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State of art

Iron metabolism: State of the art

Métabolisme du fer : état de l'art

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Abstract

Iron homeostasis relies on the amount of its absorption by the intestine and its release from storage sites, the macrophages. Iron homeostasis is also dependent on the amount of iron used for the erythropoiesis. Hepcidin, which is synthesized predominantly by the liver, is the main regulator of iron metabolism. Hepcidin reduces serum iron by inhibiting the iron exporter, ferroportin expressed both tissues, the intestine and the macrophages. In addition, in the enterocytes, hepcidin inhibits the iron influx by acting on the apical transporter, DMT1. A defect of hepcidin expression leading to the appearance of a parenchymal iron overload may be genetic or secondary to dyserythropoiesis. The exploration of genetic hemochromatosis has revealed the involvement of several genes, including the recently described *BMP6*. Non-transfusional secondary hemochromatosis is due to hepcidin repression by cytokines, in particular the erythroferone factor that is produced directly by the erythroid precursors. Iron overload is correlated with the appearance of a free form of iron called NTBI. The influx of NTBI seems to be mediated by ZIP14 transporter in the liver and by calcium channels in the cardiomyocytes. Beside the liver, hepcidin is expressed at lesser extent in several extrahepatic tissues where it plays its ancestral role of antimicrobial peptide. In the kidney, hepcidin modulates defense barriers against urinary tract infections. In the heart, hepcidin maintains tissue iron homeostasis by an autocrine regulation of ferroprotine expression on the surface of cardiomyocytes. In conclusion, hepcidin remains a promising therapeutic tool in various iron pathologies.

Keywords: Iron metabolism; Hepcidin; Iron overload; Iron loading anemia; BMP6; ERFE

Résumé

L'homéostasie du fer repose sur le taux de son absorption par l'intestin et de sa libération des sites de stockage, les macrophages. Cette homéostasie est étroitement liée à l'utilisation du fer par la moelle érythropoïétique. L'hepcidine est le régulateur principal du métabolisme du fer, synthétisé majoritairement par le foie. L'hepcidine réduit le fer sérique en inhibant l'exporteur du fer, la ferroportine exprimée dans les deux tissus, l'intestin et les macrophages. En plus, l'hepcidine inhibe l'influx du fer par les entérocytes en agissant sur le transporteur apical DMT1. Un défaut d'expression de l'hepcidine peut être d'origine génétique ou secondaire à une dysérythropoïèse. Il entraine l'apparition d'une surcharge en fer parenchymateuse toxique. L'exploration de l'hémochromatose génétique a révélée l'implication de plusieurs gènes dont celui de *Bmp6*, récemment décrit. L'hémochromatose secondaire non transfusionnelle est due à une répression de l'hepcidine par des cytokines produites directement par les précurseurs érythroïdes, notamment le facteur érythroferone. La surcharge en fer est corrélée à l'apparition d'une forme libre du fer nommée NTBI. Le NTBI semble être transporté par la protéine ZIP14 dans les hépatocytes et par des canaux calciques dans les cardiomyocytes. En outre, l'hepcidine est faiblement exprimée dans plusieurs tissus extra-hépatiques où elle joue son rôle ancestral de peptide antimicrobien. Dans le rein, par exemple, l'hepcidine module la défense contre les infections urinaires. Dans le cœur, l'hepcidine maintient l'homéostasie tissulaire en régulant d'une façon autocrine l'expression de la ferroprotine exprimée dans les cardiomyocytes. En conclusion, l'hepcidine reste un moyen thérapeutique prometteur dans diverses pathologies du fer.

Mots clés : Métabolisme du fer ; Hepcidine ; Surcharge de fer ; Anémie de surcharge en fer ; BMP6 ; ERFE

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Iron is a vital element for almost all living systems since it is required for many biological processes including erythropoiesis that needs 20 to 30 mg of iron for the daily production of 200×10^9 red blood cells. Indeed, iron is required for the synthesis of heme, the prosthetic group that mediates reversible binding of oxygen by hemoglobin. Body iron content depends on nutrition, sex and health status. In adults, the iron stock is about 3 g in man, and 2.5 g in woman. Iron is found in the body in the ferrous (FeII) or ferric (FeIII) state, and it is incorporated into mono- or heteroprotein complexes as heme and non-heme forms. The excess of iron may be very toxic for cells since it can lead to the generation of free radicals by participating in electron transfer chains like in the Fenton's reaction [1]. However, body iron homeostasis is tightly regulated, relying on the control of iron efflux from the intestine, and from macrophages following phagocytosis and degradation of senescent red blood cells and heme catabolism by heme-oxygenase.

A regular diet provides about 10 to 20 mg of iron but only 10% are absorbed to offset daily losses. Iron absorption occurs in the duodenal enterocytes where it arrives at its ferric form FeIII. FeIII is rapidly reduced to FeII by the duodenal cytochrome B (Dcyt B) ferrireductase [2] to be transported by the proton-dependent FeII transporter, Divalent Metal Transporter 1(DMT1) located at the apical side of the cell [3]. Heme derived from meat, provides an important source of dietary iron (2/3 of total absorbed iron) and is more efficiently absorbed than inorganic iron but this form of iron intake is apparently passive and does not seem to be regulated by the iron needs of the body. Nevertheless, the Heme carrier protein 1 (HCP1) has been suggested to be a potential candidate to transport intestinal heme [4], and blockade of heme catabolism in the intestine by a heme oxygenase inhibitor was shown to produce a clinical iron deficiency [5,6]. Ferroportin (FPN), the only known iron exporter so far [7,8] is responsible for the iron delivery to the bloodstream. Exported FeII is rapidly oxidized to FeIII by a membrane ferroperoxidase (hephaestin) [9] to be taken up by apotransferrin (free transferrin [Tf]) and distributed to all target tissues. Erythroid cells are the largest consumer of iron. Holo-transferrin (Tf coupled to two FeII) binds to the transferrin receptor 1 (TfR1) on the cell surface and after receptor-mediated endocytosis, iron is released from Tf by a decrease in endosomal pH, and reduced by an endosomal metalloreductase (six transmembrane epithelial antigen of the prostate 3 [STEAP3]) [10]. Iron It is then transported across the endosomal membrane by DMT1 and chaperoned by poly (rC)-binding proteins (PCBP 1 or 2) in the cytosol where it is either stored in ferritin, or used for synthesis of heme and iron-sulfur clusters in the mitochondrion.

The major regulator of systemic iron homeostasis is hepcidin, a small peptide predominantly produced by the hepatocytes. Since its discovery in 2001, numerous studies have been conducted to understand the mechanism of action of this peptide. Hepcidin, in macrophages, binds to FPN, leading to its internalization and degradation via proteasomal processing [11]. However, we and others have found that this internalization mechanism is not observed in the intestine. Indeed, in the duodenum, hepcidin was found to act rather on DMT1 localized at the apical side of the enterocytes, leading to its internalization and proteasomal degradation; and this consequently limits early dietary iron absorption [12].

Hepcidin synthesis is regulated at the transcriptional level by different signals including the level of serum iron. In high iron conditions, hepcidin is significantly upregulated, reflecting a regulatory response against iron overload. In contrast, iron deficiency significantly reduced hepcidin synthesis. This regulation is complex and involves different hemochromatotic proteins present at the plasma membrane of the hepatocyte, i.e, hereditary hemochromatosis protein (HFE), hemojuvulin (HJV) and the transferrin receptor 2 (TfR2). They tightly coordinate signaling through the bone morphogenetic protein 6 (BMP6) pathway and increase hepcidin encoding gene (*HAMP1*) expression [13]. Elevated hepatic iron level enhances the expression of BMP6 [14] which binds to the BMP receptor (BMPR) and HJV to form a complex and activate the SMAD signaling pathway involving the phosphorylation of SMAD1, 5, and 8 (pSMADs), the formation of pSMADs/SMAD4 complex, and the translocation of this complex to the nucleus where it activates the transcription of *HAMP1* gene [15]. Serum iron level may induce hepcidin expression independently of BMP6 protein. When transferrin saturation is elevated without any liver iron overload, BMP6 expression is not induced, while the phosphorylation of SMAD1, 5 and 8 is activated via mechanism involving HFE protein [14]. HFE is a protein that competes with Tf for binding to TfR1. In this condition, holo-Tf displaces HFE from TfR1, released HFE that interacts with TfR2 and HJV, which activates HAMP1 transcription through the BMPR/HJV/SMAD pathway [16,17]. Matriptase-2 (MT2), encoded by the *TMPRSS6* gene and synthesized in the liver, is the key protein involved in the inhibition of hepcidin in response to iron deficiency [18]. Under this condition, HJV is subjected to cleavage by MT2 to form a soluble HJV (sHJV), which inhibits BMPR/HJV/SMAD- mediated hepcidin expression [19]. Hepcidin inhibition in response to iron deficiency can also be mediated by the reduction of BMP6 expression, which decreases the BMPR/HJV/SMAD signaling pathway [20]. Apart of being responsive to iron, hepcidin synthesis is increased in inflammatory/infection situations. Inlerleukin-6 (IL6) is the main cytokine involved in the induction of *HAMP1* promoter [21,22]. This response of hepcidin to inflammation could serve the host defense strategy of the organism by limiting vital iron needed for invading microorganisms or malignant cells.

Due to the large need of iron for erythropoiesis, extended iron deficiency or defect in the acquisition of iron by the erythroid cells causes systematically moderate to severe anemia. It is now well documented that the erythropoietic activity of the bone marrow plays an important role in the control of iron homeostasis and hepcidin synthesis. Indeed, all situations that stimulate erythropoiesis such as bleeding, hemolysis, hypoxia, or even erythropoietin (EPO) injection completely suppress the synthesis of hepcidin. This repression remains dominant despite the presence of inflammation or iron overload explaining the paradoxical situation known as the iron-loading anemia, in which dyserythropoiesis as in thalassemia intermedia or myelodysplastic syndromes, is associated with iron overload without