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The Iron Tale

If It Does Not Kill You, It Makes You Stronger (and Hepcidin Helps)

By Laura Silvestri

Correspondence: Laura Silvestri (e-mail: silvestri.laura@hsr.it).

Iron is an essential nutrient for almost all living organisms, from plants and bacteria to humans. Although a trace element, iron participates in many important biological processes, such as oxygen transport, DNA synthesis, energy production, and metabolism. The unique property of iron resides in its ability to exchange electrons with substrates. The same property is dangerous when iron is in excess, due to the generation of reactive oxygen species. Since organisms are strictly dependent on iron, they have developed several mechanisms to control adequate iron availability. In mammals, this function is exerted by the liver-produced peptide hormone hepcidin that coordinates dietary iron absorption and iron release from stores (liver and spleen), thereby avoiding iron accumulation or deprivation.

Hepcidin binds to and degrades the iron exporter ferroportin (FPN), expressed by virtually all somatic cells, but with a crucial role in those cell types that release iron into the blood, such as duodenal enterocytes, iron-recycling splenic macrophages, and hepatocytes. When hepcidin is high, FPN is degraded and iron is retained in cells. When hepcidin is low, FPN is stabilized at the cell surface and iron enters into the circulation.[1]

Due to the central role of iron in several biological functions, hepcidin expression is subject to highly complex regulatory mechanisms. Both increased body iron concentration and inflammation upregulate hepcidin, whereas the opposite occurs when iron is limiting or in case of high erythropoietic demand.

Major lessons on how iron levels are sensed are further learned from patients and mouse models characterized by inappropriate hepcidin production, as in hereditary hemochromatosis (HH) and in iron refractory iron deficiency anemia (IRIDA), characterized by inappropriately low and high hepcidin expression, respectively. The main regulator of hepcidin is the BMP-SMAD pathway that requires BMP type I (BMPRI) and II receptors (BMPRII), the coreceptor hemojuvelin (HJV), and BMP ligands such as the recently identified BMP2[2] and the iron-induced BMP6.[1] The immunophilin FKBP12 contributes to regulate this pathway by binding BMPRI to avoid ligand-independent receptor activation[3] (Fig. 1). It was long believed that hepatocytes are sufficient to control hepcidin expression. However, recent data clearly demonstrate that liver sinusoidal endothelial cells produce the BMPs required for hepcidin synthesis in hepatocytes[2,4] (Fig. 1). In addition, the BMP-SMAD pathway is further positively modulated by the second transferrin receptor TFR2 and the MHC class I-like molecule HFE. Mutations in HFE, TFR2, HJV, and hepcidin itself cause HH, characterized by iron overload in several organs due to low hepcidin production. A key question is how this pathway senses iron availability, either via iron-bound transferrin in the blood stream or via the iron stored in the liver. We now understand that iron-bound transferrin (holo-TF) upregulates hepcidin expression through TFR2 stabilization on the plasma membrane while increased liver iron concentration activates BMP6 transcription.[1] The evidence that BMP6-dependent hepcidin regulation is conserved in HH mouse models with genetic inactivation of TFR2, HFE, or HJV suggests the existence of a second, independent branch of the hepatic BMP-SMAD pathway. This pathway responds to circulating iron, is TFR2-dependent, and participates in the maintenance of basal hepcidin levels[5] (Fig. 1).

Hepcidin should be inhibited when body iron levels are decreased and when erythropoietic activity is high. A reduction in body iron concentration transcriptionally downregulates BMP6 and inhibits the TFR2 effect on the BMP-SMAD pathway. However, the key hepcidin inhibitor is the liver transmembrane serine protease TMPRSS6 that downregulates the BMP-SMAD pathway by cleaving the BMP coreceptor HJV upon its proteolytic activation (through an unknown mechanism) in iron deficiency. Indeed, TMPRSS6 mutations leave hepcidin upregulated even in conditions of low iron, thus making anemia refractory to oral iron administration because of a block in iron absorption, and partially refractory to parenteral iron (IRIDA)[1] (Fig. 1).

Laura Silvestri
Regulation of Iron Metabolism Unit, San Raffaele Scientific Institute, Milan, Italy
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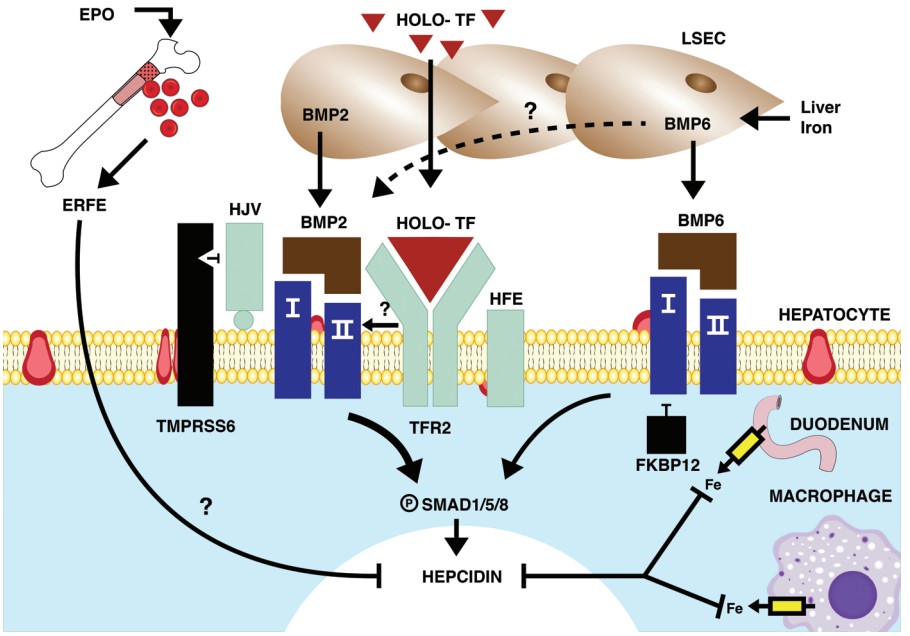

Figure 1. Model of hepcidin regulation by iron and erythropoiesis. In hepatocytes, 2 signaling pathways additively contribute to hepcidin expression. The core component of the pathway is composed of BMP type I (I) and II (II) receptors. The complex on the right responds to BMP6, is activated by increased liver iron concentration (?), and is active also in the absence of hemochromatosis proteins such as HJV, TFR2, and HFE. The complex on the left is activated by BMP2 and functionally dependent upon HJV, TFR2, and HFE. It is involved in the maintenance of basal hepcidin levels and through TFR2, whose membrane levels are stabilized by diferric (holo)-TF, it responds to changes in circulating iron (holo-TF). How TFR2 activates hepcidin is still unknown (?). BMP2 and BMP6 are predominantly produced by liver sinusoidal endothelial cells, indicating the relevance of liver cell crosstalk in hepcidin regulation. The BMP-SMAD pathway is inhibited by the serine protease TMPRSS6 through HJV cleavage. Erythropoietin (EPO), increased in hypoxia, stimulates proliferation and differentiation of erythroid precursors that release a soluble protein, erythroferrone (ERFE) in the circulation. ERFE inhibits hepcidin through an unknown mechanism (?) to sustain hemoglobin synthesis, a process that requires large amounts of iron.

Erythropoiesis, the major iron consumer in the body, signals its iron requirement to the liver by releasing soluble molecule/s that inhibit/s hepcidin. The only protein with a role as "erythroid regulator" in vivo is erythroferrone (ERFE), produced by erythroid precursors after erythropoietin (EPO) stimulation. Although the mechanism of hepcidin inhibition by ERFE is still unknown (Fig. 1), limiting the hepatic BMP-SMAD pathway is required for its effect.[6] ERFE knockout mice show blunted hepcidin downregulation after phlebotomy, confirming ERFE's role in stress erythropoiesis. TFR2 plays a dual role in this context. Being expressed not only in the liver but also in erythroid precursors, where it interacts with the EPO receptor (EPOR), it contributes to coordinate erythrocyte production with iron availability. Indeed, membrane TFR2 reduction by low circulating iron or its genetic inactivation favors EPO-EPOR signaling and inhibits hepcidin, increasing at the same time both proliferation and maturation of red blood cells and iron availability.[7]

The physiologic crosstalk between erythroid cells and the liver becomes detrimental in ineffective erythropoiesis as in β-thalassemia, in which chronic suppression of hepcidin leads to iron accumulation even independently from blood transfusions. Accordingly, hepcidin overexpression in β-thalassemic mice ameliorates iron overload as in HH, and in addition improves anemia. For these reasons, in the last years different approaches targeting hepcidin or hepcidin regulators have been proposed and tested in preclinical studies. Short hepcidin peptides (minihepcidins) effective in FPN degradation have the same efficacy of native hepcidin in reducing iron overload. An alternative method of increasing hepcidin in vivo is the inhibition of TMPRSS6 by antisense oligonucleotides or short interfering RNAs.[1] Both approaches synergize with the iron chelator deferiprone, providing a rationale for testing these compounds in patients. Another potential pharmacologic target for iron overload is FKBP12, a novel hepcidin inhibitor whose sequestration by drugs such as tacrolimus increases hepcidin in vivo.[3] Although ERFE is upregulated in β-thalassemia mice, its inactivation slightly increases hepcidin and moderately reduces iron overload, but does not improve anemia,[8] limiting its potential therapeutic role.

Hepcidin is transcriptionally activated by proinflammatory cytokines such as IL6. During infections or inflammation, the TLR4-IL6-STAT3 signaling pathway drives hepcidin upregulation and iron retention through FPN degradation. This process rapidly induces hypoferremia and is detrimental to microbes that use iron as a growth factor. However, the control of proliferation of extracellular pathogens through iron restriction becomes a double-edged sword in chronic diseases and cancer, causing anemia of inflammation (AI).[1] Hepcidin inhibition improves AI through iron mobilization from stores. Hepcidin can be inhibited by neutralizing antibodies or by antibodies that target the hepcidin-binding site of FPN. Other approaches involve the inhibition of the liver BMP-SMAD pathway as through anti-HJV antibodies or BMP receptor inhibitors such as LDN-193189[1] or momelotinib,[9] and non-anticoagulant heparins.[10]

The development of new pharmacologic approaches targeting the hepcidin–ferroportin axis may have great impact on the clinical management of patients with iron overload or iron-restricted anemia and potentially to other rare erythroid disorders.

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