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Pathophysiology in Medicine: Hepcidin and iron regulation in health and disease

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Abstract

A decade ago hepcidin, an antimicrobial peptide with iron-regulatory properties, was discovered and proposed as playing a significant role in the pathogenesis of the anemia of chronic disease. Subsequent studies have demonstrated that hepcidin is the keystone of the linked systems of iron balance and iron transport in health and in disease. The definition of the role of hepcidin and of its regulation has permitted the mechanisms of disorders of iron homeostasis to be understood at a molecular level. Future studies may identify roles for hepcidin or hepcidin-related molecules in diagnosis and therapy.

Keywords

Iron; hepcidin; hemochromatosis; anemia

It has been postulated that the anemia of chronic disease (ACD; also called the anemia of inflammation), a syndrome in which serum iron is reduced despite adequate iron stores, evolved as an intrinsic antimicrobial response: in response to an inflammatory stimulus caused by an infection, a decreased serum iron would create an environment less favorable to the proliferation of iron-dependent bacteria¹. The discovery of hepcidin, a 27 kDa peptide component of the innate immune system which induces hypoferremia, provided a mechanistic basis for this hypothesis². Originally reported as liver-enhanced antimicrobial peptide (LEAP)-1, hepcidin is a type II acute phase inflammatory response protein, primarily induced in response to interleukin (IL)-6³. Subsequently, hepcidin has been shown to be a major regulator of normal iron balance and to play a significant role in the pathogenesis of iron disorders not associated with inflammation. The story of hepcidin is an example of how observations derived from the study of mechanisms of disease can elucidate normal physiology.

Function of hepcidin in normal iron regulation

Ferrous iron is absorbed in the duodenum and transported into the enteric mucosal epithelial cell (enterocyte) by divalent metal transporter-1 (DMT1). In the cell, it is converted enzymatically to the ferric form, and then is exported to the circulation by ferroportin. Once released from the enterocyte, ferric iron becomes bound to transferrin and is transported to other cells, for either metabolism or storage. Uptake into the cells is mediated through

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Note: Due to the limited number of references permitted by the format of this journal feature, it has been necessary to rely heavily on secondary sources such as review articles and chapters. The interested reader is encouraged to consult these articles and chapters to find citations for the primary sources, which will lead to a more detailed understanding of the topics discussed.

specific transferrin receptors, typically transferrin receptor (TfR) 1. As with the enterocyte, export of iron from other cells is also dependent on ferroportin⁴.

Ferroportin is both the only defined cellular iron exporter in enterocytes, macrophages, and hepatocytes, and the only known ligand for hepcidin^{4,5}. Hepcidin binds to ferroportin and causes its internalization and degradation⁶. Thus, in the presence of increased hepcidin levels, iron export is impeded from duodenal enterocytes or from stores in hepatocytes or macrophages. In contrast, suppressed hepcidin levels favor iron transfer into the circulation.

Regulation of hepcidin transcription

Hepcidin is regulated at the transcriptional level. As noted above, inflammation is one of the major inducers of hepcidin transcription. While the best described and probably primary regulator of the hepcidin response to inflammation is IL-6³, non-IL-6 dependent pathways play a role as well⁵. However, under physiologic conditions, the primary regulators of hepcidin transcription are iron and the degree of marrow erythropoietic activity.

Regulation by iron

Hepcidin transcription decreases in response to iron deprivation and increases with iron loading. This is regulated by a complex series of interrelated molecular interactions. The central pathway appears to lie through the bone morphogenetic protein (BMP) receptor, and most specifically through its ligand, BMP6. BMP6 transcription is increased by intracellular iron. The BMP6 thus generated binds to the BMP receptor on the hepatocyte surface, which then signals through Mad-related protein 4 (Smad4) to induce hepcidin transcription⁵. The other known proteins involved in the regulation of hepcidin by iron are largely modifiers of the BMP6/BMP receptor/Smad4 axis. Hemojuvelin (HJV), the product of hemochromatosis gene 2 (*HFE2*, also called *HJV*), is a BMP co-receptor and enhances signaling through the BMP receptor. Neogenin binds to HJV and enhances its effect on the BMP receptor. Matriptase-2, the product of the gene *TMPRSS6*, opposes this effect by cleaving HJV. When iron-saturated (diferric) transferrin binds to either TfR 1 or 2, the presence of iron is signaled through the hemochromatosis protein HFE. These interactions have been reviewed in more detail elsewhere⁵, and the differing functions of TfR1 and TfR2 in iron transport and regulation are discussed below.

Regulation by erythropoiesis

Erythropoietic activity is also a regulator of hepcidin transcription. Increased erythropoiesis downregulates hepcidin transcription. While this effect appears to involve the BMP/Smad axis much like that of iron does, the initiators appear to be products of erythroid progenitors or precursors. The two erythroid-derived inhibitors of hepcidin production currently known are growth and differentiation factor 15 (GDF-15) and twisted gastrulation protein (TWSG1)⁷.

Regulation of hepcidin transcription is summarized in Table 1.

Disorders resulting from primary abnormalities of hepcidin or hepcidin signaling (Table 2)

Hereditary hemochromatosis

As noted above, iron overload should be associated with an elevated circulating hepcidin level. This would result in a reduction in iron mobilization from the duodenal enterocyte to the circulation, and retention of iron in storage in macrophages and hepatocytes. In contrast, hereditary hemochromatosis comprises a collection of disorders characterized by abnormal

tissue iron deposition and a state of systemic iron overload, but which are associated with either decreased hepcidin production or functional resistance to hepcidin. The vast majority of hemochromatosis patients have a defect in one of the signaling pathways linked to the BMP6/BMP receptor/Smad4 axis, with a relative few having a defect in ferroportin or in the hepcidin gene itself.

HFE hemochromatosis (type 1 hemochromatosis) is by far the most common form of hereditary hemochromatosis, and is one of the most common genetic disorders encountered in practice^{4,8}. An autosomal recessive disorder, HFE hemochromatosis primarily results from mutations at two sites in the *HFE* gene: codon 282 (C282Y; cysteine → tyrosine) or codon 63 (H63D; histidine → aspartate). The clinical phenotype is of variable penetrance and may include arthropathy, endocrinopathy (particularly diabetes mellitus and hypogonadism), and liver dysfunction possibly culminating in cirrhosis and hepatocellular carcinoma. Clinical iron overload occurs with the homozygous state for C282Y and sometimes in compound heterozygotes (C282Y/H63D). Significant iron overload is uncommon in H63D homozygotes and does not occur in simple heterozygotes for either C282Y or H63D. Heterozygous patients do not have significant iron overload, although they may have some abnormalities in the percentage of transferrin saturation by iron. As noted above, the degree of iron overload is typically greater in C282Y homozygotes (the more common genotype) than in H63D homozygotes⁴. This presumably reflects differences in the way the two mutations alter the interaction between HFE and TfR1 or TfR2, giving rise to different effects on BMP receptor signaling.

Juvenile hemochromatosis (type 2 hemochromatosis), is the next most common hereditary hemochromatosis syndrome. Also autosomal recessive, the clinical phenotype is qualitatively similar to that of HFE hemochromatosis, but pathologic tissue iron deposition is more severe and the onset of symptomatology is more rapid, with onset at an earlier age and a higher degree of cardiac iron deposition⁴. Juvenile hemochromatosis results predominantly from mutations in *HJV* (type 2A), although a juvenile hemochromatosis phenotype resulting from a mutation of the hepcidin gene itself has been reported (type 2B)⁸.

TfR1 is present on essentially all cells, and is the “physiologic” receptor to which iron-bearing transferrin will normally bind to be internalized for either metabolism or storage. TfR2, in contrast, appears to function primarily as a regulator of iron homeostasis, and is more limited in its cellular distribution⁴. Mutations in TfR2 produce a hereditary hemochromatosis phenotype (type 3) resembling a milder form of juvenile hemochromatosis. Iron deposition becomes detectable earlier in life than it does with HFE hemochromatosis, but is less severe and less rapidly progressive than in juvenile hemochromatosis⁸.

Type 4 hemochromatosis, also called “ferroportin disease”, is the only autosomal dominant hereditary hemochromatosis syndrome. Type 4A is associated with elevated reticuloendothelial iron stores, but no pathologic iron deposition in normal tissues and no increase in iron saturation of transferrin. Type 4B resembles HFE hemochromatosis⁴. These differences derive directly from the effects of the responsible mutations in the ferroportin gene on the function and processing of ferroportin protein. In type 4A, mutant ferroportin is not transported normally from the endoplasmic reticulum to the cell membrane, and therefore iron is not exported from the macrophage or hepatocyte but is retained intracellularly. In type 4B, the mutant ferroportin is resistant to hepcidin, and so iron is exported more readily into the circulation. Type 4 hemochromatosis is the only hereditary hemochromatosis variant not associated with decreased hepcidin production⁸, since it is the only variant due to a defect not linked to the BMP receptor/Smad4 signaling pathway.

Iron-refractory iron deficiency anemia

Uncomplicated iron deficiency should be accompanied by a decrease in hepcidin production, allowing increased absorption of gastrointestinal iron and facilitating mobilization of iron from storage into the circulation. Inappropriate elevation of hepcidin is responsible for the disorder iron-refractory iron deficiency anemia (IRIDA). IRIDA is an autosomal recessive disease in which patients have an iron deficiency anemia that is truly refractory to oral iron, and only partially responsive to intravenous iron⁹. It is associated with severe congenital hypochromic microcytic anemia with red cells exhibiting very low mean corpuscular hemoglobin concentration, very low transferrin saturation, no response to oral iron and a limited, transient response to intravenous iron, and no evidence of any nutritional or blood loss etiology or active inflammation. Bone marrow examination after intravenous iron therapy shows reticuloendothelial iron deposition but absence of normal sideroblasts, which provides a clue to the underlying mechanism⁹. IRIDA is caused by mutations in *TMPRSS6*, the gene encoding matriptase-2. As noted earlier, matriptase-2 is a negative regulator of HJV. In the absence of matriptase-2, HJV enhances signaling through the BMP receptor, leading to increased hepcidin production⁵. This in turn impairs iron mobilization from the reticuloendothelial system as well as iron absorption from the gastrointestinal tract. This explains the findings on bone marrow examination after iron infusion. Oral iron is not absorbed from the duodenum as a consequence of increased hepcidin. Intravenously administered iron, which bypasses the gastrointestinal tract, can be utilized immediately to some extent for erythropoiesis, but most will be taken up into hepatocytes and marrow macrophages. Once that has happened, the stored iron cannot be mobilized effectively for erythropoiesis due to hepcidin-induced internalization and degradation of ferroportin. Treatment of IRIDA consists of periodic intravenous iron infusion.

Disorders resulting from secondary abnormalities of hepcidin or hepcidin signaling (Table 2)

Anemia of chronic disease/inflammation

ACD is second only to iron deficiency in frequency as an etiology of anemia. It is characterized by a decreased serum iron despite adequate reticuloendothelial iron stores, a relatively decreased erythropoietin concentration, and a blunted marrow erythroid progenitor response to erythropoietin. The pathophysiologic mechanisms implicated in ACD are all linked by an association with the cytokines which mediate the immune and inflammatory response¹⁰.

There are significant data, both from model systems and actual clinical scenarios, which suggest that hepcidin is the primary mediator of the inflammation-induced hypoferremia observed in ACD^{2,3}. Elevated levels of hepcidin in ACD have been reported³. While the iron abnormalities of ACD are not the sole feature of this syndrome, other studies have provided information suggesting that hepcidin can also be implicated in the other contributing pathogenetic processes of ACD¹⁰.

Iron-loading anemias

The term “iron-loading anemia” refers to anemia syndromes characterized by ineffective erythropoiesis, and in which systemic iron overload is a common feature. The classic examples of iron-loading anemia are congenital hemolytic syndromes, such as the thalassemias, but include the congenital dyserythropoietic anemias, and acquired myelodysplastic syndromes^{4,5}. While much of the systemic iron overload can be attributed to recurrent red cell transfusions, even transfusion-naïve patients with iron-loading anemia syndromes may show unexpectedly elevated ferritin levels or other markers of increased

iron stores. Increased marrow erythropoietic mass is a characteristic feature of ineffective erythropoiesis syndromes. The erythroid precursors and progenitors produce GDF15 and/or TWSG1^{5,7}, which then suppress hepcidin production and permit increased transfer of iron from the gut and the reticuloendothelial system into the circulation.

Chronic liver disease

Iron overload is also a feature of chronic liver disease. This has been attributed to decreased hepcidin production resulting from hepatocyte dysfunction, although there has been some speculation that the responsible defect may be at the DMT1 level^{4,5}.

Hepcidin in diagnosis and treatment: speculation

Validated assays for hepcidin have been developed, and a number of studies have investigated therapeutic alterations of hepcidin or hepcidin-related peptides in disease models⁵. At present, however, these remain essentially experimental tools.

Diagnostic assays of hepcidin, when they become available for clinical use in the next few years, will likely have their primary role in distinguishing cases of iron deficiency with inflammation from ACD¹⁰. It is less clear what role they might play in evaluation of potential iron overload disorders, since the overwhelming majority of such patients would be expected to have decreased hepcidin levels regardless of specific disease entity involved, with exception of ferroportin disease (type 4 hemochromatosis).

The role of hepcidin-based therapeutics in various diseases will be an interesting topic of investigation in the future. Anti-hepcidin therapies could potentially be used as treatment for the anemia of chronic disease, IRIDA, or ferroportin disease, while hepcidin replacement could potentially mitigate early iron overload in hemochromatosis and the iron-loading anemias. Given the role of hepcidin as a component of the innate immune system, and the importance of iron and iron-containing proteins in cellular processes, any studies performed will require careful design to identify unintended consequences.

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Table 1

Regulators of hepcidin transcription

Regulators	Mediators
Inflammation	<ul style="list-style-type: none">• IL-6• Other cytokine-mediated pathways
Intracellular iron status	BMP6/BMP receptor/Smad4 Modulators: HFE; HJV, Neogenin; Matriptase-2
Erythropoiesis	BMP6/BMP receptor/Smad4 Modulators: GDF-15; TWSG1

Abbreviations as noted in text.

Table 2

Disorders of hepcidin production or signaling

Disorder	Mechanism
Primary disorders	
<i>Decreased hepcidin production</i>	
Hereditary hemochromatosis (HH) type 1 (HFE hemochromatosis)	HFE mutation
HH type 2 (Juvenile hemochromatosis)	
HH type 2A	HJV mutation
HH type 2B	Hepcidin mutation
HH type 3	TfR2 mutation
<i>Normal hepcidin production</i>	
HH type 4 (ferroportin disease)	
HH type 4A	Decreased/absent membrane ferroportin
HH type 4B	Ferroportin resistance to hepcidin
<i>Increased hepcidin production</i>	
Iron-refractory iron deficiency anemia	Matriptase-2 (TMPRSS6) mutation
Secondary disorders	
<i>Increased hepcidin production</i>	
Anemia of chronic disease/inflammation	Inflammation-induced hepcidin production
<i>Decreased hepcidin production</i>	
Iron-loading anemias	Hepcidin suppression by GDF15/TWSG1 released from marrow erythroid precursors/progenitors
Chronic liver disease	Decreased hepcidin production due to hepatocyte dysfunction

Abbreviations as noted in text.