Transfusion Medicine and Hemotherapy

Physiology of Iron Metabolism

Sophie Waldvogel-Abramowski[a]   Gérard Waeber[b]   Christoph Gassner[c]   Andreas Buser[d]
Beat M. Frey[c]   Bernard Favrat[e]   Jean-Daniel Tissot[a]

[a] Service régional vaudois de transfusion sanguine, Epalinges,
[b] Service de médecine interne, CHUV, Lausanne,
[c] Blutspende Zurich, Schlieren,
[d] Blutspende Beiderbasel, Basel,
[e] Department of Ambulatory Care and Community Medicine, Lausanne, Switzerland

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Various tests have been developed to evaluate iron metabolism and iron stores, and nowadays bone marrow examination has been replaced by the measurement of blood ferritin [1].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 it internalization and degradation (illustrations used elements from Servier Medical Art: *www.servier.fr/servier-medical-art*).
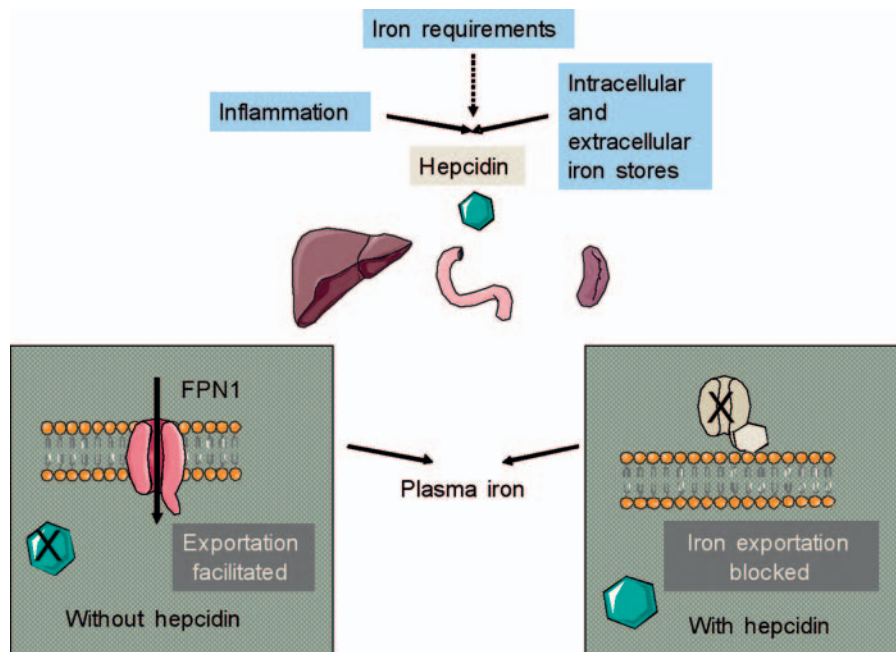
porter-1 (DMT1), ferroportin (FPN1), and transferrin receptors (Tfrs) in association with ferroxidases such as duodenal cytochrome B, ceruloplamin (Cp) and heme carrier protein (HCP1), are involved in the cellular membrane transportation of iron [23]. Others proteins such as myoglobin (Mb), Hb, and many 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].
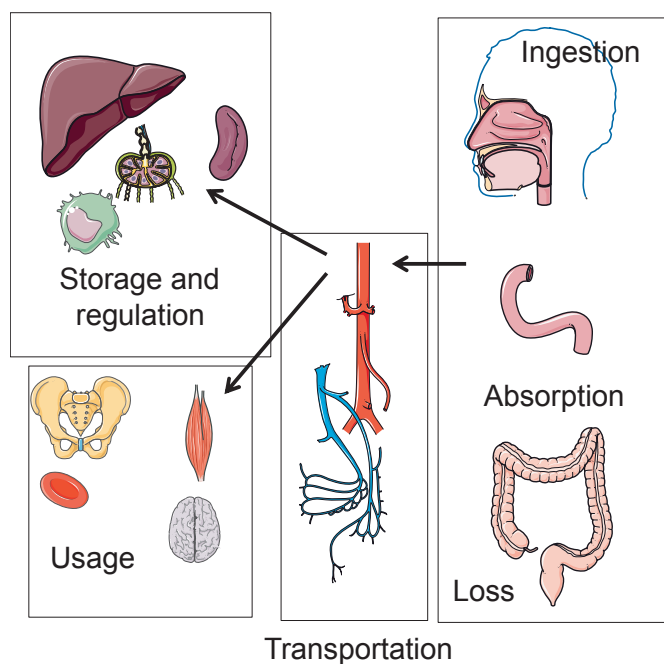
Fig. 2. Iron metabolism is finely regulated. Males contain about 4,000 mg of iron, of which 2,500 mg is within erythrocytes; 1,000 mg is stored in splenic and hepatic macrophages, and the rest is distributed in various proteins such as myoglobin, cytochromes or other ferroproteins. About 1–2 mg of iron 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 nutriments 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 degradated. 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*).
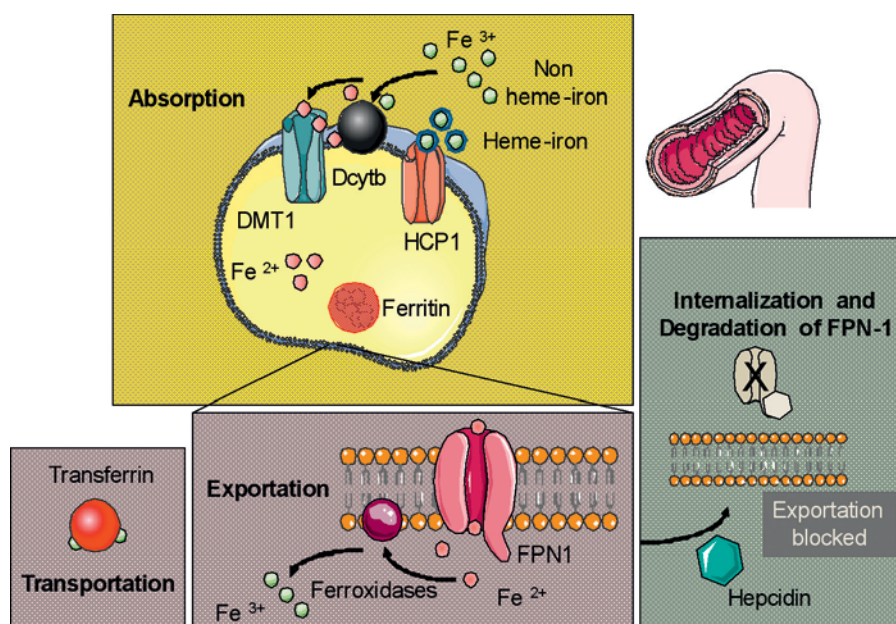
populations. This is why the knowledge of the iron content of various aliments as well as of the factors influencing its absorption should be improved [74].

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 heminic 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 precurors [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 adaptive 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 mammalians 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 supraphysiological iron depletion by blood donation.

Disclosure Statement

References

1 Guyatt GH, Oxman AD, Ali M, Willan A, McIlroy W, Patterson C: Laboratory diagnosis of iron-deficiency anemia: an overview. J Gen Intern Med 1992;7:145–153.

2 Nadakkavukaran IM, Gan EK, Olynyk JK: Screening for hereditary haemochromatosis. Pathology 2012;44:148–152.

3 Waalen J, Beutler E: Hereditary hemochromatosis: screening and management. Curr Hematol Rep 2006;5:34–40.

4 Cremonesi L, Forni GL, Soriani N, Lamagna M, Fermo I, Daraio F, Galli A, Pietra D, Malcovati L, Ferrari M, Camaschella C, Cazzola M: Genetic and clinical heterogeneity of ferroportin disease. Br J Haematol 2005;131:663–670.

5 Cazzola M: Role of ferritin and ferroportin genes in unexplained hyperferritinaemia. Best Pract Res Clin Haematol 2005;18:251–263.

6 Griffiths WJ, Mayr R, McFarlane I, Hermann M, Halsall DJ, Zoller H, Cox TM: Clinical presentation and molecular pathophysiology of autosomal dominant hemochromatosis caused by a novel ferroportin mutation. Hepatology 2010;51:788–795.

7 Aguilar-Martinez P, Grandchamp B, Cunat S, Cadet E, Blanc F, Nourrit M, Lassoued K, Schved JF, Rochette J: Iron overload in hfe c282y heterozygotes at first genetic testing: a strategy for identifying rare hfe variants. Haematologica 2011;96:507–514.

8 Cunat S, Giansily-Blaizot M, Bismuth M, Blanc F, Dereure O, Larrey D, Quellec AL, Pouderoux P, Rose C, Raingeard I, Renard E, Schved JF, Aguilar-Martinez P, CHU Montpellier AOI 2004 Working Group: Global sequencing approach for characterizing the molecular background of hereditary iron disorders. Clin Chem 2007;53:2060–2069.

9 Mendes AI, Ferro A, Martins R, Picanco I, Gomes S, Cerqueira R, Correia M, Nunes AR, Esteves J, Fleming R, Faustino P: Non-classical hereditary hemochromatosis in portugal: novel mutations identified in iron metabolism-related genes. Ann Hematol 2009;88:229–234.

10 Zamboni A, Zanin L, Tomasi N, Pezzotti M, Pinton R, Varanini Z, Cesco S: Genome-wide microarray analysis of tomato roots showed defined responses to iron deficiency. BMC Genomics 2012;13:101.

11 Lan P, Li W, Wen TN, Schmidt W: Quantitative phosphoproteome profiling of iron-deficient arabidopsis roots. Plant Physiol 2012;159:403–417.

12 Schmidt W, Buckhout TJ: A hitchhiker's guide to the *Arabidopsis* ferrome. Plant Physiol Biochem 2011;49:462–470.

13 Forman S, Paulley JT, Fetherston JD, Cheng YQ, Perry RD: *Yersinia* ironomics: Comparison of iron transporters among *Yersinia pestis* biotypes and its nearest neighbor, *Yersinia pseudotuberculosis*. Biometals 2010;23:275–294.

14 Jhurry ND, Chakrabarti M, McCormick SP, Holmes-Hampton GP, Lindahl PA: Biophysical investigation of the ironome of human jurkat cells and mitochondria. Biochemistry 2012;51:5276–5284.

15 Lindahl PA, Holmes-Hampton GP: Biophysical probes of iron metabolism in cells and organelles. Curr Opin Chem Biol 2011;15:342–346.

16 Fuqua BK, Vulpe CD, Anderson GJ: Intestinal iron absorption. J Trace Elem Med Biol 2012;26:115–119.

17 Drakesmith H, Prentice AM: Hepcidin and the iron-infection axis. Science 2012;338:768–772.

18 Pantopoulos K, Porwal SK, Tartakoff A, Devireddy L: Mechanisms of mammalian iron homeostasis. Biochemistry 2012;51:5705–5724.

19 Ganz T, Nemeth E: Iron metabolism: interactions with normal and disordered erythropoiesis. Cold Spring Harb Perspect Med 2012;2:a011668.

20 Ganz T, Nemeth E: Hepcidin and iron homeostasis. Biochim Biophys Acta 2012;1823:1434–1443.

21 De Domenico I, Ward DM, Kaplan J: Hepcidin and ferroportin: the new players in iron metabolism. Semin Liver Dis 2011;31:272–279.

22 Munoz P, Humeres A: Iron deficiency on neuronal function. Biometals 2012;25:825–835.

23 Weiss G: Iron metabolism in the anemia of chronic disease. Biochim Biophys Acta 2009;1790:682–693.

24 Pandur E, Sipos K, Grama L, Nagy J, Poor VS, Setalo Jr G, Miseta A, Fekete Z: Prohepcidin binds to the hamp promoter and autoregulates its own expression. Biochem J 2013; 451:301–311.

25 Zhao N, Zhang AS, Enns CA: Iron regulation by hepcidin. J Clin Invest 2013;123:2337–2343.

26 Schmidt PJ, Toudjarska I, Sendamarai AK, Racie T, Milstein S, Bettencourt BR, Hettinger J, Bumcrot D, Fleming MD: An RNAi therapeutic targeting Tmprss6 decreases iron overload in Hfe(–/–) mice and ameliorates anemia and iron overload in murine beta-thalassemia intermedia. Blood 2013; 121:1200–1208.

27 Camaschella C: Treating iron overload. N Engl J Med 2013;368:2325–2327.

28 Patel N, Masaratana P, Diaz-Castro J, Latunde-Dada GO, Qureshi A, Lockyer P, Jacob M, Arno M, Matak P, Mitry RR, Hughes RD, Dhawan A, Patterson C, Simpson RJ, McKie AT: BMPER protein is a negative regulator of hepcidin and is up-regulated in hypotransferrinemic mice. J Biol Chem 2012;287:4099–4106.

29 Talbot NP, Lakhal S, Smith TG, Privat C, Nickol AH, Rivera-Ch M, Leon-Velarde F, Dorrington KL, Mole DR, Robbins PA: Regulation of hepcidin expression at high altitude. Blood 2011;119:857–860.

30 Piperno A, Galimberti S, Mariani R, Pelucchi S, Ravasi G, Lombardi C, Bilo G, Revera M, Giuliano A, Faini A, Mainini V, Westerman M, Ganz T, Valsecchi MG, Mancia G, Parati G: Modulation of hepcidin production during hypoxia-induced erythropoiesis in humans in vivo: data from the highcare project. Blood 2010;117:2953–2959.

31 Houschyar KS, Ludtke R, Dobos GJ, Kalus U, Broecker-Preuss M, Rampp T, Brinkhaus B, Michalsen A: Effects of phlebotomy-induced reduction of body iron stores on metabolic syndrome: results from a randomized clinical trial. BMC Med 2012;10:1741–7015.

32 Hou Y, Zhang S, Wang L, Li J, Qu G, He J, Rong H, Ji H, Liu S: Estrogen regulates iron homeostasis through governing hepatic hepcidin expression via an estrogen response element. Gene 2012;511:398–403.

33 Goodnough JB, Ramos E, Nemeth E, Ganz T: Inhibition of hepcidin transcription by growth factors. Hepatology 2012;56:291–299.

34 Guo W, Bachman E, Li M, Roy CN, Blusztajn J, Wong S, Chan SY, Serra C, Jasuja R, Travison TG, Muckenthaler MU, Nemeth E, Bhasin S: Testosterone administration inhibits hepcidin transcription and is associated with increased iron incorporation into red blood cells. Aging Cell 2013;12:280–291.

35 Aigner E, Felder TK, Oberkofler H, Hahne P, Auer S, Soyal S, Stadlmayr A, Schwenoha K, Pirich C, Hengster P, Datz C, Patsch W: Glucose acts as a regulator of serum iron by increasing serum hepcidin concentrations. J Nutr Biochem 2012;24:112–117.

36 Troutt JS, Rudling M, Persson L, Stahle L, Angelin B, Butterfield AM, Schade AE, Cao G, Konrad RJ: Circulating human hepcidin-25 concentrations display a diurnal rhythm, increase with prolonged fasting, and are reduced by growth hormone administration. Clin Chem 2012;58:1225–1232.

37 Steinbicker AU, Sachidanandan C, Vonner AJ, Yusuf RZ, Deng DY, Lai CS, Rauwerdink KM, Winn JC, Saez B, Cook CM, Szekely BA, Roy CN, Seehra JS, Cuny GD, Scadden DT, Peterson RT, Bloch KD, Yu PB: Inhibition of bone morphogenetic protein signaling attenuates anemia associated with inflammation. Blood 2011;117:4915–4923.

38 Armitage AE, Eddowes LA, Gileadi U, Cole S, Spottiswoode N, Selvakumar TA, Ho LP, Townsend AR, Drakesmith H: Hepcidin regulation by innate immune and infectious stimuli. Blood 2011;118:4129–4139.

39 Wrighting DM, Andrews NC: Interleukin-6 induces hepcidin expression through STAT3. Blood 2006;108:3204–3209.

40 Wu X, Yung LM, Cheng WH, Yu PB, Babitt JL, Lin HY, Xia Y: Hepcidin regulation by BMP signaling in macrophages is lipopolysaccharide dependent. PLoS One 2012;7:e44622.

41 Krijt J, Frydlova J, Kukackova L, Fujikura Y, Prikryl P, Vokurka M, Necas E: Effect of iron overload and iron deficiency on liver hemojuvelin protein. PLoS One 2012;7:e37391.

42 Stirnberg M, Gutschow M: Matriptase-2, a regulatory protease of iron homeostasis: possible substrates, cleavage sites and inhibitors. Curr Pharm Des 2013;19:1052–1061.

43 Enns CA, Ahmed R, Zhang AS: Neogenin interacts with matriptase-2 to facilitate hemojuvelin cleavage. J Biol Chem 2012;287:35104–35117.

44 Lee P: Role of matriptase-2 (TMPRSS6) in iron metabolism. Acta Haematol 2009;122:87–96.

45 Ramsay AJ, Hooper JD, Folgueras AR, Velasco G, Lopez-Otin C: Matriptase-2 (TMPRSS6): a proteolytic regulator of iron homeostasis. Haematologica 2009;94:840–849.

46 Knutson MD: Into the matrix: regulation of the iron regulatory hormone hepcidin by matriptase-2. Nutr Rev 2009;67:284–288.

47 Melis MA, Cau M, Congiu R, Sole G, Barella S, Cao A, Westerman M, Cazzola M, Galanello R: A mutation in the TMPRSS6 gene, encoding a transmembrane serine protease that suppresses hepcidin production, in familial iron deficiency anemia refractory to oral iron. Haematologica 2008;93:1473–1479.

48 D'Alessio F, Hentze MW, Muckenthaler MU: The hemochromatosis proteins HFE, TfR2, and HJV form a membrane-associated protein complex for hepcidin regulation. J Hepatol 2012;57:1052–1060.

49 Soranzo N, Spector TD, Mangino M, Kuhnel B, Rendon A, Teumer A, Willenborg C, Wright B, Chen L, Li M, Salo P, Voight BF, Burns P, Laskowski RA, Xue Y, Menzel S, Altshuler D, Bradley JR, Bumpstead S, Burnett MS, Devaney J, Doring A, Elosua R, Epstein SE, Erber W, Falchi M, Garner SF, Ghori MJ, Goodall AH, Gwilliam R, Hakonarson HH, Hall AS, Hammond N, Hengstenberg C, Illig T, Konig IR, Knouff CW, McPherson R, Melander O, Mooser V, Nauck M, Nieminen MS, O'Donnell CJ, Peltonen L, Potter SC, Prokisch H, Rader DJ, Rice CM, Roberts R, Salomaa V, Sambrook J, Schreiber S, Schunkert H, Schwartz SM, Serbanovic-Canic J, Sinisalo J, Siscovick DS, Stark K, Surakka I, Stephens J, Thompson JR, Volker U, Volzke H, Watkins NA, Wells GA, Wichmann HE, Van Heel DA, Tyler-Smith C, Thein SL, Kathiresan S, Perola M, Reilly MP, Stewart AF, Erdmann J, Samani NJ, Meisinger C, Greinacher A, Deloukas P, Ouwehand WH, Gieger C: A genome-wide meta-analysis identifies 22 loci associated with eight hematological parameters in the haemgen consortium. Nat Genet 2009;41:1182–1190.

50 Tanaka T, Roy CN, Yao W, Matteini A, Semba RD, Arking D, Walston JD, Fried LP, Singleton A, Guralnik J, Abecasis GR, Bandinelli S, Longo DL, Ferrucci L: A genome-wide association analysis of serum iron concentrations. Blood 2009;115:94–96.

51 Kamatani Y, Matsuda K, Okada Y, Kubo M, Hosono N, Daigo Y, Nakamura Y, Kamatani N: Genome-wide association study of hematological and biochemical traits in a Japanese population. Nat Genet 2010;42:210–215.

52 Gan W, Guan Y, Wu Q, An P, Zhu J, Lu L, Jing L, Yu Y, Ruan S, Xie D, Makrides M, Gibson RA, Anderson GJ, Li H, Lin X, Wang F: Association of TMPRSS6 polymorphisms with ferritin, hemoglobin, and type 2 diabetes risk in a Chinese Han population. Am J Clin Nutr 2012;95:626–632.

53 Lee PL, Barton JC, Khaw PL, Bhattacharjee SY: Common TMPRSS6 mutations and iron, erythrocyte, and pica phenotypes in 48 women with iron deficiency or depletion. Blood Cells Mol Dis 2012; 48:124–127.

54 McLaren CE, McLachlan S, Garner CP, Vulpe CD, Gordeuk VR, Eckfeldt JH, Adams PC, Acton RT, Murray JA, Leiendecker-Foster C, Snively BM, Barcellos LF, Cook JD, McLaren GD: Associations between single nucleotide polymorphisms in iron-related genes and iron status in multiethnic populations. PLoS One 2012;7:e38339.

55 Ganesh SK, Zakai NA, van Rooij FJ, Soranzo N, Smith AV, Nalls MA, Chen MH, Kottgen A, Glazer NL, Dehghan A, Kuhnel B, Aspelund T, Yang Q, Tanaka T, Jaffe A, Bis JC, Verwoert GC, Teumer A, Fox CS, Guralnik JM, Ehret GB, Rice K, Felix JF, Rendon A, Eiriksdottir G, Levy D, Patel KV, Boerwinkle E, Rotter JI, Hofman A, Sambrook JG, Hernandez DG, Zheng G, Bandinelli S, Singleton AB, Coresh J, Lumley T, Uitterlinden AG, Vangils JM, Launer LJ, Cupples LA, Oostra BA, Zwaginga JJ, Ouwehand WH, Thein SL, Meisinger C, Deloukas P, Nauck M, Spector TD, Gieger C, Gudnason V, van Duijn CM, Psaty BM, Ferrucci L, Chakravarti A, Greinacher A, O'Donnell CJ, Witteman JC, Furth S, Cushman M, Harris TB, Lin JP: Multiple loci influence erythrocyte phenotypes in the charge consortium. Nat Genet 2009;41:1191–1198.

56 Chambers JC, Zhang W, Li Y, Sehmi J, Wass MN, Zabaneh D, Hoggart C, Bayele H, McCarthy MI, Peltonen L, Freimer NB, Srai SK, Maxwell PH, Sternberg MJ, Ruokonen A, Abecasis G, Jarvelin MR, Scott J, Elliott P, Kooner JS: Genome-wide association study identifies variants in TMPRSS6 associated with hemoglobin levels. Nat Genet 2009; 41:1170–1172.

57 Aurelie J, Jo C, Gac Gerald L, Claude F, Yves B, Georges F: A novel mutation in the cub sequence of matriptase-2 (TMPRSS6) is implicated in iron-resistant iron deficiency anaemia (IRIDA). Br J Haematol 2012

58 Pellegrino RM, Coutinho M, D'Ascola D, Lopes AM, Palmieri A, Carnuccio F, Costa M, Zecchina G, Saglio G, Costa E, Barbot J, Porto G, Pinto JP, Roetto A: Two novel mutations in the TMPRSS6 gene associated with iron-refractory iron-deficiency anaemia (IRIDA) and partial expression in the heterozygous form. Br J Haematol 2012;158:668–672.

59 Rochat B, Peduzzi D, McMullen J, Favre A, Kottelat E, Favrat B, Tissot JD, Angelillo-Scherrer A, Bromirski M, Waldvogel S: Validation of hepcidin quantification in plasma using LC-HRMS and discovery of a new hepcidin isoform. Bioanalysis 2013; 5:1–12.

60 Moe MK, Hardang IM, Hagve TA: Novel circulating isoforms of hepcidin. Clin Chem 2013;59:1412–1414.

61 Anderson CP, Shen M, Eisenstein RS, Leibold EA: Mammalian iron metabolism and its control by iron regulatory proteins. Biochim Biophys Acta 2012;1823:1468–1483.

62 Rushton DH, Dover R, Sainsbury AW, Norris MJ, Gilkes JJ, Ramsay ID: Iron deficiency is neglected in women's health. BMJ 2002;325:1176.

63 Milman N: Serum ferritin in danes: studies of iron status from infancy to old age, during blood donation and pregnancy. Int J Hematol 1996;63:103–135.

64 Rushton DH, Barth JH: What is the evidence for gender differences in ferritin and haemoglobin? Crit Rev Oncol Hematol 2010;73:1–9.

65 Rushton DH, Dover R, Norris MJ, Gilkes JJ: Is the recommended daily iron intake for women too low? Blood 2009;114:3972–3973.

66 Pena-Rosas JP, De-Regil LM, Dowswell T, Viteri FE: Daily oral iron supplementation during pregnancy. Cochrane Database Syst Rev 2012;12: CD004736.

67 Casgrain A, Collings R, Harvey LJ, Hooper L, Fairweather-Tait SJ: Effect of iron intake on iron status: a systematic review and meta-analysis of randomized controlled trials. Am J Clin Nutr 2012; 96:768–780.

68 Meyer R: Infant feeding in the first year. 2: feeding practices from 6–12 months of life. J Fam Health Care 2009;19:47–50.

69 Huma N, Salim Ur R, Anjum FM, Murtaza MA, Sheikh MA: Food fortification strategy – preventing iron deficiency anemia: a review. Crit Rev Food Sci Nutr 2007;47:259–265.

70 Silva MR, Dias G, Ferreira CL, Franceschini SC, Costa NM: Growth of preschool children was improved when fed an iron-fortified fermented milk beverage supplemented with *Lactobacillus acidophilus*. Nutr Res 2008;28:226–232.

71 Meng F, Wei Y, Yang X: Iron content and bioavailability in rice. J Trace Elem Med Biol 2005;18:333–338.

72 White PJ, Broadley MR: Biofortification of crops with seven mineral elements often lacking in human diets – iron, zinc, copper, calcium, magnesium, selenium and iodine. New Phytol 2009;182:49–84.

73 Gayen D, Sarkar SN, Datta SK, Datta K: Comparative analysis of nutritional compositions of transgenic high iron rice with its non-transgenic counterpart. Food Chem 2013;138:835–840.

74 Davidsson L: Approaches to improve iron bioavailability from complementary foods. J Nutr 2003;133 (5 suppl 1):1560S–1562S.

75 Martins JM: Universal iron fortification of foods: THE view of a hematologist. Rev Bras Hematol Hemoter 2012;34:459–463.

76 Mirmiran P, Golzarand M, Serra-Majem L, Azizi F: Iron, iodine and vitamin a in the middle east; a systematic review of deficiency and food fortification. Iran J Public Health 2012;41:8–19.

77 Han O: Molecular mechanism of intestinal iron absorption. Metallomics 2011;3:103–109.

78 Yersin S, Favrat B, Bodenmann P, Cheseaux M: Aneamia secondary to geophagia in a rich country? A case report (in French). Rev Med Suisse 2012; 8:604–606.

79 Bao W, Rong Y, Rong S, Liu L: Dietary iron intake, body iron stores, and the risk of type 2 diabetes: a systematic review and meta-analysis. BMC Med 2012;10:119.

80 Gunshin H, Starr CN, Direnzo C, Fleming MD, Jin J, Greer EL, Sellers VM, Galica SM, Andrews NC: Cybrd1 (duodenal cytochrome b) is not necessary for dietary iron absorption in mice. Blood 2005;106: 2879–2883.

81 Gunshin H, Fujiwara Y, Custodio AO, Direnzo C, Robine S, Andrews NC: Slc11a2 is required for intestinal iron absorption and erythropoiesis but dispensable in placenta and liver. J Clin Invest 2005;115:1258–1266.

82 Choi J, Masaratana P, Latunde-Dada GO, Arno M, Simpson RJ, McKie AT: Duodenal reductase activity and spleen iron stores are reduced and erythropoiesis is abnormal in Dcytb knockout mice exposed to hypoxic conditions. J Nutr 2012;142:1929–1934.

83 Ohgami RS, Campagna DR, McDonald A, Fleming MD: The Steap proteins are metalloreductases. Blood 2006;108:1388–1394.

84 Shayeghi M, Latunde-Dada GO, Oakhill JS, Laftah AH, Takeuchi K, Halliday N, Khan Y, Warley A, McCann FE, Hider RC, Frazer DM, Anderson GJ, Vulpe CD, Simpson RJ, McKie AT: Identification of an intestinal heme transporter. Cell 2005; 122:789–801.

85 Le Blanc S, Garrick MD, Arredondo M: Heme carrier protein 1 transports heme and is involved in heme-Fe metabolism. Am J Physiol Cell Physiol 2012;302:C1780–1785.

86 Donovan A, Lima CA, Pinkus JL, Pinkus GS, Zon LI, Robine S, Andrews NC: The iron exporter ferroportin/Slc40a1 is essential for iron homeostasis. Cell Metab 2005;1:191–200.

87 De Domenico I, Ward DM, di Patti MC, Jeong SY, David S, Musci G, Kaplan J: Ferroxidase activity is required for the stability of cell surface ferroportin in cells expressing GPI-ceruloplasmin. EMBO J 2007;26:2823–2831.

88 De Domenico I, Vaughn MB, Li L, Bagley D, Musci G, Ward DM, Kaplan J: Ferroportin-mediated mobilization of ferritin iron precedes ferritin degradation by the proteasome. EMBO J 2006;25: 5396–5404.

89 Harris ZL, Klomp LW, Gitlin JD: Aceruloplasminemia: an inherited neurodegenerative disease with impairment of iron homeostasis. Am J Clin Nutr 1998;67(5 suppl):972S–977S.

90 Vashchenko G, Macgillivray RT: Functional role of the putative iron ligands in the ferroxidase activity of recombinant human hephaestin. J Biol Inorg Chem 2012;17:1187–1195.

91 Szoke D, Panteghini M: Diagnostic value of transferrin. Clin Chim Acta 2012;413:1184–1189.

92 Sohn YS, Ghoti H, Breuer W, Rachmilewitz E, Attar S, Weiss G, Cabantchik ZI: The role of endocytic pathways in cellular uptake of plasma non-transferrin iron. Haematologica 2012;97:670–678.

93 Chen C, Paw BH: Cellular and mitochondrial iron homeostasis in vertebrates. Biochim Biophys Acta 2012;1823:1459–1467.

94 Zhang AS, Sheftel AD, Ponka P: The anemia of 'haemoglobin-deficit' (hbd/hbd) mice is caused by a defect in transferrin cycling. Exp Hematol 2006; 34:593–598.

95 Chen C, Garcia-Santos D, Ishikawa Y, Seguin A, Li L, Fegan KH, Hildick-Smith GJ, Shah DI, Cooney JD, Chen W, King MJ, Yien YY, Schultz IJ, Anderson H, Dalton AJ, Freedman ML, Kingsley PD, Palis J, Hattangadi SM, Lodish HF, Ward DM, Kaplan J, Maeda T, Ponka P, Paw BH: Snx3 regulates recycling of the transferrin receptor and iron assimilation. Cell Metab 2013;17:343–352.

96 Engle-Stone R, Nankap M, Ndjebayi AO, Erhardt JG, Brown KH: Plasma ferritin and soluble transferrin receptor concentrations and body iron stores identify similar risk factors for iron deficiency but result in different estimates of the national prevalence of iron deficiency and iron-deficiency anemia among women and children in Cameroon. J Nutr 2013;143:369–377.

97 Beutler E, Hoffbrand AV, Cook JD: Iron deficiency and overload. Hematol Am Soc Hematol Educ Program 2003;40–61.

98 Cook JD, Flowers CH, Skikne BS: The quantitative assessment of body iron. Blood 2003;101: 3359–3364.

99 Zahn C, Kaup M, Fluhrer R, Fuchs H: The transferrin receptor-1 membrane stub undergoes intramembrane proteolysis by sppl2b. FEBS J 2013; 280:1653–1663.

100 Knutson MD: Steap proteins: implications for iron and copper metabolism. Nutr Rev 2007;65:335–340.

101 Zhang F, Tao Y, Zhang Z, Guo X, An P, Shen Y, Wu Q, Yu Y, Wang F: Metalloreductase Steap3 coordinates the regulation of iron homeostasis and inflammatory responses. Haematologica 2012;97: 1826–1835.

102 Soe-Lin S, Apte SS, Mikhael MR, Kayembe LK, Nie G, Ponka P: Both Nramp1 and DMT1 are necessary for efficient macrophage iron recycling. Exp Hematol 2010;38:609–617.

103 Johnson EE, Wessling-Resnick M: Iron metabolism and the innate immune response to infection. Microbes Infect 2012;14:207–216.

104 Soe-Lin S, Apte SS, Andriopoulos B Jr, Andrews MC, Schranzhofer M, Kahawita T, Garcia-Santos D, Ponka P: Nramp1 promotes efficient macrophage recycling of iron following erythrophagocytosis in vivo. Proc Natl Acad Sci U S A 2009;106: 5960–5965.

105 Shi H, Bencze KZ, Stemmler TL, Philpott CC: A cytosolic iron chaperone that delivers iron to ferritin. Science 2008;320:1207–1210.

106 Torti FM, Torti SV: Regulation of ferritin genes and protein. Blood 2002;99:3505–3516.

107 Koziol JA, Ho NJ, Felitti VJ, Beutler E: Reference centiles for serum ferritin and percentage of transferrin saturation, with application to mutations of the HFE gene. Clin Chem 2001;47:1804–1810.

108 De Domenico I, Vaughn MB, Paradkar PN, Lo E, Ward DM, Kaplan J: Decoupling ferritin synthesis from free cytosolic iron results in ferritin secretion. Cell Metab 2011;13:57–67.

109 Mikhael M, Sheftel AD, Ponka P: Ferritin does not donate its iron for haem synthesis in macrophages. Biochem J 2010;429:463–471.

110 Ferraro S, Mozzi R, Panteghini M: Revaluating serum ferritin as a marker of body iron stores in the traceability era. Clin Chem Lab Med 2012;50: 1911–1916.

111 Lehn A, Boyle R, Brown H, Airey C, Mellick G: Neuroferritinopathy. Parkinsonism Relat Disord 2012;18:909–915.

112 Troadec MB, Warner D, Wallace J, Thomas K, Spangrude GJ, Phillips J, Khalimonchuk O, Paw BH, Ward DM, Kaplan J: Targeted deletion of the mouse mitoferrin1 gene: From anemia to protoporphyria. Blood 2011;117:5494–5502.

113 Chen W, Dailey HA, Paw BH: Ferrochelatase forms an oligomeric complex with mitoferrin-1 and Abcb10 for erythroid heme biosynthesis. Blood 2010;116:628–630.

114 Donnelly N, Gorman AM, Gupta S, Samali A: The eif2alpha kinases: their structures and functions. Cell Mol Life Sci 2013;70:3493–3511.

115 Suragani RN, Zachariah RS, Velazquez JG, Liu S, Sun CW, Townes TM, Chen JJ: Heme-regulated eif2alpha kinase activated Atf4 signaling pathway in oxidative stress and erythropoiesis. Blood 2012;119:5276–5284.

Waldvogel-Abramowski/Waeber/Gassner/
Buser/Frey/Favrat/Tissot

116 Rentschler G, Kippler M, Axmon A, Raqib R, Ekstrom EC, Skerfving S, Vahter M, Broberg K: Polymorphisms in iron homeostasis genes and urinary cadmium concentrations among nonsmoking women in Argentina and Bangladesh. Environ Health Perspect 2013;121:467–472, 472e1–7.

117 Gemmati D, Zeri G, Orioli E, De Gaetano FE, Salvi F, Bartolomei I, D'Alfonso S, Dall'osso C, Leone MA, Singh AV, Asselta R, Zamboni P: Polymorphisms in the genes coding for iron binding and transporting proteins are associated with disability, severity, and early progression in multiple sclerosis. BMC Med Genet 2012;13:70.

118 Synowiec E, Pogorzelska M, Blasiak J, Szaflik J, Szaflik JP: Genetic polymorphism of the iron-regulatory protein-1 and -2 genes in age-related macular degeneration. Mol Biol Rep 2012;39:7077–7087.

119 Yin L, Unger EL, Jellen LC, Earley CJ, Allen RP, Tomaszewicz A, Fleet JC, Jones BC: Systems genetic analysis of multivariate response to iron deficiency in mice. Am J Physiol Regul Integr Comp Physiol 2012;302:R1282–1296.

120 Benyamin B, Montgomery GW, Martin NG, Whitfield JB: Transferrin saturation and mortality. Clin Chem 2011;57:921–923; author reply 923.

121 Benyamin B, Ferreira MA, Willemsen G, Gordon S, Middelberg RP, McEvoy BP, Hottenga JJ, Henders AK, Campbell MJ, Wallace L, Frazer IH, Heath AC, de Geus EJ, Nyholt DR, Visscher PM, Penninx BW, Boomsma DI, Martin NG, Montgomery GW, Whitfield JB: Common variants in TMPRSS6 are associated with iron status and erythrocyte volume. Nat Genet 2009;41:1173–1175.

122 Benyamin B, McRae AF, Zhu G, Gordon S, Henders AK, Palotie A, Peltonen L, Martin NG, Montgomery GW, Whitfield JB, Visscher PM: Variants in TF and HFE explain approximately 40% of genetic variation in serum-transferrin levels. Am J Hum Genet 2009;84:60–65.

123 Tanaka T, Roy CN, Yao W, Matteini A, Semba RD, Arking D, Walston JD, Fried LP, Singleton A, Guralnik J, Abecasis GR, Bandinelli S, Longo DL, Ferrucci L: A genome-wide association analysis of serum iron concentrations. Blood 2010;115:94–96.

124 Pasquale LR, Loomis SJ, Aschard H, Kang JH, Cornelis MC, Qi L, Kraft P, Hu FB: Exploring genome-wide – dietary heme iron intake interactions and the risk of type 2 diabetes. Front Genet 2013;4:7.

125 An P, Wu Q, Wang H, Guan Y, Mu M, Liao Y, Zhou D, Song P, Wang C, Meng L, Man Q, Li L, Zhang J, Wang F: TMPRSS6, but not TF, TFR2 or BMP2 variants are associated with increased risk of iron-deficiency anemia. Hum Mol Genet 2012;21:2124–2131.

126 McLaren CE, Garner CP, Constantine CC, McLachlan S, Vulpe CD, Snively BM, Gordeuk VR, Nickerson DA, Cook JD, Leiendecker-Foster C, Beckman KB, Eckfeldt JH, Barcellos LF, Murray JA, Adams PC, Acton RT, Killeen AA, McLaren GD: Genome-wide association study identifies genetic loci associated with iron deficiency. PLoS One 2011;6:e17390.

127 Pelucchi S, Mariani R, Calza S, Fracanzani AL, Modignani GL, Bertola F, Busti F, Trombini P, Fraquelli M, Forni GL, Girelli D, Fargion S, Specchia C, Piperno A: Cybrd1 as a modifier gene that modulates iron phenotype in HFE p. C282Y homozygous patients. Haematologica 2012;97:1818–1825.