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Critical Review

Systemic Regulation of Intestinal Iron Absorption

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Summary

The intestinal absorption of the essential trace element iron and its mobilization from storage sites in the body are controlled by systemic signals that reflect tissue iron requirements. Recent advances have indicated that the liver-derived peptide hepcidin plays a central role in this process by repressing iron release from intestinal enterocytes, macrophages and other body cells. When iron requirements are increased, hepcidin levels decline and more iron enters the plasma. It has been proposed that the level of circulating diferric transferrin, which reflects tissue iron levels, acts as a signal to alter hepcidin expression. In the liver, the proteins HFE, transferrin receptor 2 and hemojuvelin may be involved in mediating this signal as disruption of each of these molecules decreases hepcidin expression. Patients carrying mutations in these molecules or in hepcidin itself develop systemic iron loading (or hemochromatosis) due to their inability to down regulate iron absorption. Hepcidin is also responsible for the decreased plasma iron or hypoferremia that accompanies inflammation and various chronic diseases as its expression is stimulated by pro-inflammatory cytokines such as interleukin 6. The mechanisms underlying the regulation of hepcidin expression and how it acts on cells to control iron release are key areas of ongoing research.

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INTRODUCTION

Iron plays an important role in a wide variety of metabolic processes and is an essential nutrient for almost all living organisms. However, in excess it is potentially toxic to cells due to its ability to catalyse the production of reactive oxygen species. Tight regulation of iron uptake and storage at both the cellular and whole body levels is therefore essential. For the maintenance of body iron homeostasis, there must be effective communication between the key sites of iron utilization (e.g., the erythroid marrow) and storage (e.g., the liver and reticuloendothelial system), and the site of absorption in the small intestine. Since these sites are anatomically distant, the most likely form of communication is via a plasma-borne factor. Candidates for a circulating signal influencing iron absorption have been sought for some time, particularly in various plasma mediators of iron status and erythropoiesis e.g. transferrin (Tf), Tf-bound iron, non-transferrin bound iron, ferritin and erythropoietin. However, with recent advances in our understanding of iron metabolism, there is now significant evidence to suggest that the circulating liver-derived peptide hepcidin is the key systemic regulator of iron homeostasis.

BODY IRON LEVELS ARE CONTROLLED THROUGH INTESTINAL ABSORPTION

Since it is not actively excreted, the amount of iron in the body must be controlled at the point of absorption in the small intestine. Iron absorption occurs mainly in the duodenum and upper jejunum, though small amounts may also be absorbed from the stomach, ileum and colon (*1*). At the cellular level, iron is absorbed through the differentiated epithelial cells of the mid to upper villus. Iron is provided to the body in various forms through the diet, but is primarily absorbed as either inorganic iron or as heme iron. The passage of iron through the enterocyte into the circulation is depicted in Fig. 1. The first step is termed brush border or mucosal uptake. In this step, dietary Fe^{3+} (ferric iron) is first reduced to Fe^{2+} (ferrous iron), most likely by the ferric reductase duodenal cytochrome b (Dcytb), making it available for transport across the brush border membrane by divalent metal transporter 1 (DMT1). The absorption of heme iron across the brush border occurs more efficiently but the mechanism is poorly characterized. Once inside the enterocyte, heme and non-heme iron enter a common transit pool, where iron may be chelated by low molecular weight compounds or bound to a protein ligand such as ferritin. The second stage of iron absorption is termed basolateral or serosal transfer, where iron is transported from the enterocytes into the intestinal capillaries across the

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basolateral membrane via the iron transporter ferroportin 1 (also known as Ireg1). The ferroxidase hephaestin (Hp) is also essential for basolateral transfer, although whether it acts on the basolateral membrane or intracellularly has yet to be resolved. Iron that is not transferred across the basolateral membrane of the enterocyte is stored within ferritin and is lost after 1–2 days when the epithelial cells are sloughed at the villus tip. Once absorbed, Fe^{3+} is bound to circulating plasma Tf which transports it around the body to various tissues. The transferrin-bound iron is delivered to the cells after binding to Tf receptors (TfR1 and, in some tissues, TfR2 as well) on the cell surface. Iron may also be released from these cells and re-enter the pool of transferrin-bound iron after export by ferroportin1 and oxidation to Fe^{3+} by the ferroxidase ceruloplasmin (Cp).

ABSORPTION IS ALTERED IN RESPONSE TO CHANGES IN BODY IRON REQUIREMENTS

There are many factors that influence intestinal iron absorption, including the systemic stimuli of inflammation, hypoxia and pregnancy. However, the two most prominent factors are the level of body iron stores (mainly represented by iron in the liver and reticuloendothelial macrophages) and the iron requirements of the developing erythroid mass. Quantitatively, the most significant pool of iron in the body lies in the red blood cells. In the marrow, iron is used both to meet the metabolic requirements of the developing erythrocytes and for incorporation into new hemoglobin molecules, with the latter being the major sink. At the end of their life, senescent red cells are taken up by the reticuloendothelial (RE) macrophages where hemoglobin is degraded and the iron is either stored or released (presumably via ferroportin 1) back to the plasma transferrin pool. When erythropoiesis is stimulated, iron will be drawn from the plasma transferrin pool and macrophage iron release may be increased to meet the enhanced demand. If the level of erythropoiesis is sufficiently high, then the rate at which iron is recycled through the RE system will be insufficient and iron absorption will also be stimulated. Similarly, the body appears to contain an optimum level of storage iron and when stores decline, iron absorption increases.

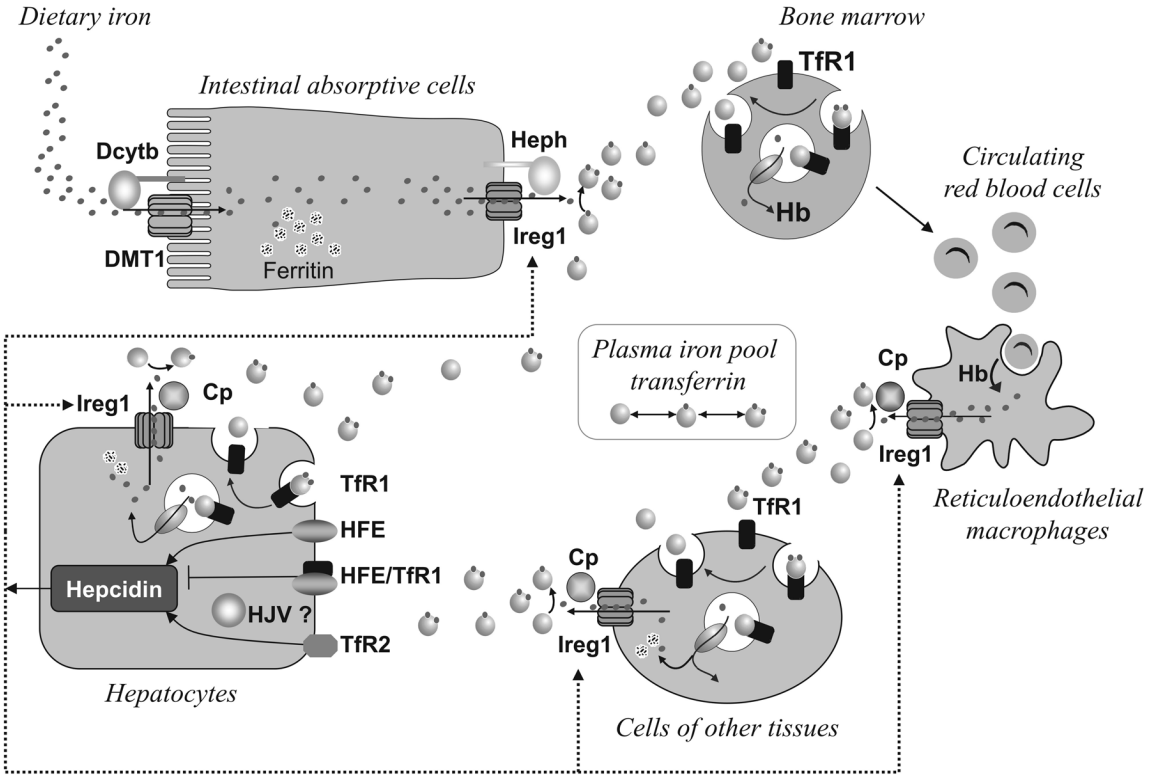

Figure 1. Regulation of intestinal iron absorption and body iron homeostasis. Variations in body iron demand manifest themselves as changes in the level of diferric transferrin in the plasma. These changes are recognized in the liver (and likely by the hepatocyte) by the HFE/TfR1 complex and TfR2, and these molecules in turn signal alterations in the expression of the regulatory peptide hepcidin. Hepcidin is secreted into the circulation and acts on the intestinal enterocytes, macrophages, and probably other body cells, to modulate iron efflux.

INHERITED DISORDERS OF IRON HOMEOSTASIS AND THE REGULATION OF ABSORPTION

The analysis of inherited disorders of iron homeostasis in humans and mice over the last decade has played a pivotal role in helping us to understand the mechanism of iron transport across the intestinal epithelium and how this process is regulated. Some examples are shown in Table 1. Of particular importance have been investigations into various iron loading syndromes. For example, the iron overload disorder hereditary hemochromatosis (HH) results from mutations in the genes encoding HFE (commonly) (*2*), TfR2 (rarely) (*3*) or ferroportin1 (rarely) (*4*). A more severe form of the disease, juvenile hemochromatosis (JH), has been linked with mutations in hepcidin (*5*) or hemojuvelin (HJV) (*6*). Several studies have shown that HFE appears essential for hepcidin regulation (*7, 8*) and that it is able to bind to TfR1 at a site which overlaps with the Tf binding site (*9*). The current hypothesis for systemic regulation of iron homeostasis suggests that hepcidin is regulated by HFE and TfR2 in response to changes in plasma transferrin saturation (*10*). HJV may play a modulatory role in this pathway, or it may affect hepcidin independently (*11*). Hepcidin then acts on its target cells, the enterocytes and reticuloendothelial macrophages, to modulate iron efflux.

HEPCIDIN

Hepcidin was originally isolated from human urine as an antimicrobial peptide (*12*), then later identified as a molecule upregulated during states of iron loading and downregulated during iron deficiency (*13*). A strong relationship between the regulation of iron homeostasis and hepcidin expression has been confirmed in two mouse models. In the first, the absence of hepcidin expression resulted in a severe iron loading phenotype (*14*), whilst in the second, overexpression of hepcidin led to severe iron deficiency anemia and death shortly after birth (*15*). The relationship between hepcidin and iron homeostasis was confirmed in humans with the discovery of mutations in hepcidin in some patients with JH (*5*). Since its identification in 2001, hepcidin has been strongly implicated by multiple studies as a humoral factor playing a key role in the regulation of iron homeostasis.

How is Hepcidin Regulated?

Systemic stimuli that modulate hepcidin levels include changes in body iron stores (*16*), stimulated erythropoiesis (*17*), inflammation (*18, 19*), hypoxia (*18*) and pregnancy (*20*). However, the precise pathways that lead to altered hepcidin expression in response to such stimuli remain unclear. We recently hypothesized that diferric Tf plays a key role linking body iron requirements to hepcidin regulation by competing with HFE for binding to TfR1 at the hepatocyte cell surface (*10*). Thus increased body iron levels would lead to an increase in the concentration of diferric Tf which out-competes HFE for binding to TfR1. An increased amount of unbound HFE at the cell surface then signals to the nucleus and causes increased hepcidin production (*16*). In iron deficiency, where Tf saturation is decreased, there is less diferric Tf and a relative increase in HFE binding to TfR1 at the hepatocyte cell surface. A decrease in the level of free HFE on the plasma membrane leads to a reduction in the HFE-mediated signal for hepcidin expression. In support of this hypothesis, it is well known that Tf saturation, and therefore diferric Tf levels, are positively correlated with body iron status, and we found that a decrease in the level of diferric transferrin preceded a decrease in hepcidin expression when body iron requirements were rapidly increased by phenylhydrazine-induced hemolysis (*17*). In addition, competition between HFE and diferric Tf for binding to TfR1 has recently been demonstrated in cell culture studies (*21*). Further evidence in support of diferric Tf as a key

Table 1. Some genetic disturbances of iron homeostasis

Disease	Gene affected	Species	Phenotype
Hemochromatosis	HFE	Human	Iron loading; mainly parenchymal cells
Hemochromatosis	TfR2	Human	Iron loading; mainly parenchymal cells
Hemochromatosis	Ferroportin1	Human	Iron loading (mainly macrophages e.g., Kupffer cells); early mild anemia
Juvenile Hemochromatosis	Hemojuvelin	Human	Severe iron loading; mainly parenchymal cells
Juvenile Hemochromatosis	Hepcidin	Human	Severe iron loading; mainly parenchymal cells
Atransferrinemia	Transferrin	Human/Mouse	Severe iron loading
Aceruloplasminemia	Ceruloplasmin	Human	Iron loading; early mild anemia
Hereditary hyperferritinemia	L-ferritin	Human	Iron loading
Fredreich Ataxia	Frataxin	Human	Iron loading (mitochondria)
Refractory microcytic anemia	DMT1	Human/ Mouse/Rat	Iron deficiency anemia
Sex-linked anemia	Hephaestin	Mouse	Iron deficiency anemia

signalling molecule has come from the demonstration that patients with mutations in TfR2, a Tf-binding cell surface molecule, develop iron overload (*3*) and have reduced hepcidin levels. We have thus proposed that hepcidin is regulated in response to changes in plasma diferric Tf levels by a dual pathway involving HFE and TfR2 (*10*).

Another piece in the puzzle has been provided by the identification of the gene mutated in most cases of JH as HJV (*6*). Hepcidin levels are reduced in these patients, implying that HJV plays an upstream role in hepcidin regulation and, or synthesis. Little is known about HJV and how it fits into the hepcidin regulatory pathway remains unclear. Particularly puzzling from the standpoint of iron homeostasis is the finding that HJV is most strongly expressed in skeletal and cardiac muscle. It has been proposed recently that HJV exerts and effect on hepcidin that is independent of the HFE and TfR2 pathways (*11*), although there is no direct evidence for this.

The pathway described above may not be the only way in which hepcidin is regulated. During an acute phase response (APR), for example, a change in hepcidin expression precedes any alteration in Tf saturation (*22*). Induction of acute or chronic inflammation by the administration of lipopolysaccharide (*13*), Freund's complete adjuvant (*22*) or turpentine (*18*) causes a rapid increase in hepcidin expression (within 8 h) and a subsequent decrease in both intestinal iron absorption and iron release from the reticuloendothelial system resulting in reduced plasma iron levels. Hepcidin is essential for this response since hypoferremia does not follow an acute phase stimulus in hepcidin deficient mice (*18*). Two studies have recently shown that the regulation of hepcidin in the APR is independent of HFE (*19, 23*), suggesting that there are at least two independent regulatory pathways for hepcidin expression, however, a third study (*24*) suggested that the hepcidin response was HFE-dependent and indicates that further work is needed in this area. Following an acute phase stimulus, hepcidin expression is induced by interleukin-6 (*25*) as part of the classical inflammatory response.

How does Hepcidin Repress Iron Absorption?

For many years it has been considered that the intestinal crypt cell is programmed by body iron requirements to absorb more or less iron after it migrates up the villus and matures (*1*). However, the recent advances in our understanding of the biology of hepcidin suggest that such a scenario is unlikely. It is now considered that hepcidin secreted from the liver exerts a direct effect on iron export from mature intestinal enterocytes as the time between changes in hepcidin expression and changes in iron transport is too short to support the crypt cell maturation model (*10*). We found a close inverse relationship between changes in hepcidin expression and changes in the level of intestinal iron transport molecules (Dcytb, DMT1 and ferroportin1) after switching rats from a control diet to an iron deficient diet (*16*), and confirmed this close temporal relationship by examining hepcidin and iron transporter gene expression after induction of an acute phase response (*22*) or following phenylhydrazine-induced hemolysis (*17*). We and others (*26*) have since shown a direct effect of hepcidin on transporter expression *in vitro*, and when the human intestinal epithelial cell line Caco-2 is incubated with hepcidin, a decrease in DMT1 and ferroportin1 mRNA and protein results. Very recently it has been shown, also in Caco-2 cells, that hepcidin is able to interact directly with ferroportin1 and cause its internalization (*27*).

Whilst many of the details of how hepcidin interacts with enterocytes and other cell types to alter iron transport have yet to be elucidated, the evidence that this peptide represses iron release from these cells is now very strong. Since ferroportin1 is the major cellular iron export protein, the ability of hepcidin to alter ferroportin localization, as well as its expression, provides a mechanism for its effects on iron absorption. These contemporary data support early kinetic studies indicating that the rate limiting step for iron absorption is iron release from the enterocytes (summarized in *1*). In addition, recent molecular studies have shown that ferroportin1 expression is responsive to changes in systemic iron levels, but not to variations in the enterocyte iron concentration, whereas the brush border transport system responds rapidly to changes in enterocyte iron content (*28, 29*). These data are consistent with the proposal that basolateral export of iron from the intestinal epithelial cells represents the primary site at which iron absorption is regulated, whereas the locally responsive brush border transport components act to buffer the body against the absorption of excessive iron.

CONCLUSION

The marriage of contemporary genetic and molecular techniques with clinical and physiological studies has led to enormous advances in our understanding of intestinal iron absorption in recent years. The discovery of hepcidin as a central regulator of body iron homeostasis and the identification of a number of its target iron transport molecules have been key developments. Future challenges will centre on the detailed biochemical analysis of these molecules and the application of this knowledge to develop therapeutic agents for human disorders where iron metabolism is disturbed.

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