Iron Metabolism: Interactions with Normal and Disordered Erythropoiesis

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Hemoglobinopathies and other disorders of erythroid cells are often associated with abnormal iron homeostasis. We review the molecular physiology of intracellular and systemic iron regulation, and the interactions between erythropoiesis and iron homeostasis. Finally, we discuss iron disorders that affect erythropoiesis as well as erythroid disorders that cause iron dysregulation.

Iron overload is a common complication of hemoglobinopathies treated by erythrocyte transfusions (1 mL of packed erythrocytes contains about 1 mg of iron) and those associated with ineffective erythropoiesis, which stimulates the hyperabsorption of dietary iron. With the increasing use of transfusion therapy, iron overload has become a major cause of morbidity and premature mortality. More recently, the effective treatment of iron overload by iron chelation has dramatically improved survival (Cunningham 2008; Telfer 2009). This work reviews recent advances in our understanding of the molecular basis of iron homeostasis and its disorders.

IRON BIOLOGY AND HOMEOSTASIS

Iron Intake

Iron is the most abundant element on Earth by mass and the fourth most abundant in the Earth's crust but it readily oxidizes into insoluble compounds with poor bioavailability. In

this environment, biological organisms evolved to conserve iron. Quantitative analysis of tissue iron distribution and fluxes in humans illustrates how this is accomplished (Finch 1994). The typical adult human male contains about 4 g of iron of which about 2.5 g is in hemoglobin, 1 g is stored predominantly in hepatocytes and hepatic and splenic macrophages, and most of the rest is distributed in myoglobin, cytochromes, and other ferroproteins. Only about 1–2 mg/d, or <0.05%/d, is lost from the body predominantly through desquamation and minor blood loss. In the steady state, this amount is replaced through intestinal iron absorption. Although the loss of iron may increase slightly with increasing iron stores, these changes do not significantly contribute to homeostasis; intestinal iron absorption is by far the predominant determinant of the iron content of the body. A typical Western diet provides about 15 mg of iron per day and only ~10% is absorbed. Recovery from blood loss causes an increase in iron absorption up to 20-fold, indicating that the

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duodenum where iron absorption takes place has a large reserve capacity for iron absorption. Pathological increase of intestinal iron absorption is a common cause of iron overload, accounting for the excess iron in hereditary hemochromatosis and untransfused β -thalassemia. Blood transfusions and parenteral administration of iron compounds bypass the regulatory bottleneck of iron absorption and constitute the other major cause of iron overload.

Iron Recycling

Under normal circumstances, the reutilization of iron recycled from senescent cells accounts for most of the iron flux in humans. With the erythrocyte lifespan of 120 d, 20–25 mg of iron is required to replace the 20–25 mL of erythrocytes that must be produced every day to maintain a steady state. Other cell types also turn over but their much lower iron content contributes relatively little to the iron flux. Macrophages in the liver, spleen, and marrow (formerly called the reticuloendothelial system) phagocytose senescent or damaged erythrocytes, degrade their hemoglobin to release heme, extract iron from heme using heme oxygenase (Poss and Tonegawa 1997), and recycle the iron to the extracellular fluid and plasma. Steady-state iron flux from recycling can increase up to 150 mg/d in conditions with ineffective erythropoiesis in which the number of erythroid precursors is increased and accompanied by the apoptosis of hemoglobinized erythrocyte precursors in the marrow and shortened erythrocyte survival (Beguín et al. 1988).

Iron Distribution and Storage

Free iron is highly reactive and causes cell and tissue injury through its ability to catalyze the production of reactive oxygen species. In living organisms, iron is complexed with proteins or small organic molecules (citrate, acetate), which mitigate its reactivity. Transferrin is the physiological carrier of iron in plasma. Normally, only 20%–40% of the available binding sites on transferrin molecules are occupied by ferric iron. The iron content of plasma is only 2–3 mg

so this compartment must turn over every few hours. Erythrocyte precursors take up iron almost exclusively through transferrin receptors (TfR1) so the iron supply to erythrocyte precursors is completely dependent on plasma transferrin. In contrast, hepatocytes and other non-erythroid cells can also take up iron that is not bound to transferrin (nontransferrin-bound iron or NTBI), a process that becomes important during iron overload when plasma transferrin saturation reaches 100% (Breuer et al. 2000). The predominant cellular storage form of iron is the hollow spherical protein ferritin whose cavity contains iron in ferric form complexed with hydroxide and phosphate anions.

Regulation of Plasma Iron Concentrations

Despite varying dietary iron intake and changes in erythropoietic activity owing to occasional or periodic blood loss, iron concentrations in plasma normally remain in the 10–30 μ M range. Chronically low concentrations decrease iron supply to erythropoiesis and other processes leading to anemia and dysfunction of other cell types sensitive to iron deprivation. Chronically high iron concentrations lead to intermittent or steady-state saturation of transferrin with iron and the generation of NTBI with consequent deposition of excess iron in the liver, endocrine glands, cardiac myocytes, and other tissues. Excess cellular iron may cause tissue injury by catalyzing the generation of reactive oxygen species, which can cause DNA damage, lipid peroxidation, and oxidation of proteins.

Systemic Iron Homeostasis

Phenomenological description of systemic iron homeostasis was developed starting in the 1930s (Finch 1994). Homeostatic mechanisms regulate dietary iron absorption and iron deposition into or withdrawal from stores depending on the amount of stored iron (“stores regulator”) and the requirements of erythropoiesis (“erythropoietic regulator”). The description of the molecular processes that underlie iron homeostasis has progressed rapidly in the last two decades but is still not complete.

CELLULAR IRON REGULATION

Cellular Iron

Cells require iron predominantly for incorporation into various ferroproteins, where iron exists in iron–sulfur clusters, in heme or hemelike prosthetic moieties, or in other more loosely associated forms. It now appears that most cell types in the body autonomously regulate their iron uptake solely to meet their individual requirements for iron. These cells do not export appreciable amounts of iron and are presumed to give up their iron only when they undergo cell death and are recycled by macrophages. In contrast, several specialized cell types supply or store iron to meet the needs of the entire organism, and are therefore equipped to export iron into extracellular fluid and plasma. Iron-exporting cells include duodenal enterocytes that absorb dietary iron, macrophages that recycle iron from senescent or dead cells, and macrophages and hepatocytes that store iron and release it to meet systemic demand. During pregnancy, the placental syncytiotrophoblast must transport maternal iron into the fetal circulation to meet the iron requirements of fetal growth and development. The endothelial cells that form the blood–brain barrier must also selectively transport iron as it now appears that the iron concentrations in the brain are not appreciably increased in systemic iron overload disorders. Finally, erythroid precursors need much more iron than any other cell type as each cell synthesizes more than a billion heme molecules, therefore facing greater iron-homeostatic challenges.

Cellular Iron Uptake

Transferrin-mediated iron uptake is the best understood mechanism of cellular iron import. Although the transferrin receptor (TfR1) is expressed in many cell types, erythrocyte precursors contain most of the TfR1 molecules and take up the great majority of iron-transferrin in the organism. Iron-transferrin is endocytosed via the cell membrane TfR1 and internalized into endosomal recycling vesicles. As the vesicle acidifies, the low pH releases the transferrin-bound ferric iron and the iron-free (apo)trans-

ferrin-TfR1 complex returns to the cell membrane (Fig. 1). The neutral pH at the membrane causes the apotransferrin to dissociate from TfR1, whereupon apotransferrin diffuses away to be loaded with iron again, repeating the cycle. From the vesicle, iron is delivered to mitochondria where it is incorporated into protoporphyrin IX to form heme, or incorporated into nascent iron–sulfur clusters. Alternatively, iron can be exported from the vesicle into the cytoplasm where it is incorporated into cytoplasmic ferroproteins or stored in cytoplasmic ferritin.

Nontransferrin-bound iron (NTBI) (Breuer et al. 2000) usually accumulates when the iron-binding capacity of transferrin is exceeded and then circulates complexed mostly with citrate or acetate. Hemoglobinopathies such as β -thalassemia major and intermedia are associated with particularly high levels of NTBI. Some cells, including hepatocytes, cardiomyocytes, and cells of endocrine glands can take up NTBI, although the precise mechanism is not well understood. Candidate NTBI transporters include L-type voltage-gated calcium channels, DMT-1 and Zip14.

Intracellular Iron Transport

To undergo transport to the cytoplasm or mitochondria, ferric iron must be reduced to its ferrous form through the action of ferrireductases. Recent studies indicate that Steap (six-transmembrane epithelial antigen of the prostate) proteins 1–4 are among the relevant ferrireductases, with Steap3 having a particular importance in erythroid precursors (Fig. 1), assisted perhaps by Steap2 and Steap4 (Ohgami et al. 2006). To reach the cytoplasm, ferrous iron must cross the membrane of the vesicle. In many cells, the proton-dependent ferrous iron transporter divalent metal transporter-1 (DMT1) appears essential for iron transport from the vacuole into the cytoplasm but in macrophages its homolog natural resistance-associated macrophage protein (Nramp1) may also contribute (Soe-Lin et al. 2009). Because of its chemical reactivity, iron is chaperoned in the cytoplasm, at least in part by multifunctional poly(RC)-binding proteins (PCBPs) (Shi et al. 2008). In

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Figure 1. Iron traffic in erythrocyte precursors synthesizing hemoglobin. Iron is taken up as diferric transferrin by the transferrin receptor (TfR1). Acidification of the endocytic vesicle releases ferric iron from transferrin, and the membrane ferrireductase Steap3 reduces it to ferrous iron, which is then exported to the cytoplasm by DMT1. The complex of iron-free apotransferrin (Tf) and TfR1 is returned to the plasma membrane where the neutral pH causes Tf to dissociate from its receptor. The transferrin cycle is completed when Tf is reloaded with ferric iron by duodenal enterocytes or iron-recycling macrophages. Ferrous iron exported by DMT1 may be delivered to mitochondrial mitoferrin-1 (Mfrn1) by direct contact (the kiss-and-run mechanism, K&R) or through intermediate transport by as-yet uncharacterized cytoplasmic chaperones (Fe^{2+}Ch). Mitoferrin-1 imports iron into mitochondria where iron is incorporated into newly synthesized heme. Heme is exported via an unknown exporter (Heme export) and incorporated into globin chains to generate hemoglobin. Under some circumstances, iron is exported as ferrous iron via ferroportin (Fpn) or as heme via feline leukemia virus C receptor (FLVCR1).

particular, PCBP1 mediates the delivery of iron to cytoplasmic ferritin and both PCBP1 and 2 are involved in the delivery of iron to cytoplasmic iron-dependent prolyl and asparaginyl hydroxylases that mediate oxygen sensing (Nandal et al. 2011). It is not known how iron is transported to mitochondria. In erythroid cells, there is evidence for a “kiss-and-run” mechanism (Fig. 1) whereby iron could be transferred from endosomal vesicles directly to mitochondria (Sheftel et al. 2007) but it is not clear how much this mechanism contributes to the iron flux into mitochondria and whether it also functions in nonerythroid cell types.

Mitochondria and Iron

Consistent with their autonomous evolutionary origin, mitochondria are equipped with distinct iron transporters. Iron uptake into mitochondria depends on the inner mitochondrial membrane proteins mitoferrin 1 and 2, with the former predominantly expressed in erythroid cells and the latter ubiquitously (Paradkar et al. 2009; Troadec et al. 2011). In erythroid cells, mitoferrin 1 interacts with the ATP-binding transporter Abcb10 and with ferrochelatase to form a plausible pathway for the delivery of iron for heme formation (Chen et al. 2010). How heme is

exported from mitochondria for incorporation into hemoglobin and other hemoproteins is not known. Mitochondria also contain a distinct ferritin, mitochondrial ferritin, for local iron storage.

Cellular Iron Homeostasis

Cellular, as opposed to systemic, iron homeostasis assures that sufficient but not excessive amounts of iron are taken up by each cell to meet its individual requirement for ferroprotein synthesis. The system that has evolved relies on posttranscriptional regulation through the interaction of iron-regulatory proteins (IRP1 and IRP2) with iron-regulatory elements (IREs) in messenger RNAs (mRNAs) that encode key iron transporters, ferroproteins, and enzymes involved in iron-utilizing pathways. The IRE/IRP system effectively regulates iron uptake, provides for the storage of excess iron in ferritin, and coordinates the synthesis of heme, iron–sulfur clusters, and ferroproteins with the availability of iron. The system in effect acts to decrease wasted expenditure of synthetic energy and substrates, and to prevent accumulation of toxic forms of iron. Target mRNAs contain IREs that form characteristic stem-loop structures either in the 5' region, where IRP binding represses translation and decreases protein synthesis, or in the 3' region where IRP binding prevents endonucleases from cleaving sensitive regions of the mRNA, thus stabilizing mRNA and increasing protein synthesis (Casey et al. 1988). IRP1 and IRP2 are structurally related but interact with iron in distinct ways. Both proteins bind to IREs when cellular iron levels are low. In the presence of iron, IRP1 incorporates an iron–sulfur cluster, does not bind IREs, and acts as an aconitase enzyme converting citrate to isocitrate in the Krebs cycle. In contrast, IRP2 is ubiquitinated by a complex iron-dependent process and then degraded in proteasomes (Salahudeen et al. 2009; Vashisht et al. 2009). The dual specificity of IRP1/aconitase may have a functional role in the regulation of erythropoiesis by iron availability, as the provision of the aconitase product isocitrate reverses some of the suppressive effect of iron deprivation on erythropoiesis

and the enzymatic inhibition of aconitase has the opposite effect (Bullock et al. 2010; Talbot et al. 2011). Many mRNAs are regulated by the IRP/IRE system (Sanchez et al. 2011) and fall into three classes: (1) iron acquisition, generally with IREs in the 3' region resulting in increased protein synthesis during cellular iron deprivation; (2) iron utilization and storage, with IREs in the 5' region, resulting in repressed protein synthesis during iron deprivation; and (3) iron export, with IREs also in the 5' region and protein synthesis repressed during iron deprivation. Proteins subject to IRE/IRP regulation include TfR1 and DMT1 involved in cellular iron uptake, aminolevulinic acid synthase 2, which catalyzes the first step of the heme synthesis pathway in erythroid cells, the heavy and light subunits of ferritin involved in iron storage, and ferroportin, the iron exporter expressed in tissues and cells involved in iron export to plasma. The net effect of the IRE/IRP response during cellular iron deficiency is to increase cellular iron uptake, mobilize iron from cellular storage, decrease iron utilization, and, when iron becomes sufficient or excessive to reverse these responses and direct more iron into cellular storage and export. Further fine-tuning of iron import and export is achieved by differential splicing of target mRNAs in different tissues to either include or exclude IREs. As an example, systemic adaptation to iron deficiency may be facilitated by a ferroportin mRNA isoform that lacks IRE, which may allow iron-transporting duodenal enterocytes to deliver iron to plasma for systemic needs even if the enterocyte is sensing iron deficiency, and may transfer iron from erythroid cells to other tissues more critically dependent on iron (Zhang et al. 2009).

Generalized Regulation of Protein Synthesis by Iron in Erythroid Cells

In addition to the regulation of the synthesis of individual proteins by iron, erythroid cells also contain a mechanism for a generalized adaptive response to iron deficiency. This response is affected by the heme-regulated inhibitor kinase (HRI) belonging to a class of kinases activated by cellular stress, including nutrient deprivation,

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viral infection, and endoplasmic reticulum stress (Chen 2007). During iron deficiency as heme concentrations drop, heme dissociates from HRI, causing it to undergo specific autophosphorylation to become a catalytically active kinase targeting the α subunit of eukaryotic translational initiation factor 2 (eIF2 α). Activated HRI inhibits translational initiation by phosphorylating eIF2 α . Not all protein synthesis is inhibited however, as activated HRI may promote the synthesis of transcription factors that are protective during iron-deficient erythropoiesis (Liu et al. 2008). A priori, it is not obvious how iron deficiency results in the production of smaller, less-hemoglobinized erythrocytes rather than fewer normally sized and hemoglobinized cells. Studies with HRI-deficient mice showed that HRI protects erythroid precursors from apoptosis induced by excessive production of globin chains and contributes to the microcytosis and hypochromia seen in iron deficiency, erythropoietic protoporphyria, and β -thalassemia.

Iron and Hypoxia Sensing

The hypoxia-sensing pathway may also contribute to cellular iron homeostasis. Prolyl and asparaginyl hydroxylases, which inactivate the HIF transcription factors, are not only sensitive to oxygen tension but also to iron concentrations because they use iron as a catalytic cofactor. In support of the potential role of HIF in iron regulation, tissue-specific deletion of HIF2 α in mouse enterocytes decreased intestinal iron absorption as well as the expression of DMT1 in enterocytes (Mastrogiannaki et al. 2009). HIF2 α bound to the DMT1 promoter and transactivated it. The broader physiologic function of HIF in cellular iron homeostasis still remains to be established and may vary in different tissues depending on oxygen tension and other factors.

SYSTEMIC IRON HOMEOSTASIS

The Central Role of Hepcidin

Systemic iron homeostasis encompasses the regulatory circuitry that controls the absorption of dietary iron, the concentration of iron in extra-

cellular fluid and blood plasma, and the release of iron from macrophages involved in iron recycling and from iron-storing hepatocytes. It now appears that there is a single systemic regulator of iron, the hepatic peptide hormone hepcidin. The hormone inhibits iron delivery to plasma and extracellular fluid thereby controlling the concentration of iron in plasma. Hepcidin inhibits the transfer of dietary iron from duodenal enterocytes to plasma, the release of recycled iron from macrophages to plasma, and the release of stored iron from hepatocytes (Fig. 2). Fetal hepcidin inhibits the transfer of maternal iron across the placenta to the fetal circulation. At the molecular level, hepcidin acts by binding to its receptor, ferroportin, and causing its endocytosis and proteolysis, which results in decreased iron release from cells to plasma and extracellular fluid. Ferroportin is found at very low concentrations in most cell types but much higher amounts in professional iron-transporting tissues, including the duodenal enterocytes and splenic macrophages. Intermediate concentrations of ferroportin are detectable in hepatocytes.

Regulation of Hepcidin Synthesis

Hepatocytes are the main source of hepcidin, with much lower amounts produced by macrophages, adipocytes, and perhaps other cells. Hepcidin synthesis is controlled predominantly at the transcriptional level and is increased by plasma iron-transferrin as well as by iron stored in hepatocytes (the “stores” regulator), is suppressed in response to increased iron requirements of erythroid precursors (the “erythroid” regulator), and is potentially stimulated by inflammation (Fig. 2).

Regulation of Hepcidin Synthesis by Iron

Iron regulation of hepcidin is mediated by the canonical bone morphogenetic protein pathway adapted for hepcidin regulation by iron-specific molecular components (Fig. 3). Normal iron regulation in the murine model requires the iron-specific ligand bone morphogenetic protein 6 (BMP6), interacting with the

Figure 2. Iron homeostasis. Through membrane ferroportin (Fpn), iron flows into plasma (pale blue arrows) from duodenal enterocytes, iron-storing hepatocytes, and iron-recycling macrophages predominantly in the spleen. Iron-transferrin (Fe-Tf) is mostly delivered to the marrow (pale blue arrow) where iron is incorporated into erythrocyte hemoglobin (red). When the erythrocytes live out their lifespan (normally 120 d in humans), their hemoglobin and heme are degraded in the macrophages, mostly in the spleen, and iron is returned into the plasma iron pool. Hepatocytes secrete hepcidin under the control of stimulatory signals that reflect liver iron stores and plasma iron concentrations (blue), inhibitory signals reflecting erythropoietic activity (red), and inflammatory cytokines (green). Hepcidin causes the degradation of Fpn and thereby inhibits iron delivery to plasma and the erythropoietic bone marrow.

BMP receptor. Another iron-specific component required for normal hepcidin regulation by iron is the membrane protein hemojuvelin, which interacts with BMPs as well as with the BMP receptor. The BMP receptor is a ligand-activated serine/threonine kinase, which phosphorylates the cytoplasmic proteins Smad1, 5, and 8. Together with the common Smad4, the phosphorylated Smads form heterodimers, which reach the nucleus and enhance the transcription of hepcidin. The synthesis of the BMP6 ligand appears to be responsive predominantly to iron stores rather than transferrin saturation, and compared to the large changes in hepcidin expression, BMP6 changes in a relatively narrow range. In contrast, changes in extracellular iron-transferrin concentration affect signal transduction by the BMP receptor even in the absence of changes in BMP6 mRNA concentration, indi-

cating that iron-transferrin modulates the sensitivity of the receptor to its ligands. It is not known with certainty how the concentration of iron-transferrin is sensed but ablation of HFE or Tfr2, and especially the combined loss of both molecules, decreases hepcidin expression and interferes with the sensing of transient changes in iron-transferrin while preserving the increase in BMP6 and the chronic hepcidin response to iron loading (Wallace et al. 2009; Ramos et al. 2011; Corradini et al. 2011). A plausible current model postulates that iron-transferrin is sensed by Tfr1 and Tfr2, with HFE shuttling between the two molecules depending on iron-transferrin concentrations. At higher iron-transferrin concentrations, the association of Tfr2 and HFE somehow potentiates BMP receptor complex signaling. Two other proteins, GPI-linked hemojuvelin (Papanikolaou et al. 2004) and the

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Figure 3. Regulation of hepcidin by iron and inflammation. Hepcidin synthesis is transcriptionally regulated by iron through the BMP receptor complex and its Smad pathway (shades of blue) and by inflammation predominantly via the IL-6 receptor and its JAK-STAT3 pathway (green). Extracellular iron is sensed by transferrin receptors (TfR1 and TfR2) aided by HFE, which can associate with either TfR but is displaced from TfR1 when TfR1 binds diferric transferrin (HoloTf). When HoloTf concentrations are high, HFE is associated mostly with TfR2 and stabilizes it. HFE-TfR2 then potentiates BMP receptor signaling through an unknown mechanism. Stored hepatic intracellular iron increases the concentrations of BMP6 mRNA and presumably BMP6 protein in the liver thereby stimulating the BMP receptor, its Smad pathway, and hepcidin transcription.

membrane protease matriptase 2 (MT2, also called transmembrane serine proteinase 6, TM-PRSS6) (Du et al. 2008) respectively enhance and dampen BMP signaling, with hemojuvelin acting as a BMP pathway coreceptor, and MT2 exerting its effect by an inactivating cleavage of hemojuvelin (Silvestri et al. 2008).

Regulation of Hepcidin by Erythropoiesis

Hepcidin mRNA is suppressed during anemia or hypoxia (Nicolas et al. 2002) but it now appears that this is an indirect effect dependent on increased erythropoietin production and the resulting expansion of erythroid precursors in the marrow (Pak et al. 2006; Vokurka et al. 2006; Mastrogiannaki et al. 2011) and not a direct effect of hypoxia-regulated pathways on the hepcidin promoter. In normal volunteers, the administration of erythropoietin was sufficient to lower serum hepcidin profoundly within less than 1 day,

in the absence of any significant changes in serum iron (Ashby et al. 2010). Apparently, stimulated erythrocyte precursors produce one or more hepcidin-suppressive factors but the molecular nature of this putative physiological erythroid regulator of hepcidin is not yet known. The suppressive effect on hepcidin is even more prominent under pathological conditions of expanded but ineffective erythropoiesis, seen in β -thalassemia and congenital dyserythropoietic anemias (Adamsky et al. 2004; Papanikolaou et al. 2005) where the large number of apoptosing erythrocyte precursors could generate additional suppressive factors. Two members of the BMP family, growth differentiation factor (GDF) 15 and twisted gastrulation (TWSG) 1, have been proposed to play a role in pathological hepcidin suppression during ineffective erythropoiesis (Tanno et al. 2007, 2009; Casanovas et al. 2011) but their specific regulatory role in iron homeostasis or pathology remains to be established.

Regulation of Hepcidin by Inflammation

During infections and inflammation, the synthesis and serum concentrations of hepcidin are greatly increased (Pigeon et al. 2001; Nicolas et al. 2002; Nemeth et al. 2003, 2004; Ganz et al. 2008). This regulatory circuitry is thought to be related to the possible role of hepcidin in host defense whereby hepcidin-mediated iron restriction may limit microbial growth. Multiple cytokines stimulate hepcidin transcription during inflammation, chief among them IL-6 (Nemeth et al. 2003, 2004) and the members of the BMP family (Maes et al. 2010). Interleukin-6 activates the JAK-STAT3 pathway (Fig. 3), with STAT3 binding to canonical binding sites in the hepcidin promoter, leading to transcriptional stimulation of hepcidin synthesis (Wrighting and Andrews 2006; Pietrangelo et al. 2007; Verga Falzacappa et al. 2007). The BMP and IL-6 pathways are synergistic through a mechanism that is not yet fully defined (Verga Falzacappa et al. 2008; Maes et al. 2010). Inflammation may contribute to elevated serum hepcidin levels seen in many adult patients with sickle cell anemia (Kroot et al. 2009; Porter 2009).

DISORDERS OF IRON HOMEOSTASIS

Iron Deficiency

Worldwide, iron deficiency is the most common iron disorder (see Miller 2012). Although it is thought of as a predominantly acquired problem caused by blood loss and inadequate iron intake, genetic predisposition may modulate the susceptibility to this condition as illustrated by genome-wide association studies (Benyamin et al. 2009a,b; Chambers et al. 2009; Tanaka et al. 2010). Not surprisingly, associations have been reported between serum iron concentrations and polymorphisms and mutations in transferrin, HFE, and MT2 (TMPRSS6).

Anemia of Inflammation (Anemia of Chronic Disease)

Infections and inflammatory disorders are a common cause of iron maldistribution, mediated by increased plasma hepcidin concentrations

that restrict the release of recycled iron from macrophages and hepatocyte stores, and interfere with the absorption of dietary iron. Iron restriction limits hemoglobin synthesis and contributes to anemia although other factors (inadequate erythropoietin production, cytokine effects on the marrow, decreased erythrocyte lifespan) may also participate, depending on the underlying disease. Clinically, this disorder is manifested most often as a normocytic normochromic anemia with hypoferremia, but the anemia can be microcytic, especially in children or very chronic inflammatory disorders.

Iron-Refractory Iron Deficiency Anemia

This relatively rare condition is detected in children who present with an unexplained hypoferremia and microcytic anemia resistant to oral iron administration, and partially resistant even to intravenous iron supplementation. The patients have elevated or high normal hepcidin levels (Finberg et al. 2008) in stark contrast to common iron deficiency in which serum hepcidin is very low or undetectable (Ganz et al. 2008).

Iron Overload from Transfusions

Blood transfusions deliver ~1 mg of iron for each mL of packed erythrocytes or more than 200 mg per each unit transfused, effectively bypassing the regulatory mechanisms that control iron intake. Excess iron may eventually cause toxicity and organ damage, and can only be removed by phlebotomy (contraindicated if patient is still anemic) or by treatment with chelating agents. Extrapolating from clinical data for iron-related toxicity in hereditary hemochromatosis, chelation therapy is recommended after 10–20 transfusions for those patients who need chronic erythrocyte transfusions (Brittenham 2011).

Hereditary Hemochromatosis and Related Disorders

Hereditary hemochromatosis is a group of genetic disorders that impede either hepcidin production or its regulation by iron (Nicolas et al.

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2001; Papanikolaou et al. 2005) or, very rarely, cause the resistance of ferroportin to internalization by hepcidin (Fernandes et al. 2009; Sham et al. 2009). In the order of increasing severity of hepcidin deficiency and iron overload, autosomal recessive forms can result from mutations in genes encoding HFE, Tfr2, hemojuvelin, and hepcidin. Ferroportin resistance to hepcidin is attributable to autosomal-dominant mutations in ferroportin that either interfere with hepcidin binding or with ferroportin internalization. Additional genes that caused iron overload in transgenic mouse models but have not yet been implicated in humans include BMP6 (Andriopoulos Jr. et al. 2009; Meynard et al. 2009) and neogenin (Lee et al. 2010). Hepatic iron overload can also develop as a part of more complex genetic diseases, including deficiencies of transferrin and ceruloplasmin and loss-of-function mutations in DMT1 (Pietrangelo et al. 2011). In these disorders, iron-restrictive anemia develops because of diminished iron release from macrophages (ceruloplasmin deficiency), iron delivery to erythrocytes (transferrin deficiency), or iron utilization by erythrocyte precursors (DMT1 loss of function). In contrast, simple hereditary hemochromatosis in humans has only modest effects on erythropoiesis, limited to a slight increase in mean corpuscular volume (McLaren et al. 2007).

Iron Overload Associated with Ineffective Erythropoiesis

Ineffective erythropoiesis is a condition in which large numbers of marrow erythrocyte precursors undergo apoptosis and so fail to complete maturation into erythrocytes. Genetic lesions that cause ineffective erythropoiesis prominently include thalassemias and congenital dyserythropoietic anemias. In these disorders, hepcidin is suppressed (Adamsky et al. 2004; Papanikolaou et al. 2005; Kearney et al. 2007; Casanovas et al. 2011) causing hyperabsorption of dietary iron and iron overload even in the absence of erythrocyte transfusions (Origgi et al. 2007). Transfusions partially relieve the erythropoietin-driven expansion of ineffective erythropoiesis and raise hepcidin concentrations (Kearney

et al. 2007) but cause iron overload owing to the iron content of transfused blood.

Modulation of Ineffective Erythropoiesis by Iron Availability

Recent studies in mouse models of thalassemia suggest that increased concentrations of plasma iron in this condition may further unbalance heme and globin synthesis and worsen ineffective erythropoiesis, and conversely, that restricting the iron supply through the administration of apotransferrin or hepcidin may improve erythropoiesis (Gardenghi et al. 2010a,b; Li et al. 2010). It remains to be seen whether similar interventions will be helpful in human disease.

CONCLUDING REMARKS

Iron homeostasis is intimately intertwined with erythropoiesis, the main destination of iron in humans and other vertebrates. Iron overload is a clinically important aspect of various hemoglobinopathies because of transfusion-induced iron overload and because of pathological suppression of hepcidin synthesis with resulting hyperabsorption of dietary iron. Advances in the understanding of iron homeostasis and its interactions with erythropoiesis should translate into improved outcomes for patients with hemoglobinopathies.

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