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Review

Hepcidin: Iron-hormone and anti-microbial peptide

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Abstract

Hepcidin is a β-defensin-like peptide and a principle regulator of systemic iron homeostasis. In concordance with this dual function its expression is modulated by systemic iron requirements and in response to infectious and inflammatory stimuli. Studies of hepcidin provide novel insight into the molecular mechanisms involved in maintaining iron homeostasis in the healthy state and iron redistribution in response to chronic infections and inflammation. Furthermore, a deregulation of hepcidin may cause elevated intestinal iron absorption that hallmarks a group of frequent iron overload disorders, the Hereditary Hemochromatosis. The aim of this review is to discuss hepcidin function in iron-homeostasis under normal physiological and pathophysiological conditions.

Keywords: Hepcidin; Iron metabolism; Hereditary hemochromatosis; Anaemia of chronic diseases; Anti-microbial peptide

1. Introduction

Iron plays a central role in biology. It is an indispensable cofactor for enzymes involved in cell proliferation, respiration, folate metabolism and DNA synthesis. However, excess 'free' iron is toxic. Ferrous iron participates in 'Fenton chemistry' to catalyze the conversion of hydrogen peroxide to highly reactive hydroxyl radicals that damage DNA, proteins and lipids. Many diseases arise from imbalances in iron homeostasis. Too much iron accumulates in hereditary hemochromatosis, African siderosis, porphyria cutanea tarda and the thalassemias, whereas the clinical consequences of sideroblastic anemia, iron-deficiency anemia, as well as the 'anaemia of inflammation' result from too little iron in the right place. A delicate balance in body iron must also be maintained for resistance to infection. While host organisms have developed countermeasures to limit the availability of iron to the pathogen, it needs to assure that sufficient iron is available for essential cellular functions including its antimicrobial defence.

The control of iron homeostasis acts both at the cellular and the systemic level. Cellular iron metabolism is maintained at the level of iron uptake, storage, export and intracellular iron distribution. Systemic iron homeostasis regulates iron entry into and mobilization from stores (principally the liver) to sustain erythropoietic demands. Aging erythrocytes are recycled through the reticuloendothelial system to free iron for a further cycle of erythropoieses. There is no physiologic pathway for active iron excretion from the body. Blood loss and sloughing mucosal cells account for most of the iron that leaves the organism, and iron absorption from the diet compensates for these losses. To maintain systemic iron homeostasis, communication between cells that consume iron (mainly erythroid precursors), store iron (hepatocytes and tissue

Abbreviations: aa, amino acids; C/EBP, CCAAT/enhancer binding protein; DCYTB, cytochrome *b*-like ferriductase; DMT1, divalent metal transporter-1; FPN1, ferroportin 1; hepc hepcidin; HFE, hemochromatosis gene; HH, hereditary hemochromatosis; HJV, hemojuvelin; HNF4a, hepatocyte nuclear factor 4; IAP, intracisternal A-particle; IL-1, interleukin 1; IL-10, interleukin 10; IL-1b, interleukin-1 beta; IL-6, interleukin 6; IRE, iron responsive element; IREGI, iron regulated trasporter 1; LEAP-1, liver-expressed antimicrobacterial peptide; LPS, lipopolysaccharide; MHC, major histocompatibility complex; NRAMP2, natural resistance associated macrophage protein 2; RGM, repulsive guidance molecule; RGMC, RGM domain family member C; TfR1, transferrin receptor 1; Tfr2, transferrin receptor 2; TNF-a, tumor necrosis factor alpha; Usf2, upstream stimulatory factor 2; UTR, untranslated region; WT, wild type; b2M, beta 2 microglobulin.

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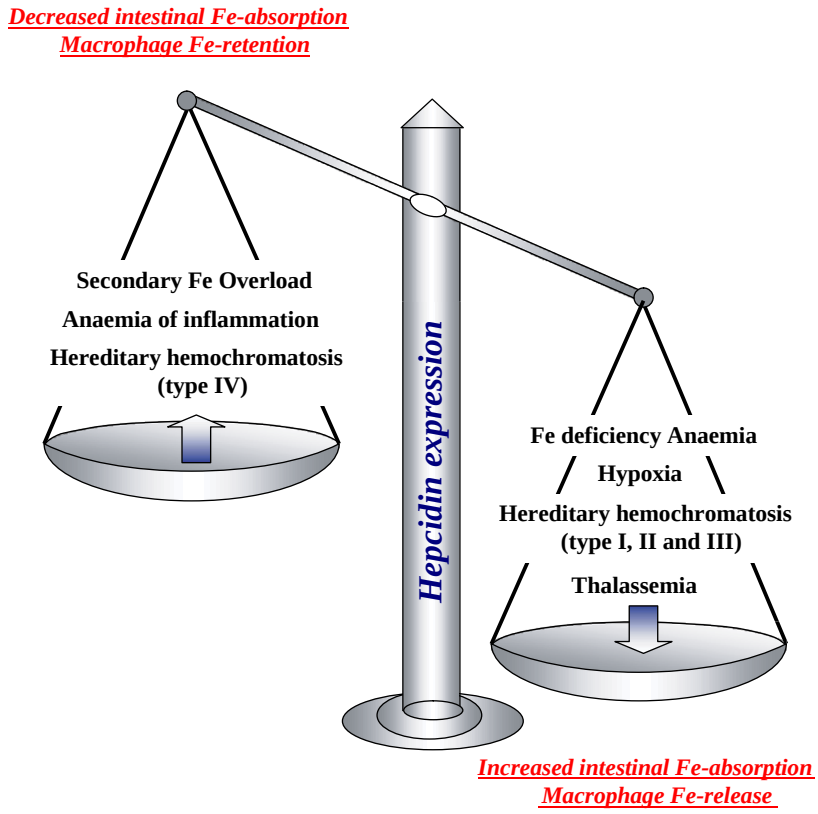

Fig. 1. The physiological equilibrium of hepcidin is affected by different pathologies. Elevated hepcidin levels are associated with secondary iron overload, type IV HH and chronic infectious or inflammatory diseases resulting in "anaemia of inflammation". Decreased hepcidin levels are observed during conditions of increased iron absorption such as hypoxia, iron deficiency anaemias and in HH and thalassemia. The available hepcidin directly modifies intestinal iron absorption and macrophage iron release to balance iron homeostasis of the organism.

macrophages) and absorb iron from the diet (duodenal enterocytes) must be tightly regulated. The anti-microbial peptide hepcidin acts as an iron hormone to control iron absorption and macrophage iron release. Its hepatic expression is regulated depending on iron availability in the stores, the needs for erythropoiesis, as a result of hypoxia as well as in response to infectious and inflammatory conditions. (Figs. 1 and 2).

2. Hepcidin a β-defensin-like antimicrobial peptide

A few years ago, Park et al. isolated a novel peptide from human urine and called it "hepcidin" based on its hepatic expression and its antimicrobial activity in vitro (Park et al., 2001). Independently, Krause et al. discovered the same peptide from plasma ultrafiltrate and named it LEAP-1 (liver-expressed antimicrobial peptide) (Krause et al., 2000). Hepcidin is active against Gram-positive (e.g. *Bacillus subtilis*) and Gram-negative (e.g. *Neisseria cinerea*) bacteria as well as yeasts (e.g. *Saccharomyces cerevisiae*) (Krause et al., 2000). Hepcidin is part of the innate immune system and thus constitutes the first line defence against infections. It contains basic amino acids that confer a positive total charge and a tendency to assume amphipathic secondary structures. This property enables anti-microbial peptides to permeate membranes of invading micro-organisms. Hepcidin does not show sequence similarity to any of the known antimicrobial-peptides, but resembles structurally the defensin family because of the four disulfide bridges in its tertiary structure. It is translated in the liver as an 84-aminoacid pre- pro-peptide. After processing and excretion through the kidneys a 25 amino-acid peptide (hepc-25) is the predominant form in the urine, but shorter peptides (hepc-22 and hepc-20) are also detected (Park et al., 2001). Surprisingly, the 84-aminoacid precursor is also detectable in human serum but its function needs further evaluation (Kulaksiz et al., 2004). The hepcidin mature peptide forms a simple hairpin structure, where the two arms are linked by disulfide bridges. It is noteworthy that the formation of a bond between the fourth and the fifth adjacent cysteine may confer high chemical reactivity to this region (Hunter et al., 2002).

Like some other antimicrobial peptides hepcidin has a dual function. In addition to its antimicrobial activity, it acts as an iron regulatory hormone which negatively regulates intestinal iron absorption and macrophage iron release. Thus, hepcidin acts in a double fashion against bacteria: it reduces the amount of iron available for pathogens and attacks them directly.

3. Hepcidin in the anaemia of inflammation

Upon infection, iron is sequestered in macrophages and hepatocytes and iron absorption is decreased to reduce serum iron levels and thus to limit the iron available for bacterial growth. If low serum iron levels are maintained or demand for