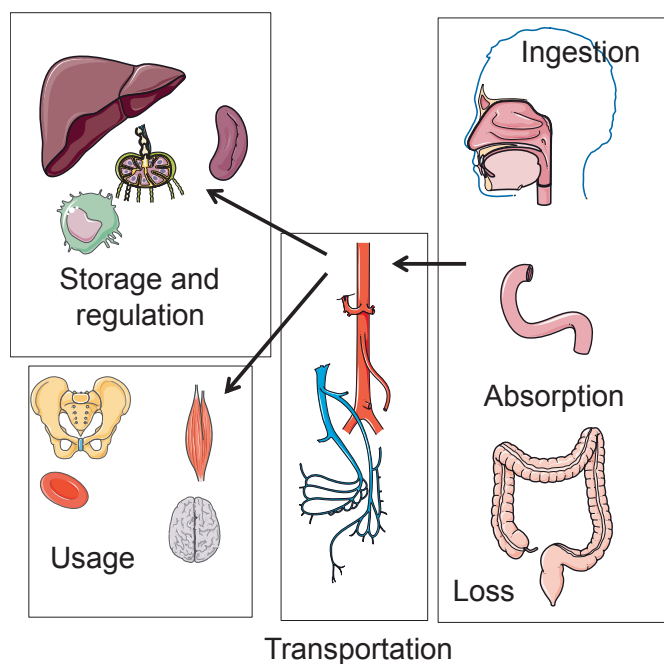


Fig. 2. Iron metabolism is finely regulated. Males contain about 4,000 mg of iron, of which 2,500 mg is within erythrocytes; 1,000 mg is stored in splenic and hepatic macrophages, and the rest is distributed in various proteins such as myoglobin, cytochromes or other ferroproteins. About 1–2 mg of iron is lost every day, through skin and enteric desquamation and minor blood losses. This loss is balanced by intestinal absorption. Therefore, iron recycling accounts for most of the iron homeostasis in human. The situation is different in menstruating women where there are discussions about iron stores, ferritin and hemoglobin levels (illustrations used elements from Servier Medical Art: www.servier.fr/servier-medical-art).

Iron Regulatory Proteins

Iron is present in many different types of cells, having specific functions such as iron supply or iron storage. Iron-exporting cells include enterocytes, which absorb iron from the digested food, macrophages and hepatocytes, which both recycle iron according to demand. In addition, placental syncytiotrophoblast cells transport iron into the fetal circulation. Cellular iron homeostasis is maintained by IRP1 and IRP2 (reviewed in [61]). IRPs bind to iron-responsive elements (IREs) located in the untranslated regions of genes and mRNAs encoding proteins involved in iron uptake, storage, utilization, and export. The IRP/IRE system is thus effectively involved in the fine-tuning of the synthesis as well as suppression of the many proteins involved in the multiple ‘ironomics’ pathways.

Iron in the Body

Males contain about 4,000 mg of iron, of which 2,500 mg are within erythrocytes; 1,000 mg is stored in splenic and hepatic macrophages, and the rest is distributed in various pro-

teins such as Mb, cytochromes, or other ferroproteins. Only about 3 mg are bound to plasma Tf and constitute the mobile iron compartment which supplies the various intracellular iron stores. Figure 2 presents the main steps of iron metabolism.

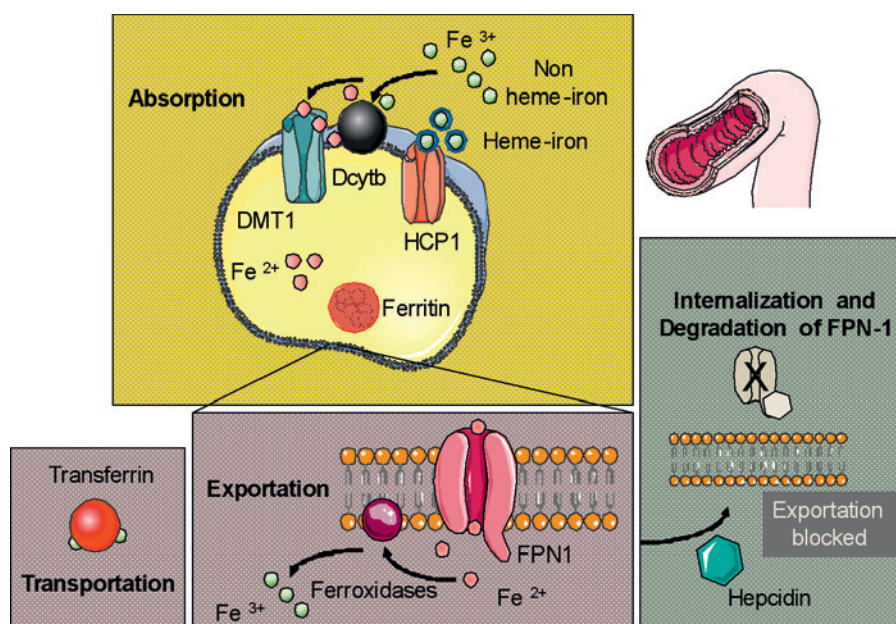
About 1–2 mg of iron is lost every day, through skin and enteric desquamation and minor blood losses. This loss is balanced by intestinal absorption. Therefore, iron recycling accounts for most of the iron homeostasis in human. The situation is different in menstruating women [62, 63] where there are controversial discussions about iron stores, ferritin, and Hb levels [64, 65]. It appears that lower Hb and ferritin values in menstruating women have been accepted as normal rather than possibly representing widespread iron deficiency. The situation is even more complex in pregnant women; nevertheless, iron substitution has been shown to be beneficial for them [66, 67]. Similarly, increased iron demand occurs during infancy and childhood due to growth and development demands [68–70].

Iron in the Food; Unusual Aspects

Iron is the most abundant element on earth, with potential of high toxicity to living cells. However, it has poor bioavailability, and efforts have been made to provide iron for everybody, notably by food fortification within rice [71], because it represents one of the most essential nutrients for human beings. Rice and most staple cereals contain low iron levels, since most iron-containing components are lost during grain processing. Populations with monotonous diets consisting mainly of cereals are especially prone to iron deficiency, which affects about two billion people.

Food fortification programs to supplement nutrition with iron have not been very successful. One alternative solution is iron biofortification. Different approaches have been studied, including conventional breeding and directed genetic modification, which offer the most rapid way to develop iron-rich rice plants [71]. Biofortification of crops is also an interesting approach [72], and at least two complementary approaches have been successfully adopted to increase the concentrations of bioavailable mineral elements in food crops. First, application of mineral fertilizers and/or improving the solubilization and mobilization of mineral elements in the soil has been implemented. Secondly, crops have been developed with increased abilities to acquire mineral elements and accumulate them in edible tissues. In the same context, it seems necessary to highlight the efforts made by some investigators, who developed high-iron rice, using transgenic approaches. They created high-iron rice by insertion of soybean ferritin gene under the control of the endosperm-specific glutelin promoter into the genome of the Indica rice line [73]. However, and because of widespread skepticism about transgenic food, it is still necessary to know the iron content of the usual food taken by our

Fig. 3. Regulation of iron absorption and exportation by enterocytes. Both heme and non-heme iron are absorbed by specific pathways, including divalent metal transporter-1 (DMT-1) and heme carrier protein (HCP1), in association with the ferrireductase, duodenal cytochrome B (Dcytb). Within the cell, iron can be stored within the ferritin molecule. The metal is exported by the protein ferroportin (FPN1), and transported into the blood by transferrin. In presence of hepcidin, ferroportin is internalized and degraded. Thus, iron exportation is blocked. Inversely, in the absence of hepcidin, ferroportin is maintained on the cell membrane, and iron transportation is facilitated (illustrations used elements from Servier Medical Art: www.servier.fr/servier-medical-art).



populations. This is why the knowledge of the iron content of various aliments as well as of the factors influencing its absorption should be improved [74].

Finally, from a hematologist point of view, universal iron fortification of the food may be problematic, notably for individuals with hemochromatosis and other iron loading diseases [75]. Even if iron fortification of food has been recognized by some authors as a suitable strategy to combat iron deficiency, some health authorities have abandoned it. Readers interested in iron fortification, iron food, and other deviancies are referred to the recent reviews published in 2012 [67, 76].

Intestinal Iron Absorption

A typical European diet provides about 15 mg of iron, and only 10% is absorbed. Iron absorption is the result of complex mechanisms that takes place in the upper parts of the gut, notably in the duodenum and the proximal jejunum [16, 77] (fig. 3).

On the brush border of enterocytes, various iron import proteins are present, and specific pathways of absorption have been described for the two ionic forms of iron (Fe^{2+} and Fe^{3+} ; both being non-heme iron molecules) and also for iron associated with heme (heme iron) [16]. Non-heme iron is associated with various storage proteins, including ferritin, whereas hemic iron is present within hemoproteins such as Mb or Hb. At acidic pH in the stomach, heme is dissociated from hemoproteins, whereas non-heme iron stabilizes in its reduced form (Fe^{2+}). It is important to note that non-heme iron is captured by several complexes which can interfere with its absorption, notably plant-derived phytates or tannins [78]. Ascorbic acid and other acidic components derived from the diet can increase iron absorption. Nevertheless, it is known that different

pathways exist for the absorption of non-heme iron and heme iron. The distinction is of potential interest, because it has been shown that high heme iron intake leads to increased body iron stores which are significantly associated with higher risk to develop type 2 diabetes mellitus [79]. In contrast, total dietary iron, non-heme iron, and intake of iron supplements were not associated with type 2 diabetes mellitus.

Several well regulated gate keeper proteins are expressed in the duodenum enterocytes and are differently regulated as compared to the same proteins in liver cells. DMT1 is the most important transporter of ferrous iron (Fe^{2+}), [80, 81]. Of note, ferric reductase activities due to duodenal cytochrome B [82] and STEAPs (six transmembrane epithelial antigen of the prostate proteins) [83] are present on the brush border of duodenum allowing reduction of ferric to ferrous iron, thus facilitating its absorption by DMT1.

Heme iron is an important nutritional source of iron in carnivores and omnivores that is more readily absorbed than non-heme iron derived from vegetables and grain. Most heme is absorbed in the proximal intestine, with absorptive capacity decreasing distally, and the role of specific proteins such as hephaestin has been deciphered [84, 85]. HCP1, which presents homology to bacterial metal-tetracycline transporters, mediates heme uptake by the cells at the luminal brush border membrane of duodenal enterocytes. HCP1 mRNA has been shown to be highly expressed in the duodenum and regulated by hypoxia and by IRPs.

Intestinal Iron Exportation

Once iron is present in the enterocyte, its fate depends on the iron pool within the cell. Iron has to be exported from

cells to the circulation, and a specific protein, FPN1, has been identified in this function. FPN1 is a multipass protein found in the basolateral membrane of the enterocytes. Furthermore, FPN1 is the unique iron export membrane protein that is present in large quantities on macrophages. Over-expression of FPN1 is induced by cellular iron, and it is suppressed by hepcidin. Hepcidin binds to cell surface FPN1 inducing its internalization which is followed by lysosomal degradation [21]. Thus, as a consequence, the iron efflux from enterocytes or macrophages is suppressed, leading to reduced iron absorption by duodenal enterocytes. Deletion of the *FPN1* gene results in a complete block of iron exportation associated with accumulation of the metal within enterocytes and macrophages [86].

Once exported by FPN1, iron needs to be transformed from the ferrous into the ferric form by ferroxidases such as Cp in order to bind iron to Tf (which can only fix Fe^{3+}). Without activity of ferroxidases, FPN1 is internalized and degraded [87, 88]. Thus, the ferroxidases at the cell surface mediate stability of FPN1. In humans with aceruloplasminemia, anemia is associated with impaired cellular iron export [89]. As previously mentioned, HCP1, which is also a ferroxidase, has also an important role during iron export from intestinal enterocytes and its subsequent loading to Tf. Structurally, the ectodomain of HCP1 resemble Cp [90].

Iron Transportation in Blood and Import

Tf is the main protein involved in iron transport in plasma. Normally, between 20 and 40% of the binding sites of the protein are occupied by ferric iron. The diagnostic value of Tf has just been reviewed [91]. It proved to be a useful parameter for assessing both iron deficiency and iron overload. The saturation of Tf is a strong indicator of iron overload. However, from a physiological point of view, the iron binding capacity of plasma Tf is often exhausted, with concomitant generation of non-Tf-bound iron (NTBI) as observed in transfused patients. Using fluorescent tracing of labile iron in endosomal vesicles and cytosol, Kloss-Brandstatter et al. [92] showed that NTBI fractions derived from sera of polytransfused thalassemia major patients entered cells via endocytosis.

Erythrocyte precursors restrictively take up iron by using Tfr, notably Tfr1, whereas hepatocytes and other non-erythroid cells are also able to use NTBI. Iron-Tf binds to Tfr, and the complexes are internalized within the cell by the endosomal recycling vesicles. Thus, the Tf cycle is dependent on the Tf-Tfr complex trafficking, involving internalization of the complex within endosome, followed by iron release upon acidification of the endosome and recycling of the Tf-Tfr complex to the cell surface. Each of these steps is mediated by a specific pathway and specific machinery [93–95]. Finally, at the cell surface, at neutral pH, Tf dissociates from Tfr, and is used to repeat the iron cycle. In addition, Tfr is cleaved and

shed as a soluble form (sTfr) into the extracellular and intravascular space. This shedding of Tfr1 is known for more than 30 years, and its assessment is well accepted as a diagnostic marker of iron-depleted erythropoiesis [96–98]. Very recently, the cleavage site as well as the cleaving proteases of membrane Tfr1 have been identified [99].

Intracellular Iron Storage

Only ferric iron is transported to the cytoplasm or to mitochondria. It is therefore mandatory to reduce ferrous irons; a family of ferrireductase has been identified. These proteins are known under the acronym STEAP. STEAP 1–4 are the most relevant [100], STEAP 3 being particularly important within erythroid precursors [101]. DMT1 is also an essential protein involved in iron transportation from vacuole into the cytoplasm [102]. In macrophages, another protein (Nramp1) is involved [103, 104]. Due to its toxicity, iron within the cytoplasm is associated with proteins such as poly(RC)-binding protein 1 [105], functioning as cytosolic iron chaperone in the delivery of iron to ferritin. Within the ferritin molecule, iron is stored in the ferric form associated with hydroxide and phosphate anions [106]. Each ferritin molecule can sequester up to approximately 4,500 iron atoms. Ferritin also has enzymatic properties, converting ferric to ferrous iron, as iron is internalized and sequestered in the ferritin mineral core. Small quantities of ferritin are also present in human serum and are elevated in conditions of iron overload and inflammation. Serum ferritin is iron-poor, and may contain a novel 'G' (glycosylated) subunit [107]. De Domenico et al. [108] showed that ferritin secretion results when cellular ferritin synthesis occurs in the relative absence of free cytosolic iron. An interesting observation was made by Mikhael et al. [109] who showed that ferritin in macrophages is not a significant source of iron for the cell's own metabolic functions. For decades, serum ferritin has been used for assessing iron disorders, and its value as a marker of body iron has been recently reviewed [110].

Several genetic alteration of ferritin genes have been reported [107], notably in association with a specific neurological disease [111].

Iron and Erythropoiesis

Erythroid precursors need much more iron than any other type of cells in the body, and, as previously mentioned, they take up iron almost exclusively through Tfr1. Iron transport into mitochondria is provided by mitoferrin-1, the mitochondrial iron transporter 1 of erythroid precursors [112]. Mitoferrin-1 interacts with an ATP-binding transporter and binds to ferrochelatase to form an oligomeric complex [113], allowing iron uptake and heme biosynthesis.

Erythroid cells contain adaptative mechanisms to face iron deficiency and a class of kinases activated by different cellular stresses. For example, during iron deficiency, and as heme concentration drop, heme dissociate from the heme-regulated inhibitor kinase (HRI), leading to its autophosphorylation and phosphorylation of the α -subunit of eukaryotic translation initiation factor 2 [114, 115]. HRI-deficient mice have allowed identifying HRI as a protector of apoptosis and being involved in the formation of microcytes.

Genetic Polymorphism of Proteins Involved in Iron Metabolism

Several groups reported on the genetic polymorphism of the proteins involved in iron homeostasis, but not related to iron deficiency or overload [116–118]. Genetic analysis of iron deficiency in mice has been evaluated [119]. This study revealed that polymorphisms in multiple genes cause individual variations in iron regulation, especially in response to dietary iron challenge. In humans, genome-wide association studies found linkage of various gene polymorphism (single nucleotide polymorphism; SNP) and iron status, notably polymorphism of the gene coding for Mt2 [56, 120–123]. Other investigators showed an association between Mt2 polymorphism and the risk to develop type 2 diabetes [52]. The authors observed that individuals homozygous for iron-lowering alleles of Mt2 had a reduced risk of iron overload and of type 2 diabetes. In a genome-wide association study looking at heme iron uptake polymorphisms, no significant association with type 2 diabetes and iron metabolic pathways were identified [124]. An et al. [125] presented evidence that genetic polymorphism of the Mt2 gene is associated with the risk to develop iron deficiency

anemia. McLaren et al. [126] evaluated the association between polymorphic loci and iron deficiency defined by hypoferritinemia. They found significant association of SNPs at the Tf gene as well as at the HFE gene with iron deficiency. In an analysis of several genes modulating iron status, Pelucchi et al. [127] showed that CYBRD1 modulates the phenotype of homozygous C282Y hemochromatosis, indicating a role of CYBRD1 in regulation of iron metabolism.

Conclusions and Perspective

Iron is a key player in hemoglobin synthesis an erythrocyte production. At the same time, it is a potent poison to mammalian cells and an indispensable nutrient for many disease-causing germs and microbes. Therefore, its metabolism in mammals is very complex and stringently controlled by many different genes and proteins. Identification of the genes and their polymorphic alleles may shed light into the metabolic interplay of relevant proteins. ‘Ironomics’ may prove useful to better characterize patients with either iron deficiency or iron loading diseases. Finally, ‘ironomics’ may be the ultimate goal for qualification and selection of individuals for blood donation according to their iron stores and of their capacity to maintain adequate iron metabolism despite supra-physiological iron depletion by blood donation.

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