

# Iron in Hematology

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## Hepcidin and Its Role in Regulating Systemic Iron Metabolism

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Maintenance of stable extracellular iron concentrations requires the coordinate regulation of iron transport into plasma from dietary sources in the duodenum, from recycled senescent red cells in macrophages and from storage in hepatocytes. Moreover, during fetal development, the iron requirements of the fetus must be matched by the transport of maternal iron across the placenta. Hepcidin is a 25-amino acid disulfide-rich peptide synthesized in the liver that acts as a systemic iron-regulatory hormone by regulating iron transport from iron-exporting tissues into plasma. Hepcidin inhibits the cellular efflux of iron by binding to, and inducing the degradation of, ferroportin, the sole iron exporter in iron-transporting cells. In turn, hepcidin synthesis is increased by iron loading and decreased by anemia and hypoxia. Additionally, hepcidin synthesis is greatly

increased during inflammation, trapping iron in macrophages, decreasing plasma iron concentrations and causing iron-restricted erythropoiesis characteristic of anemia of inflammation (anemia of chronic disease). Recent studies indicate that hepcidin deficiency underlies most known forms of hereditary hemochromatosis. This implies that, with the exception of very rare mutations that affect the hepcidin gene itself or modify ferroportin to make it less responsive to hepcidin, hemochromatosis genes encode molecules that regulate hepcidin synthesis. The central involvement of hepcidin in iron regulation and its pathologies should make the eventual hepcidin assay useful for the diagnosis of iron disorders and the monitoring of their treatments. The development of hepcidin agonists and antagonists may provide useful therapeutics for the treatment of iron disorders.

### Absorption and Recycling of Iron

Iron is an essential component of hemoglobin and myoglobin and of many enzymes involved in redox reactions and energy metabolism. Iron is strictly conserved, in large part by recycling the iron (about 20 mg/day) from hemoglobin of senescent erythrocytes. Most of the iron in plasma is destined for erythropoiesis in the bone marrow. The daily loss of iron from the body is small (1-2 mg/day) and Western diets usually contain more iron than is necessary to replace the losses. Dietary iron is absorbed predominantly in the duodenum and absorption increases in response to increased iron requirements due to systemic iron deficiency,

anemia or hypoxia. Humans and other mammals lack effective mechanisms to excrete excess iron, and therefore the sole means of maintaining iron balance is by regulating intestinal iron absorption to match systemic iron requirements. In hereditary hemochromatosis dietary iron absorption is increased above the amount required to replace losses, and excess iron is deposited in the liver, endocrine glands, the heart and the skin. Eventually, the iron-overloaded organs suffer tissue damage, presumably through the iron-catalyzed generation of reactive oxygen species. At the opposite end of the spectrum of iron disorders are conditions in which dietary iron intake is adequate but iron absorption, recycling and distribution from iron stores are insufficient to meet the needs of hemoglobin synthesis in the bone marrow. These "iron-refractory" anemias include most prominently the anemia of inflammation (also called anemia of chronic disease). The discovery of hepcidin, its interaction with the iron exporter ferroportin, and its role in the regulation of iron transport has provided a molecular explanation of the homeostatic regulation of iron absorption and distribution, and of its malfunction in hereditary hemochromatosis and anemia of inflammation.

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## Hepcidin

Human hepcidin is a 25–amino acid peptide first identified in human urine and plasma.<sup>1,2</sup> The hepatocytes are the main cellular source of hepcidin<sup>1–3</sup> but recent studies also detected hepcidin synthesis in bacteria-activated neutrophils and macrophages,<sup>4</sup> albeit at a lower level than in hepatocytes. In addition to the 25–amino acid form, the urine also contains 20– and 22–amino acid forms truncated at the N-terminus. Hepcidin genes have also been identified in other vertebrates including mice, rats, pigs and several species of fish. The structure of the bioactive 25–amino acid form of hepcidin is a simple hairpin with 8 cysteines that form 4 disulfide bonds in a ladder-like configuration, including an unusual disulfide bond that connects two adjacent cysteines.<sup>5</sup> The hepcidin structure resembles that of many antimicrobial peptides, and indeed hepcidin exerts modest antimicrobial activity *in vitro*. Based on measured and estimated concentrations of hepcidin in biological fluids it is unlikely that the antimicrobial activity of hepcidin is an important biological function, but may be a residuum of its evolutionary origin or a consequence of the structural constraints dictated by its activity as an iron-regulatory hormone. The human hepcidin gene contains three exons that encode an 84–amino acid preprohepcidin with a characteristic furin cleavage site immediately N-terminal to the 25–amino acid major hepcidin species found in plasma<sup>6</sup> and in urine.<sup>1</sup> Because of the small size of hepcidin, its highly crosslinked structure, and evolutionary conservation, the generation of antibodies for immunoassays has been problematic. Despite these difficulties, early versions of urinary<sup>7</sup> and plasma<sup>6</sup> hepcidin assays have already proven useful in human research studies.

## Hormonal Activity of Hepcidin

The involvement of hepcidin in iron metabolism was suggested by the observation that hepcidin synthesis is induced by dietary iron,<sup>3</sup> but the specific role of hepcidin was demonstrated by the effects of hepcidin deficiency or excess in transgenic mouse models.<sup>8,9</sup> A mouse lacking hepcidin was a byproduct of targeting a nearby gene, *USF2*, and was found to have hemochromatosis with iron deposition in the liver and pancreas and sparing of the macrophage-rich spleen. This phenotype indicated that hepcidin controlled intestinal iron uptake and the retention of iron in macrophages. *USF2* disruption played no role in the phenotype since an independent *USF2* knockout line expressed normal amounts of hepcidin mRNA and had normal iron metabolism. Any doubts that hepcidin was essential for iron homeostasis were dispelled by the identification of two human families with severe juvenile hemochromatosis and hepcidin deficiency.<sup>10</sup> In each family, affected members had distinct homozygous destructive mutations in the hepcidin gene. The effects of hepcidin excess were shown in mice that overexpressed hepcidin-1 under the control of a liver-specific promoter.<sup>9</sup> The newborn mice with hepcidin excess suffered from severe iron-deficiency

indicating that fetal hepcidin inhibited the placental transport of iron to the developing fetus. Excessive hepcidin also blocked intestinal iron uptake as shown by the dependence of surviving mice on parenteral iron injections. These observations suggested that hepcidin was a negative regulator of iron transport in the small intestine and in the placenta and that it induced iron retention in (mainly splenic) macrophages engaged in the recycling of iron from senescent erythrocytes. Synthetic 25–amino acid hepcidin (but not its 20–amino acid N-terminally truncated variant) is the bioactive form of the peptide as shown by the hypoferremic effect of hepcidin in mice.<sup>11</sup> Injected hepcidin caused 75% decrease in serum iron levels within 1 hour and the effect persisted for more than 48 hours.

## Regulation of Hepcidin Synthesis by Iron

Hepcidin synthesis in mice is increased within 1 day of placement on a high iron diet<sup>7</sup> as well as by chronic iron loading,<sup>3</sup> and urinary hepcidin concentrations in humans are greatly increased within less than 1 day after iron ingestion.<sup>7</sup> It is not known how hepcidin is regulated by iron. The hepcidin gene and mRNA lack any canonical binding sites for iron-regulatory proteins, and the study of patients with hemochromatosis whose hepcidin regulation is defective (discussed in more detail later in this chapter) suggests the involvement of a previously uncharacterized pathway involving the proteins hemojuvelin and transferrin receptor 2. The receptor for bone morphogenic protein (BMP) may also be important for the regulation of hepcidin by iron and other stimuli, as suggested by the ability of hemojuvelin to potentiate BMP signaling,<sup>12</sup> by the strong stimulatory effects of bone morphogenetic proteins 2, 4 and 9 on hepcidin synthesis,<sup>13</sup> and by hemochromatosis and greatly diminished hepcidin synthesis in mice with liver-specific ablation of *SMAD4*,<sup>14</sup> an essential component of the BMP-signaling pathway. Although primary human and mouse hepatocytes in culture respond to inflammatory stimuli by increasing hepcidin mRNA,<sup>3,7,15</sup> iron loading of isolated primary hepatocytes does not affect hepcidin mRNA, indicating that other hepatic or extra-hepatic cell types may be involved in iron-dependent regulation of hepcidin synthesis by hepatocytes.

## Regulation of Hepcidin Synthesis by Anemia and Hypoxia

Most of the iron absorbed from the diet or recycled from hemoglobin is destined for developing erythrocytes whose production is increased after such erythropoietic stimuli as blood loss or hypoxia. It is therefore not surprising that hepcidin production is also homeostatically regulated by anemia and hypoxia.<sup>16</sup> When oxygen delivery is inadequate, the homeostatic response is to produce more erythrocytes. Thus hepcidin levels decrease, its inhibitory effects diminish, and more iron is made available from diet and from the storage pool in macrophages and hepatocytes. Although the human hepcidin promoter contains several consensus

binding sites for hypoxia-inducible factor (HIF), these are not typical and not conserved in other mammals, and their role, if any, has not yet been experimentally tested. In principle, the hepcidin response to anemia could be mediated by tissue hypoxia, increased erythropoietin levels, increased erythropoietic activity, or decreased plasma or tissue iron consequent to its consumption by the expanded pool of erythrocyte precursors. The importance of erythropoietic activity and the consequent iron utilization for hepcidin regulation is further supported by experiments in which anemic mice are prevented from mounting an erythropoietic response. In one study,<sup>17</sup> stimulation of erythropoiesis by phenylhydrazine-induced hemolysis resulted in hepcidin suppression as expected, but the simultaneous inhibition of erythropoiesis by irradiation prevented hepcidin suppression despite severe anemia. In addition, irradiation prevented hepcidin suppression after erythropoietin administration, ruling out the direct effect of erythropoietin on hepcidin synthesis. Although the study evaluated tissue iron rather than serum iron levels, it suggested that erythropoietic activity and the resulting changes in iron balance are the determining factors for the regulation of hepcidin in anemia. In another study<sup>18</sup> suppression of hepcidin by phlebotomy was reversed when erythropoietic response was inhibited by chemotherapeutic agents or by antibody to erythropoietin. These interventions also reversed the hypoferrremia due to increased erythropoiesis leaving open the possibility that both increased erythropoietic activity and the resulting hypoferrremia contribute to hepcidin suppression after phlebotomy. It appears that the erythropoietic signal predominates over the iron signal. Patients with thalassemia intermedia develop iron overload even if never transfused, and their urinary hepcidin levels are remarkably low despite high plasma transferrin saturations and systemic iron overload.<sup>19,20</sup> These observations point to erythropoietic activity as the most potent suppressor of hepcidin synthesis, but the specific mediator that conveys this signal from the bone marrow to the sites of hepcidin synthesis in the liver is not yet known.

### **Regulation of Hepcidin Synthesis by Inflammation**

Hepcidin is not only an iron-regulatory hormone but also an important link between host defense and iron metabolism. During infection and inflammation, hepcidin synthesis is markedly increased by a mechanism that is independent of iron status or erythropoietic activity.<sup>3,7,15,16</sup> The cytokine interleukin-6 (IL-6) is an important inducer of hepcidin synthesis during acute inflammation both in mouse models of inflammation and in humans.<sup>7,15</sup> In human volunteers who received IL-6 infusions, urinary hepcidin excretion was increased an average of 7.5-fold within hours, and hepcidin increase was accompanied by a 30% decrease in serum iron and in transferrin saturation. Similarly, during inflammation induced by subcutaneous injections of turpentine, normal mice showed a marked

decrease in serum iron (hypoferrremia) but this response was completely ablated in hepcidin-deficient mice and in IL-6-deficient mice. It therefore appears that the IL-6-hepcidin axis is critically important for the hypoferrremic response and that hepcidin is the main mediator of hypoferrremia of inflammation, at least acutely. However, recent data from mouse models indicate that other cytokines including IL-1, transforming growth factor- $\beta$  (TGF- $\beta$ ), and BMP 2, 4 and 9 also regulate hepcidin synthesis,<sup>12-14</sup> but their physiologic role in iron regulation in humans has not yet been documented. It remains to be seen whether other cytokines may also contribute to this response in humans.

It is worthwhile to consider briefly how and why hypoferrremia develops so rapidly within hours of an inflammatory stimulus. The plasma transferrin compartment contains about 3 mg of iron and functions as a transit compartment through which about 20 mg of iron flows each day, largely generated by recycling of senescent erythrocytes. In simplified terms, this means that plasma iron turns over every 3-4 hours. If hepcidin could completely block iron recycling, this would result in about a 30% drop in plasma iron in an hour. Because of the shorter lifespan of their erythrocytes, hypoferrremia develops even more rapidly in mice. The hypoferrremic response is likely to have a role in host defense but it remains to be shown which microbes are effectively targeted by this mechanism.

### **Mechanism of Action of Hepcidin**

Depending on the cell type, iron can be taken up by several distinct pathways. Bioavailable iron in the diet is mostly present either in its ferric ( $\text{Fe}^{3+}$ ) form or as heme. The uptake of ferric iron is mediated by a combination of a ferric reductase (such as the duodenal cytochrome B), which reduces iron to its ferrous ( $\text{Fe}^{2+}$ ) form, and a ferrous iron transporter DMT1 that moves iron across the cell membrane. Although DMT1 is essential for dietary iron absorption,<sup>21</sup> it is not certain which, if any, ferric reductase is required for this process. Dietary heme is absorbed by an important parallel pathway. A heme transporter, the apical heme carrier protein 1 (HCP1), was recently found in duodenal enterocytes,<sup>22</sup> but the contribution of specific heme transporters to iron absorption has not yet been established. Macrophages that recycle iron from senescent erythrocytes first phagocytose the erythrocytes and lyse them, then extract the iron from heme using heme oxygenase. Other cells import iron through transferrin receptors that capture and endocytose diferric transferrin, and then use low vacuolar pH to strip ferric iron from the transferrin-transferrin receptor complex. The transport of iron across vacuolar membranes into the cytoplasm of macrophages probably involves DMT1, which is specific for ferrous iron. The requisite iron reduction is likely catalyzed by a recently described erythroid endosomal ferric reductase that is essential for iron utilization in erythrocytes.<sup>23</sup> In the cytoplasm, iron is stored bound to ferritin. Some cell types, including duodenal enterocytes, placental syncytiotrophoblasts, macrophages and hepato-

cytes can export cellular iron to plasma. A transmembrane protein ferroportin is the sole known cellular exporter of iron and is highly expressed in cells that export iron. Studies of knockout mice with either constitutive or tissue-specific absence of ferroportin have confirmed that ferroportin is critically important for iron transfer from the mother to the fetus, for iron absorption in the intestine, and for iron export from macrophages.<sup>24</sup> The role of ferroportin in iron export from hepatocytes is much less certain. Ferroportin is assisted by a ferroxidase (hephaestin in enterocytes and ceruloplasmin in macrophages) to deliver ferric iron to plasma transferrin.<sup>25,26</sup> Recent studies indicate that hepcidin regulates major systemic iron flows by binding to ferroportin and inducing its internalization and lysosomal degradation.<sup>27,28</sup> As ferroportin is removed from cell membranes, iron export into plasma is proportionately decreased (**Figure 1**; see Color Figures page 507). This mechanism is sufficient to explain the regulation of iron absorption because absorptive enterocytes only perform their function for about 2 days before being shed from the tips of the villi into the intestinal lumen. Therefore, the transport of iron by ferroportin across the basolateral membrane of duodenal enterocytes determines whether the iron is delivered to plasma transferrin or removed from the body when the enterocytes shed into the intestinal lumen. When iron stores are adequate or high, the liver produces hepcidin, which circulates to the small intestine. There hepcidin causes ferroportin to be internalized, blocking the sole pathway for the transfer of iron from enterocytes to plasma. When iron stores are low, hepcidin production is suppressed, ferroportin molecules are displayed on basolateral membranes of enterocytes, and there they transport iron from the enterocyte cytoplasm to plasma transferrin. Similarly, the hepcidin-ferroportin interaction also explains how macrophage recycling of iron is regulated and accounts for the characteristic finding of iron-containing macrophages in inflammatory states characterized by high production of hepcidin. When hepcidin concentrations are high, hepcidin binds to ferroportin, ferroportin is internalized, iron export is blocked and iron is trapped within (predominantly splenic) macrophages. The regulation of iron flows by the hepcidin-ferroportin interaction is sufficient to explain the normal systemic iron homeostasis and its pathological alterations (**Figure 2**; see Color Figures page 507).

However, the direct interaction of hepcidin with ferroportin need not be the only pathway by which ferroportin density on cell membranes is regulated. There is evidence that ferroportin mRNA levels are also regulated by iron. In addition to direct effects on ferroportin and iron export, hepcidin would be expected to have secondary effects on cellular iron intake. These indirect effects could be activated by rising intracellular iron concentrations in enterocytes, macrophages or hepatocytes.

## The Role of Hepcidin in Hereditary Hemochromatosis

Hereditary hemochromatosis is characterized by excessive intestinal iron absorption from the diet, leading to accumulation of iron and eventually to the saturation of transferrin and the deposition of iron in vital organs. Free iron is toxic, probably due to its ability to catalyze the production of reactive oxygen products. Hemochromatosis may progress to liver failure, cardiomyopathy, destruction of endocrine glands and damage to joints. The specific genetic defects that cause this group of disorders have been discovered over the last decade, but the understanding of how these defects lead to iron overload has been much more elusive. The most common form of hereditary hemochromatosis in populations of European origin is due to mutations in the *HFE* gene, resulting in an autosomal recessive disorder of low penetrance that clinically predominantly affects older men. Mutations in transferrin receptor 2, *TfR2*, are much rarer but cause a similar phenotype. The autosomal recessive diseases due to mutations in the hepcidin gene *HAMP* or the hemojuvelin gene *HJV* most often cause a much more severe phenotype (“juvenile hemochromatosis”) affecting young men and women equally. The autosomal dominant hemochromatosis due to mutations in the ferroportin gene differs from other hemochromatoses by causing early iron overload in the Kupffer cells (liver macrophages) rather than hepatocytes, but more recent evidence suggests that some ferroportin mutations cause the classical pattern of parenchymal iron overload.<sup>29-32</sup>

It now appears that most forms of hemochromatosis are due to hepcidin deficiency (**Figure 2B**; see Color Figures page 507), and the autosomal dominant form is due to the deficiency or malfunction of the main target of hepcidin, the cellular iron exporter ferroportin.<sup>33-35</sup> In acquired (nongenetic) iron overload due to frequent transfusions, urinary hepcidin excretion and, presumably, hepcidin production are appropriately increased. This is not the case with the common form of hereditary hemochromatosis due to mutations in *HFE*, as several studies indicate that hepcidin is inappropriately low<sup>36,37</sup> in iron-overloaded patients with this disorder. Moreover, in the mouse model of *HFE* hemochromatosis, correction of the defect is achieved by overexpressing hepcidin-1.<sup>38,39</sup> This would suggest that the *HFE* gene contributes to the normal regulation of hepcidin synthesis and that the deleterious effects of *HFE* mutations are caused by hepcidin deficiency. Hepcidin is also deficient in patients with homozygous *TfR2* mutations.<sup>40</sup> In the more severe form of the disease, juvenile hemochromatosis, which results from defects in the hepcidin gene itself or a newly discovered gene, hemojuvelin,<sup>10,41</sup> urinary hepcidin is absent or nearly absent. In contrast, urinary hepcidin is elevated in some patients with autosomal dominant ferroportin mutations,<sup>19</sup> indicating that iron accumulation in this disorder could stimulate hepcidin production. Genetic lesions in ferroportin that decrease its

ability to export iron should cause iron overloading of macrophages, predominantly those recycling large amounts of iron, accompanied by mild anemia, whereas mutations that cause hyporesponsiveness of ferroportin to hepcidin should cause increased duodenal iron absorption and hepatocyte and other parenchymal iron overload. Early studies confirm that this is indeed the case.<sup>33-35</sup> The term “ferroportin disease” has been increasingly favored for those ferroportin defects that cause predominantly iron loading of macrophages to distinguish them from hemochromatoses that cause iron-loading of hepatocytes and other parenchymal cells.

### The Role of Hepcidin in Iron-Loading Anemias

Iron-loading anemias are characterized by ineffective erythropoiesis and increased intestinal iron absorption. Erythrocyte transfusions further exacerbate the iron overload. The most common iron-loading anemias are the intermediate and major forms of  $\beta$ -thalassemia, but other rare anemias are also complicated by iron loading, including congenital dyserythropoietic anemia, X-linked sideroblastic anemia and anemias associated with DMT1 mutations. In the presence of systemic iron overload, urinary hepcidin concentrations were low in patients with thalassemia intermedia and congenital dyserythropoietic anemia as well as in a patient with DMT1 mutation<sup>19,20</sup> (Pospisilova D et al, submitted). Patients with thalassemia major in whom iron overload was more severe and anemia was partially relieved by transfusions, had urinary hepcidin concentrations that were higher than in thalassemia intermedia. We interpret these findings as supporting the dominant effect of erythropoietic drive as a suppressor of hepcidin synthesis. It is likely that the administration of exogenous hepcidin could prevent the iron overload in iron-loading anemias, but this may be a delicate balancing act because excess hepcidin could impair the release of recycled iron from macrophages,

limit the supply of iron to the erythroid compartment and compromise erythropoiesis.

### The Role of Hepcidin in Anemia of Inflammation

Anemia of inflammation is a common consequence of chronic infections, noninfectious generalized inflammatory disorders and some cancers, but anemia of inflammation can also develop within days during sepsis. These anemias are characterized by decreased iron and iron-binding capacity (transferrin), increased ferritin, and the presence of iron in bone marrow macrophages, indicating impaired mobilization of iron from stores. The link between infections, hypoferremia and anemia of inflammation suggests that hypoferremia and anemia of inflammation are a part of the host defense response to infection. Induction of hepcidin by IL-6 and other inflammatory cytokines,<sup>7,15,42,43</sup> and the resulting limitation of iron supply to the bone marrow (Figure 2C; see Color Figures page 507), is a major contributor to the pathogenesis of anemia of inflammation.<sup>9,11,44,45</sup> Because most of the iron in the transferrin compartment is destined for the bone marrow, hypoferremia resulting from excess hepcidin diminishes the amount of iron available for hemoglobin synthesis and erythrocyte production. Indeed, clinical and experimental situations in which hepcidin is overproduced are commonly associated with anemia. In addition to the transgenic mice that overproduce hepcidin-1 and suffer from lethal anemia,<sup>9</sup> severe anemia is also seen in rare patients with liver tumors that autonomously produce hepcidin.<sup>44</sup> Patients with hypoferremia and anemia due to infections or inflammatory disorders have increased urinary hepcidin excretion. Patients on experimental IL-6 therapy developed anemia, as do patients with diseases associated with IL-6 excess such as Castleman’s syndrome, multiple myeloma and juvenile rheumatoid arthritis. Based on these observations, we and

**Table 1. Hepcidin in the pathogenesis of iron disorders.**

Disease	Defect	Hepcidin	Iron Absorption	Iron in Macrophages	Plasma Iron	Ferritin
Hereditary hemochromatoses (autosomal recessive)	Hepcidin gene (rare), regulators of hepcidin (common)	<b>Too low for iron load, decreased or absent*</b>	Increased	Decreased until late in the disease	Increased	Increased
Hereditary hemochromatosis (autosomal dominant)	Some ferroportin mutations	Insufficient data	Increased	Variable	Increased	Increased
Ferroportin disease (autosomal dominant)	Some ferroportin mutations	Variable, depending on mutation and age	Normal until late in the disease?	Increased	Normal until late in the disease	Increased
Iron-loading anemias	Increased “erythropoietic regulator,” expanded erythropoiesis	<b>Decreased unless frequent transfusions*</b>	Increased	Increased (due to hemolysis)	Increased	Increased
Anemia of inflammation	Increased IL-6 and other cytokines	<b>Increased*</b>	Decreased	Increased	Decreased	Increased

\***Bold** denotes that the hepcidin abnormality importantly contributes to pathogenesis

others have proposed that the pathogenic (as well as host defense) cascade that produces anemia of inflammation leads from IL-6 to hepcidin to hypoferrremia, and then to anemia of inflammation. Future studies should address the relative role of IL-6 and other cytokines in anemia of inflammation, and the relative contribution of hepcidin-independent mechanisms such as decreased erythropoietin production and direct suppressive effect of cytokines on erythroid progenitors.

## Summary

Hepcidin is the hormone responsible for the regulation of iron recycling and iron balance. It may have evolved from an antimicrobial peptide such as those expressed in the fat body (liver) of insects. Like the synthesis of insect antimicrobial peptides, hepcidin synthesis is induced by infection and inflammation. Specifically, IL-6, produced early during host defense, induces hepcidin production, which then inhibits iron recycling by macrophages, leading rapidly to hypoferrremia. The contribution of hypoferrremia to defense against microbes is not well understood, and almost certainly varies depending on the capability of the invading microbial species to obtain iron in the infected tissues. Hepcidin excess has emerged as the key pathogenic feature of anemia of inflammation, and hepcidin deficiency is responsible for most cases of familial hemochromatosis and for increased iron absorption in anemias with ineffective erythropoiesis (**Table 1**). The key role of hepcidin in iron homeostasis and its disorders suggests that its assay in blood or urine could prove useful for the diagnosis and monitoring of iron disorders. The development of pharmacologic hepcidin agonists and antagonists should be useful in the treatment of these conditions.

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