

Hepcidin: a crucial peptide for normal and pathological iron metabolism

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Abstract

The recently discovered liver hormone hepcidin appears to be the central regulator of iron homeostasis. It offers a unifying explanation for as different abnormalities in iron metabolism as those seen in anemia of chronic disease and hereditary hemochromatosis and a better understanding of how iron absorption and distribution are regulated in health and in certain diseases. Besides hepcidin's potential use in diagnosis, hepcidin agonists and antagonists may prove valuable in disease prevention and therapy.

Keywords: *hepcidin, iron homeostasis, hereditary hemochromatosis, anemia in chronic disease*

Both iron deficiency and its excess in the body may have severe pathological consequences. Mechanisms must therefore exist that strictly regulate iron metabolism to maintain body iron content within fairly narrow limits.

Iron homeostasis regulation is performed exclusively at the level of entry of iron in the body by intestinal absorption. Evidence for a humoral regulatory factor was provided by early experiments: serum from iron-loaded rats inhibited iron absorption in the duodenum of normal rat. For many years it remained unidentified, but recent studies indicate that a peptide hormone - hepcidin - may play a crucial regulatory role in normal iron homeostasis, hemochromatosis and the anemia of chronic disease.

Hepcidin was discovered in 2000 by two independent groups searching for novel antimicrobial peptides in body fluids. The peptide found in serum was called LEAP-1 (liver - expressed antimicrobial peptide 1) and the same cysteine-rich peptide, described in the urine,

was named hepcidin (hepatic bactericidal protein). The role of hepcidin in iron homeostasis was revealed by two French groups working independently: dietary iron loading increased hepcidin mRNA in mice and the accidentally removing of the hepcidin gene (during knock-out mice generation) resulted in an iron-loading pattern that mimicked hereditary hemochromatosis^{5, 8, 9}.

Enterocytes, macrophages of the reticuloendothelial system and hepatocytes - the cells involved in iron absorption and storage - are the cellular targets of hepcidin. By binding to and causing degradation of ferroportin (the iron exporter protein), hepcidin prevents iron exit from these cells determining thus the amount of iron absorbed from the intestine and released from the storage sites.

Liver expression of hepcidin is regulated by factors long ago known to regulate intestinal iron absorption (iron stores, erythropoietic activity, hemoglobin, oxygen, cytokine lev-

els in the blood). When any of these factors undergoes a change, iron absorption varies inversely with hepcidin expression.

Normally, low body iron levels decrease hepcidin expression, while high ones increase it. However, hepcidin expression is inappropriately low in hereditary hemochromatosis (HH) and increased in the anemia of chronic disease (ACD). Several genes have been implicated in the pathogenesis of hereditary hemochromatosis characterized by excessive iron absorption in the intestine and iron deposition in vital organs. The HFE gene is mutated in most of the HH patients, the gene coding for hepatocyte-expressed transferrin receptor type 2 (TfR2, that may act as a sensor of circulating iron) in others, hepcidin being deficient in both conditions. The hepcidin gene itself (HAMP gene) or a recently discovered gene, hemojuvelin, are affected in the more severe juvenile form of HH and hepcidin is absent or nearly absent. Finally, some of the mutations in the ferroportin gene are associated with deficiency or malfunction of the ferroportin protein, while others result in partial or complete ferroportin resistance to inhibition by hepcidin. The iron homeostasis abnormalities in ACD (an anemia of infections, inflammatory disorders and some cancers) are the converse of those in HH. Hepcidin expression is increased due to the inflammatory cytokine IL-6, causing iron retention in enterocytes and reticuloendothelial macrophages; hypoferremia and iron-restricted erythropoiesis result. The sequence of pathogenic events (and host defense) leads thus from cytokine to anemia^{2, 3, 5}.

Hepcidin levels in the serum of chronic renal insufficiency (CRI) patients without anemia are significantly higher than in hereditary hemochromatosis patients or healthy subjects, suggesting that the kidneys may be involved in metabolism and/or elimination of the circulating peptide. The kidney hormone erythropoietin (EPO) was recently shown to downregulate liver hepcidin gene expression. Accordingly, EPO

could act as an erythropoiesis stimulatory factor on the one hand and as a hepcidin inhibitory hormone on the other. Thus, another explanation for enhanced hepcidin concentrations in CRI patients could be the EPO deficiency encountered in renal insufficiency. However, enhanced levels of serum hepcidin were measured in CRI patients in spite of being treated with the hepcidin inhibitory hormone EPO, supporting the renal filtration of hepcidin, impaired in this clinical setting. In contrast, CRI patients with anemia show serum hepcidin levels significantly lower than in CRI patients without anemia, despite renal insufficiency leading to accumulation of the peptide hormone. Down-regulation of hepcidin in CRI anemia may reflect reactive physiological modulation of the peptide to enhance intestinal iron absorption and iron release from reticulo-endothelial macrophages, the negative effect of anemia on hepcidin gene expression dominating over the positive effect of iron. Blood loss appears to be the cause of decreased hepcidin in CRI anemia, EPO therapy being ruled out by results in CRI patients without anemia⁷.

Alcohol consumption causes, besides alcoholic liver disease, body iron overload by down-regulating hepcidin transcription in the liver; this will result in further aggravation of the already existing disease of the liver. Moreover, alcohol renders synthesis of hepcidin insensitive to body iron levels. In hereditary hemochromatosis, increased down-regulation of hepcidin expression caused by alcohol intake increases disease severity of these patients. Thus, alcohol and iron, acting synergistically, augment each other's deleterious effects⁶.

Hepatic iron overload is also encountered in chronic hepatitis C patients, involving, as in alcoholic liver disease, mainly the Kupffer cells. Hepcidin expression has been found to be significantly lower in HCV+ patients as compared to the HBV+ group of patients or the HCV&HBV negative group investigated, and TfR2 expression in the liver is higher in HCV+

patients when compared with HBV+ patients. Hepcidin expression was shown to be decreased by Tfr2 gene mutations, both in humans and mice. However, hepcidin expression is low in chronic hepatitis C despite increased Tfr2 expression, further investigations being needed to clarify the distinct interactions between hepcidin, Tfr2 and iron accumulation in the liver of HCV patients.

Multiregulatory mechanisms of hepcidin production are suggested by hepcidin correlating with several iron store, hematological and inflammatory parameters in patients with various liver diseases⁴.

Iron-loading anemias (the intermediate and major forms of beta-thalassemia for example) are characterized by inefficient erythropoiesis and increased intestinal iron absorption. The higher urinary hepcidin is a consequence of higher hepcidin synthesis in thalassemia major (severe iron overload but anemia partially solved by transfusions). This may support the dominant effect of erythropoiesis as a stimulant. Erythropoiesis is higher in thalassemia intermedia and acts a suppressor of hepcidin synthesis⁵.

Hepatic hepcidin production is increased by IL-6, the same IL-6 being essential for the survival of myeloma cells - malignant plasma cells in the bone marrow in multiple myeloma (MM). Anemia, a prominent feature of MM, appears thus to be related to inflammatory cytokines, acting through hepcidin. MM would be an ideal clinical setting to test hepcidin's role in ACD pathogenesis. Hepcidin levels should be higher in MM patients and might correlate with prognosis (in accordance with the high IL-6 levels correlating with a poor progno-

sis). Also, anemic MM patients would probably benefit from hepcidin targeted therapy¹.

In addition to the potential usefulness of hepcidin in diagnosis and in providing a better understanding of iron disorder pathogenesis, hepcidin agonists and antagonists may become effective new tools in disease prevention and therapy^{1, 4, 6, 7}.

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