

Research Update on Iron Metabolism and Its Regulation Mechanisms

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Iron metabolism disorder is an important public health problem both in the United States and developing world. Iron deficiency cases are over 2 billion worldwide. In the U.S., 9 million people are iron deficient and 1 million are at genetic risk of iron overload. Recent advances in research on iron-related diseases, coupled with new insights into the molecular mechanisms for iron metabolism, have strengthened our understanding of iron metabolism and iron disorder and have the potential to improve clinical and laboratory assessments of patients. In this article, I aim to provide a brief summary of recent developments in the molecular mechanisms underlying iron metabolism.

Iron homeostasis depends on the regulated absorption of dietary iron and recycling of heme iron by macrophages. Eukaryotic cells and most prokaryotic organisms require iron for survival and proliferation. Cellular iron deficiency arrests cell growth and leads to cell death. Therefore, iron homeostasis is within such a limited range that delicate regulation is needed. The most susceptible cells to iron deficiency are those in active and proliferative states, like immune cells. On the other hand, excess iron impairs immune cell functions as well.⁸

As shown in **Figure 1**, for mammals, iron absorption takes place in the duodenum. Iron has to traverse both the apical and basolateral membranes of enterocytes to reach into circulation. At the apical membrane, duodenal cytochrome b (Dcytb) can reduce dietary ferric iron to Fe^{2+} , the substrate for divalent metal transporter 1 (DMT1), which will transport Fe^{2+} across the membrane and into the enterocytes. Heme ferrous iron will be transported from the gut lumen into enterocytes through the heme carrier protein 1.⁷ In the cells, heme is disassembled by heme oxygenase and Fe^{2+} is released into the intracellular iron pool. Ferroportin (FPN) is important for basolateral transport of iron out of enterocytes and for the export of iron from macrophages. Similar to DMT1, FPN conducts Fe^{2+} ions. Fe^{2+} must be oxidized to Fe^{3+} by hephaestin in the duodenum or ceruloplasmin to circulate (**Figure 1**). In normal circumstances, transferrin (TF) carries nearly all serum iron with high affinity in circulation, dampens its reactivity and delivers it to either erythroid bone marrow for erythropoiesis, or other tissues.

Almost 25 mg iron per day are needed, yet only 1-2 mg of iron enters the body through the intestine each day, therefore,

nearly all the available iron is derived from a recycling pool of macrophages that phagocytose old and damaged erythrocytes, particularly in the spleen.⁴ In macrophages, hemoglobin is catabolized by heme oxygenase to liberate iron. FPN is critical for macrophage iron export.¹ Macrophages and hepatocytes serve as depots for iron storage. Most storage iron is in the form of ferritin, which can be mobilized when needed elsewhere in the body. The stimuli known to modulate the iron homeostatic mechanism are iron needs, hypoxia, iron deficiency, iron overload, and inflammation (**Figure 1**).

Multiple genes are involved in the regulation of iron recycling (macrophages), storage (spleen and liver), and absorption (duodenum). Much of the regulation is controlled by hepcidin. Functional hepcidin, a 25-amino acid peptide synthesized in the liver, is the principal regulator of iron homeostasis.⁵ Its production increases with iron loading and inflammation, while its production decreases with iron deficiency, anemia, and hypoxia.⁵ The expression of hepcidin is regulated by *hyperferritinemia* (HFE), which is a 343-amino acid, β_2 -microglobulin-associated MHC class I-like cell surface protein expressed on hepatocytes, macrophages and intestinal crypt cells.² HFE works as a circulatory iron status sensor. Interaction of diferric-transferrin complex (Fe-TF) with transferrin receptors on cell surface influences HFE's association with transferrin receptor 1 and transferrin receptor 2 which will lead to a subsequent signal pathway that regulates hepcidin expression.^{3,6} Hepcidin can bind to FPN, which is abundantly expressed in macrophages and basolateral membrane of duodenal enterocytes, and induce its internalization and degradation. Therefore, hepcidin interrupts cellular iron export in at least two sites: the intestinal epithelium and tissue macrophages. The posttranslational regulation of FPN by hepcidin level may thus complete an iron homeostatic loop. Increased plasma iron stimulates the secretion of hepcidin by liver cells. Hepcidin binds FPN and then causes its internalization and degradation. As a result, iron is trapped in macrophages and enterocytes. Rise of cytoplasmic iron would reduce iron uptake in these cells. Continuous hemoglobin synthesis will soon deplete plasma iron, restoring the iron level to a steady state.⁴ Hepcidin deficiency, or FPN mutation resistant to hepcidin regulation, appears to be the cause of most types of hereditary hemochromatosis (HH).⁵

Summary

The HFE-dependent synthesis of hepcidin and the hepcidin-dependent down-modulation of FPN constitute an important regulatory loop which carefully maintains iron homeostasis.

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Iron metabolism regulation is one of the most delicate control systems in mammalian body.

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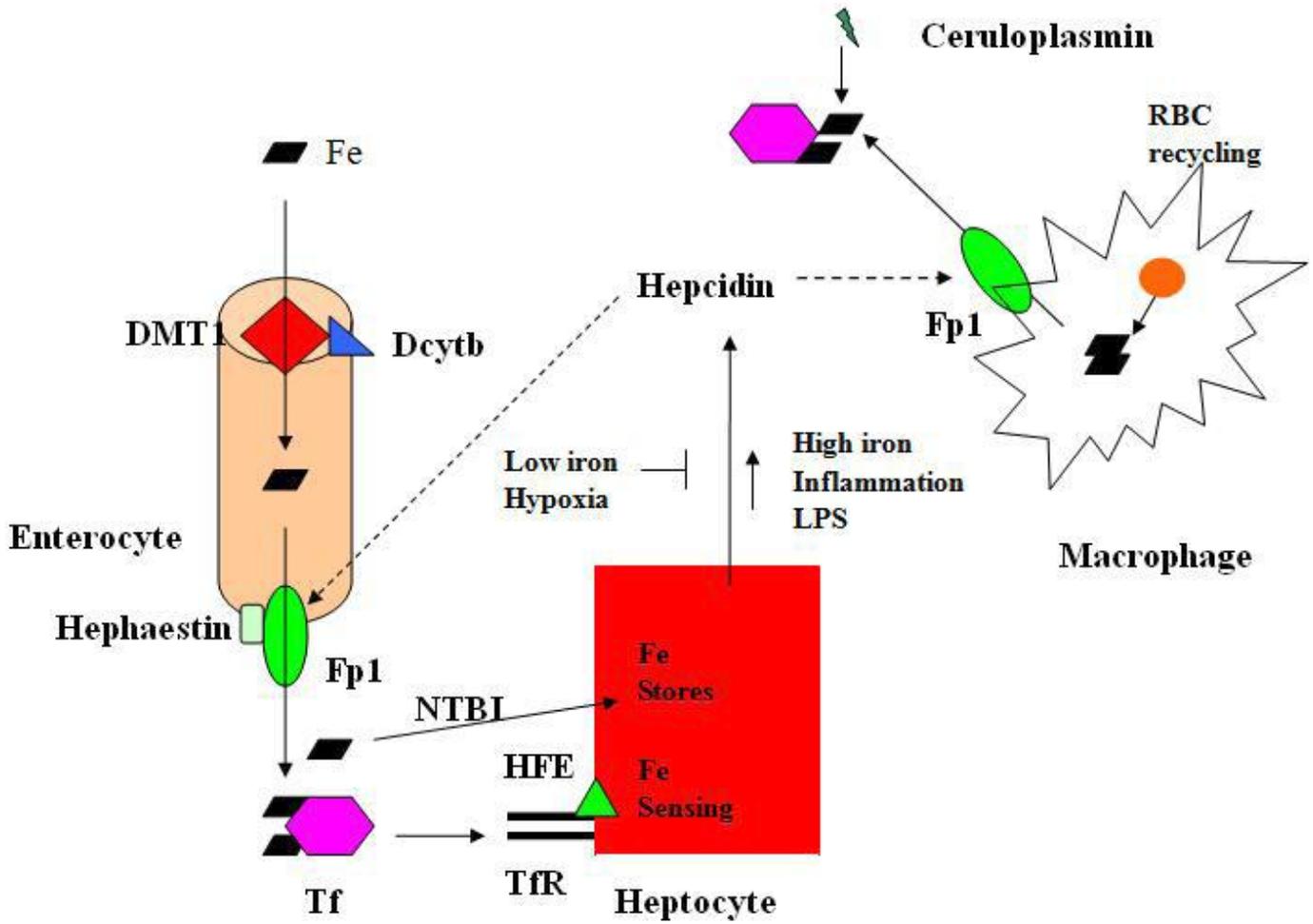


Figure 1. Iron metabolism regulation.