Hepcidin, the Recently Identified Peptide that Appears to Regulate Iron Absorption[1]

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ABSTRACT A newly identified iron regulator, hepcidin, appears to communicate body iron status and demand for erythropoiesis to the intestine, and in turn, modulates intestinal iron absorption. Hepcidin was first purified from human blood and urine as an antimicrobial peptide and was found to be predominantly expressed in the liver. A lack of hepcidin expression has been associated with iron overload and overexpression of hepcidin results in iron-deficiency anemia in mice. In addition, hepcidin levels decrease in mice fed a low iron diet and increase in mice fed a high iron diet. These observations support the role of hepcidin as a signal that limits intestinal iron absorption. Hepcidin expression is also affected by hypoxia and inflammation and is decreased in hemochromatosis patients. Thus, the relationship between body iron status and hepcidin is altered in hemochromatosis patients. In addition, hepcidin is decreased in HFE knockout mice, which demonstrates characteristics of iron overload as in hemochromatosis patients. Hence, HFE is suggested to act as a regulator of hepcidin expression. Transcription factors, such as C/EBPα, are also suggested to be involved in the regulation of hepcidin gene expression. However, much remains to be investigated in the regulation of hepcidin by iron, hypoxia and inflammation. J. Nutr. 134: 1–4, 2004.

KEY WORDS: • hepcidin • iron • iron absorption • iron stores

Under normal circumstances, organisms have a system to maintain normal iron homeostasis, because both iron deficiency and overload are associated with cellular dysfunction. Because mammals lack a regulated pathway for iron excretion, the regulation of iron absorption from the intestine and the recycling of iron from senescent red blood cells are crucial in maintaining iron balance. Several regulators of iron absorption have been suggested: *1*) the stores regulator, which modulates intestinal iron absorption in response to the level of body iron stores (1); *2*) the erythropoietic regulator, which adjusts intestinal iron absorption in response to the iron requirement for erythropoiesis independent of body iron stores (2); and *3*) the dietary regulator, which influences iron absorption by recent dietary iron intake independent of iron stores and rate of erythropoiesis. The enterocytes resist absorbing additional iron after being given an enteral bolus of iron, usually referred to as "mucosal block." The dietary regulator has received less attention, possibly because dietary iron intake is often correlated with the size of iron stores. The first two regulators communicate the iron status and the erythropoietic demand of the organism to the intestine to regulate intestinal iron absorption. However, the sites for both iron storage and erythropoiesis are remote from the intestine. Therefore, soluble components in plasma have been suggested to be the communicating signal between these sites. Only recently, with the identification of hepcidin, has the molecular component involved in communication between these sites become unraveled.

Identification of Hepcidin. Hepcidin has been independently isolated as a circulating antimicrobial peptide from human urine (3) and blood (4) by two research groups. This peptide of 20, 22 or 25 amino acids, differing by amino-terminal truncation, was named hepcidin (*hep*atic bacteric*id*al prote*in*). It contains four intrachain disulfide bonds and eight cysteine residues that are conserved among species (3,5,6) (**Fig. 1**). Even though the peptide was first isolated from urine and blood, hepcidin is predominantly expressed in liver in both mice and humans. Expression is also detectable in the heart and brain, but to a much less extent (3,6). Only one copy of the gene exists in humans, whereas two hepcidin genes (Hepc 1 and 2) were reported in mice (5,6). The genomic organization of hepc 1 and hepc 2 is similar, and expression of both genes is increased in carbonyl-iron–fed and iron-dextran–overloaded mice (7). Both the human and mouse hepcidin genes consist of three exons and two introns, and the third exon encodes the mature peptide found in urine. The exons encode an 84 amino acid (aa)[3] prepropeptide containing a typical 24 aa leader peptide at the N-terminal, a 35 aa pro-region, and the C-terminal 20 or 25 aa mature peptide (3,6) (Fig. 1).

Hepcidin and Iron Metabolism. The first link between hepcidin and iron metabolism arose from the study of Pigeon et al. (6), who were searching for new genes upregulated during iron excess. Hepcidin was isolated by suppressive subtractive hybridization performed between livers from carbonyl iron-loaded and control mice. Hepcidin mRNA was found to be increased in the liver of experimentally (carbonyl iron) and spontaneously (β_2-microglobulin knockout mice) iron-overloaded mice. The amount of mRNA was directly linked to liver iron concentration as evidenced by the dose dependence of mRNA induction in the carbonyl-iron–treated mice and the decreased expression of hepcidin when β_2-microglobulin knockout mice were fed a low iron diet. Thus, hepcidin expression increases with iron overload and decreases with iron depletion. Further studies conducted by Nicolas et al. (5,8)

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[3] Abbreviations used: aa, amino acid; C/EBPα, CCAAT/enhancer-binding protein; EPO, erythropoietin; HH, hereditary hemochromatosis; IL-6, interleukin-6; IRE, iron-responsive element; PHZ, phenylhydrazine; RE, reticuloendothelial; USF2, Upstream Stimulatory Factor 2.

human	RRRRRDTHFPIC I FCCGCCHRSH-C GM CCKT
pig	RLRR– DTHFPIC I FCCGCCRXAI–C GM CCKT
rat	KRRKRDTNFPIC LFCCKCCKNSS-C GL CC IT
mouse (1)	KRRKRDTNFPIC I FCCKCCNNSQ-C GI CCKT
mouse (2)	KRRKRD INFPIC RFCCQCCNKPS-C G I CCEE

FIGURE 1 Amino acid sequence of human hepcidin and the conserved eight cysteine residues among various species [modified from Nicolas et al. (8)].

increased our understanding of the role of hepcidin in iron metabolism. They investigated the iron overload phenotype of the USF2 (Upstream Stimulatory Factor 2) knockout mouse, which resembles that observed in human hemochromatosis (5). Iron accumulation was observed in the liver of *Usf2*$^{-/-}$ mice, serum iron was elevated, and macrophages did not accumulate iron. However, both HFE and TfR2, genes that are mutated in some human hemochromatosis patients, were not altered in *Usf2*$^{-/-}$ mice. This led the group to identify new genes that are accountable for this iron overload phenotype in *Usf2*$^{-/-}$ mice. Hepcidin was then isolated and found to be absent in the liver of *Usf2*$^{-/-}$ mice. The iron overload phenotype in the *Usf2*$^{-/-}$ mice was associated with the lack of hepcidin, rather than USF2 deficiency, because iron metabolism and hepcidin gene expression were found to be completely normal in other *Usf2*$^{-/-}$ mice (8). Because hepcidin is located downstream of the Usf2 gene in the genome (6), it is believed that the extinction of hepcidin in *Usf2*$^{-/-}$ mice is due to a specific *cis* effect of the targeting construct. To prove that hepcidin can directly fulfill the role of a sensor for iron homeostasis, transgenic mice overexpressing hepcidin in the liver were generated. The transgenic mice died perinatally with severe iron-deficiency anemia. The transgenic animals had decreased body iron levels and presented severe microcytic anemia (8). These results strongly support the role of hepcidin as a putative iron-regulatory hormone, limiting intestinal iron absorption and promoting iron retention in RE cells.

A potential role of hepcidin in fetal iron regulation has also been suggested (8). Hepcidin mRNA is normally undetectable at the end of gestation and reaches high levels only at adult age apart from a strong transient induction at birth in wild-type mice; however, in the transgenic mice overexpressing hepcidin, hepcidin was found in the developing liver even at the end of gestation, and remained high throughout development (8). The presence of hepcidin in the fetus at the end of gestation might alter maternal-fetal iron transport, leading to severe iron-deficiency anemia in newborn mice. Nicolas et al. (5) proposed that increased hepatocellular uptake of transferrin-bound iron by TfR2 leads to increased synthesis and secretion of hepcidin from the liver; hepcidin in plasma interacts with the β_2M-HFE-TfR1 complex and increases iron uptake into the duodenal crypt cells from the basolateral side, and increases iron retention by the RE macrophage. Crypt cells then differentiate into mature enterocytes, programmed to express less iron transport proteins, resulting in decreased dietary iron absorption (**Fig. 2***A*).

Another model from Anderson et al. (9) suggests that the liver detects any changes in diferric Tf levels via TfR2 and HFE/TfR1. This modulates liver hepcidin gene expression and secretion of hepcidin. A decreased diferric Tf/TfR ratio reduces hepcidin production and vice versa. Circulating hepcidin then modulates intestinal iron absorption by influencing FPN1 expression in the mature villous enterocyte instead of acting on the crypt cell (Fig. 2*B*).

An inverse correlation between hepcidin expression and the expression of duodenal iron transporters and iron absorption in rats was found (10). Rats fed an iron-replete diet were switched to an iron-deficient diet, and iron absorption increased, which was accompanied by an increase in duodenal expression of ferric reductase (Dcytb) and the duodenal iron transporters, DMT1 and FPN1. These changes correlated with decreases in hepatic hepcidin expression and transferrin saturation. At no time was a 2- to 3-d lag period evident between decreased hepcidin expression and increased expression of iron transporters, suggesting that hepcidin acts directly on mature villus enterocytes instead of crypt cells, which may take 2–3 d to mature and migrate to the villus. This may support the latter proposed model.

No change in iron stores nor hematological parameters were observed in these animals, suggesting that hepcidin expression can be regulated before iron stores and erythropoiesis are affected. Furthermore, the results indicate that cellular iron

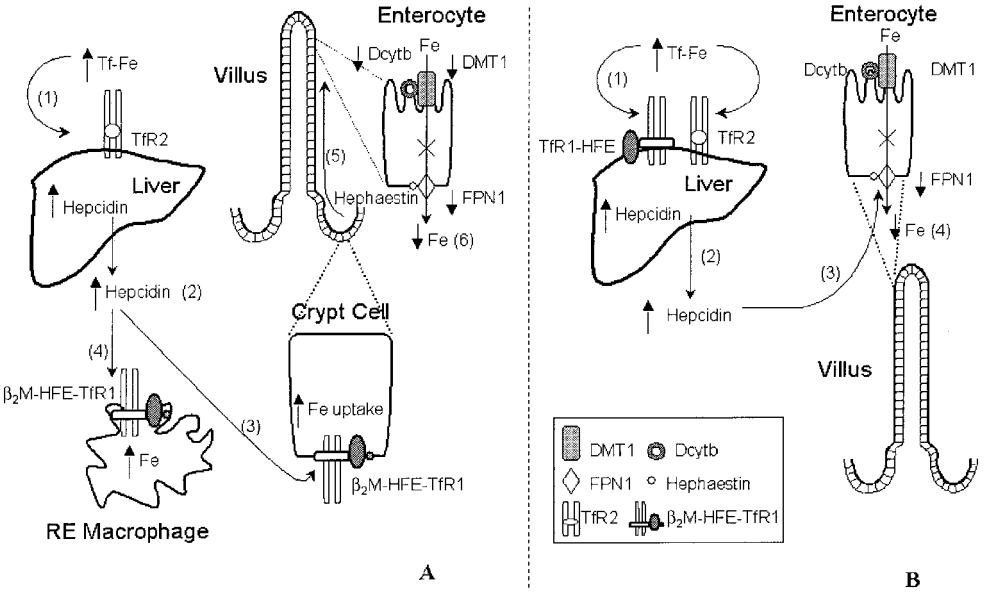

FIGURE 2 Proposed models of the hepcidin role in iron metabolism by (*A*) Nicolas et al. (5) and (*B*) Anderson et al. (9). *A*: (1) Increased transferrin-bound iron uptake by TfR2 leads to increased synthesis and secretion of hepcidin by the liver. (2) Hepcidin in the plasma interacts with the β_2-HFE-TfR1 complex and causes (3) increased iron uptake into the crypt cells and (4) increased iron retention by RE macrophage. (5) Crypt cells then mature into enterocytes, which are programmed to express less iron transport proteins, and hence (6) decrease iron absorption. *B*: (1) Increased transferrin-bound iron is detected by the liver via TfR2 and HFE/TfR1. (2) This leads to increased synthesis and secretion of hepcidin by the liver. (3) Hepcidin in the plasma interacts directly with the mature enterocytes and regulates FPN1 expression, and thus (4) influences iron absorption.

concentration is not the only factor affecting hepcidin expression.

Hepcidin gene expression was also examined in two other models of anemia in mice: *1*) acute hemolysis, provoked by phenylhydrazine (PHZ); and *2*) bleeding provoked by repeated phlebotomies (11). Hepcidin was dramatically decreased in both situations. The inhibitory effect of PHZ was still observed in mice experimentally iron-loaded by iron-dextran injection, suggesting that the anemia-induced decrease in hepcidin gene expression was independent of iron stores. In addition, the hepatic iron level was not decreased in either model of anemia, suggesting that apart from iron, another signal may be regulating hepcidin, which led the investigator to examine the effect of hypoxia on hepcidin.

Hepcidin and Hypoxia. Hepcidin has been identified as the regulator that communicates the body iron stores to the intestinal absorptive cells. Evidence also suggests that hepcidin may act as the erythroid regulator that transmits the erythroid demand of the organism to the enterocyte. Erythropoietin (EPO) production is stimulated when hypoxia occurs, which in turn increases RBC synthesis, resulting in increased oxygen supply. Increased intestinal absorption is also seen in hypoxia (12). Downregulation of hepcidin gene expression in mice housed in hypobaric hypoxia chambers and in human HepG2 and Hep3B hepatoma cells under hypoxic conditions was reported (11). This decrease in hepcidin could explain the increased iron release from reticuloendothelial cells and the increased intestinal iron absorption during hypoxia, which helps to supply more iron for erythropoietic activity. Indeed, injection of EPO was found to dramatically decrease liver hepcidin gene expression in mice (11). This suggests that hypoxia acts on both erythropoiesis induction and hepcidin gene downregulation through EPO.

Hepcidin and Inflammation. Hepcidin is also enhanced by inflammatory stimuli, such as bacterial challenge in bass liver (13). In mice, hepcidin mRNA increases after partial hepatectomy (14), by lipopolysaccharide (6) and turpentine (11). Inflammation and infection are associated with anemia of chronic disease, which is characterized by decreased RBC survival, impairment of iron efflux from macrophages and enterocytes, and erythroid precursors respond poorly to EPO (15–17). Weinstein et al. (18) reported that turpentine injection results in anemia in mice, a reduction in RBC mass, hemoglobin and serum iron, which is accompanied by increased liver hepcidin gene expression. However, this hyposideremic effect of turpentine was completely blunted in hepcidin-deficient mice. The upregulation of hepcidin induced by turpentine could explain the inhibition of iron release by RE cells, occurring during inflammation, and inhibition of iron absorption, thus contributing to the anemia. This demonstrated that hepcidin acts as a positive acute-phase response peptide, and plays a major role in the dysregulation of iron homeostasis during inflammation. In humans, urinary excretion of hepcidin is greatly increased in patients with iron overload, infections, or inflammatory diseases (19). Hepcidin excretion in the urine correlates well with serum ferritin levels, which are regulated by similar pathologic stimuli (19). The response in hepcidin to stress and inflammation most likely reflects the original antimicrobial role of this peptide. Weinstein et al. (18) also studied severe anemia of chronic disease in a group of patients with glycogen storage disease type 1a, and found that the anemia is directly related to the presence of hepatic adenomas, which expressed inappropriately high amounts of hepcidin in these patients. Interestingly, unaffected liver tissue of the same patients produces very low amounts of hepcidin, which is expected during iron deficiency. The anemia resolved after the adenomas were removed. The high level of hepcidin produced by the adenoma tissue is believed to alter iron homeostasis causing anemia in those patients.

Hepcidin in Mutant Mice. *Sla* mice have a mutation in the hephaestin gene, which causes impairment of iron release from the intestine, resulting in iron-deficiency anemia. The *mk* mice have a mutation in the DMT1 gene, also resulting in iron deficiency anemia, but this is due to decreased intestinal iron absorption and uptake by erythroid precursors. Both of these mutant mice have markedly decreased liver hepcidin gene expression (18). The *hpx* mice are anemic because of an aberrant splicing of the transferrin gene, which leads to decreased iron uptake by erythroid precursors, but also to systemic iron overload. Despite the severe liver iron load, hepcidin gene expression is decreased in *hpx* mice also (18), suggesting that the inhibitory effect of hepcidin by iron-restricted erythropoiesis occurs even with abundant iron stores.

Hepcidin and Hemochromatosis. The absence of the hepcidin gene results in hepatic iron accumulation, decreased iron in RE macrophages and elevated serum iron that mimics human hereditary hemochromatosis (HH) (5). HFE knockout ($HFE^{-/-}$) mice also demonstrate abnormal iron homeostasis similar to patients with hereditary hemochromatosis and mice lacking hepcidin. Therefore, several groups have examined hepcidin expression in HH patients or $HFE^{-/-}$ mice. Because hepatic iron loading is associated with increased hepcidin expression, one would expect increased hepcidin gene expression in $HFE^{-/-}$ mice and HH patients. However, decreased liver hepcidin expression was reported in $HFE^{-/-}$ mice (20). The authors speculate that decreased hepcidin expression relative to body iron stores contributes to the abnormalities in iron homeostasis characteristic of HH. In addition, the appropriate expression of hepcidin is dependent upon HFE. How HFE senses body iron and instigates an appropriate hepcidin response has yet to be elucidated. When $HFE^{-/-}$ and wild-type mice were fed a 2% carbonyl iron diet, which led to similar iron loading in both groups, it induced a fivefold increase in liver hepcidin in the wild-type mice but no change in $HFE^{-/-}$ mice. The lack of upregulation of hepcidin in the $HFE^{-/-}$ mice was associated with sparing of iron deposition into the spleen. Furthermore, decreased hepcidin expression was found in HH patients and $HFE^{-/-}$ mice (21). This also demonstrates a lack of upregulation of hepcidin in HFE-associated HH despite hepatic iron overload. Using microarray to assess changes in duodenal and hepatic gene expression in $HFE^{-/-}$ mice, a reduction in hepcidin expression was reported (22). When $HFE^{-/-}$ mice were crossed with transgenic mice overexpressing hepcidin it was found that hepcidin inhibits the iron accumulation normally observed in $HFE^{-/-}$ mice. These results indicate that sustained high levels of hepcidin expression prevents liver iron accumulation in spite of the absence of HFE. The authors suggest a model in which HFE acts as a regulator of hepcidin expression and hepcidin, in turn, modulates intestinal iron absorption at the level of the enterocyte.

Mutations in the hepcidin gene were identified in two families with juvenile hemochromatosis (23). The first mutation is a deletion of a guanine in exon 2 at position 93 of hepcidin cDNA, which results in a frameshift, which may translate as an elongated abnormal pro-hepcidin peptide. Because the frameshift occurs after residue 31, the active peptides

and the cysteine motif are completely disordered. The second mutation is a C→T substitution at position 166 in exon 3 of hepcidin cDNA, which changes arginine at position 56 to a stop codon, and this produces a truncated pro-hepcidin lacking all mature peptide sequences. The association of mutations in the hepcidin gene with juvenile hemochromatosis strengthens the role of hepcidin in maintaining iron balance in humans.

Regulation of Hepcidin. The cellular and molecular mechanisms regulating hepcidin gene expression in response to iron status are not yet understood. Because no iron-responsive element (IRE) has been identified in the transcript, hepcidin expression is not regulated by the IRE/iron-regulatory protein system. The transcription factor CCAAT/enhancer-binding protein (C/EBPα) has been proposed to be involved in this iron-mediated increase in hepcidin expression (24). The sequence analysis of the 5′-flanking region of the human and mouse hepcidin gene identified several binding sites for liver-enriched transcription factors (C/EBP) and hepatocyte nuclear factor 4 (HNF4). Hepatic C/EBPα null mice exhibit a pronounced decrease in hepcidin gene expression, which is accompanied by iron accumulation in periportal hepatocytes. Iron overload results in an increase in both C/EBP protein and hepcidin transcripts. Hepcidin expression has also been shown to be dependent on hepatocyte differentiation status (6,24) as it decreases spontaneously in conventional mouse hepatocyte culture, is undetectable in hepatic cell lines, and the expression is higher in adult liver as compared to fetal liver. In vitro iron loading of primary human hepatocytes downregulates hepcidin mRNA (19), which is inconsistent with in vivo findings, suggesting that in vivo regulation of hepcidin expression by iron stores involves complex indirect effects. Interleukin-6 (IL-6), a macrophage produced cytokine, but not IL-1 and TNF-α, has been shown to stimulate hepcidin expression by hepatocytes (19). This observation establishes a direct connection between cytokine production and hepcidin expression. However, much remains to be investigated in the regulation of hepcidin by hypoxia, inflammation and iron.

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