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Mini-review

The interaction of iron and the genome: For better and for worse

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ABSTRACT

Iron, as an essential nutrient, and the DNA, as the carrier of genetic information which is physically compacted into chromosomes, are both needed for normal life and well-being. Therefore, it is not surprising that close interactions exist between iron and the genome. On the one hand, iron, especially when present in excess, may alter genome stability through oxidative stress, and may favor cell cycle abnormalities and the development of malignant diseases. The genome also receives a feedback signal from the systemic iron status, leading to promotion of expression of genes that regulate iron metabolism. Conversely, on the other hand, DNA mutations may cause genetic iron-related diseases such as hemochromatosis, archetype of iron-overload diseases, or refractory iron deficiency anemia (IRIDA).

Iron is an essential nutrient needed for cell life whose dysregulation impacts human well-being [1]. The spectrum of biological processes implicating iron is broad and includes oxygen transport, mitochondrial respiration, immune response, xenobiotics biotransformation, lipid and protein metabolisms, cell growth and DNA synthesis. Maintaining a homeostasis of iron that is compatible with cell survival is accomplished through tight regulations at cellular and systemic levels. Abnormal cellular or systemic iron concentrations induce subtle toxicities whose accumulations can affect cell functions and processes including genome stability.

The genome is the support of genetic information. Schematically, in eukaryotes, the genome consists of DNA molecules compacted around proteins, assembled into chromosomes that are duplicated and separated during mitosis. In addition, mitochondrial DNA is transmitted from mother to children. Here again, genome stability –the faithful transmission of genome from generation to generation- is ensured by strict mechanisms.

The purpose of this review is to explore the crosstalk between iron and the genome, both entities requiring tight regulation and stability. The interactions between iron and the genome are numerous, and can be considered in two opposite yet complementary ways. On the one hand, iron status is implicated in chromosome maintenance –especially in telomere length-, as well as in genome stability, and is likely a key actor in human evolution. On the other hand, genetic mutations in various loci can lead to modifications in iron metabolism and are potential causes of human diseases mainly characterized by iron overload, iron deficiency or iron maldistribution. When considering iron and the genome, instability of one may lead to destabilize the other.

We mainly focus the present overview to humans, citing animal models to highlight conserved mechanisms within mammals, especially when discussing iron metabolism. In the first part, we briefly introduce the major systems of iron homeostasis. In the second part of the review, we examine the role of iron on genome stability and the ensuing consequences of iron dysregulation on genome stability and cell cycle progression. Finally, on the third part, we expose the main genetic mutations that disrupt iron homeostasis.

1. Human body iron trafficking, homeostasis, and dysregulation

1.1. Iron trafficking

The sole source of iron is alimentary (10–20 mg per day). Iron is absorbed at the duodenal level at a rate of 1–2 mg per day. This absorption process involves many proteins [1] (Fig. 1). First, DCYTB (duodenal cytochrome B, official gene symbol *CYBRD1*) reduces non heminic Fe(III) ferric iron into Fe(II) ferrous iron (the only iron redox form able to cross membranes). Then, DMT1 (divalent metal transporter 1) carries the iron through the luminal membrane of the enterocyte. In parallel, heminic iron is taken up using independent mechanisms that could involve the heme carrier protein 1 (HCP1) protein,

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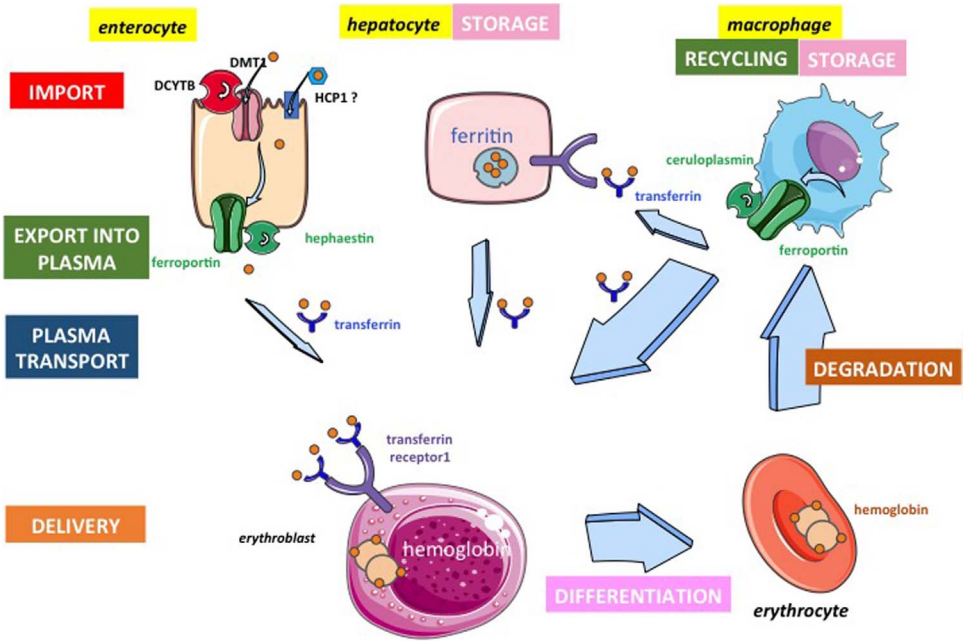

Fig. 1. Iron trafficking. Ferric iron is taken up by enterocytes by DMT1 after DCYTB-mediated reduction into ferrous iron. At the enterocyte plasma membrane, iron is exported from enterocyte by ferroportin and hephaestin-oxidation. Alternatively, heminic iron is taken up using independent mechanism that could involve HCP1 protein (encoded by *SLC46A1* gene). Iron is then transported into blood plasma by binding to transferrin. At the utilization sites, for example, bone marrow, iron-transferrin is internalized by binding to transferrin receptor1, and incorporated into iron-bound molecules such as hemoglobin in erythroblasts. Maturation of erythroblasts gives raise to erythrocytes which are –at the end of their life- degraded by spleen macrophages. Degradation of hemoglobin allows the release of iron through ferroportin and ceruloplasmin oxidation. Plasma iron- once again transported into plasma by transferrin- can end up either into ferritin in storage sites, such as in hepatocytes or re-enter the iron utilization cycle. Note that the different elements of the scheme are not at scale.

encoded by *SLC46A1* gene, and is released from heme by heme oxygenase. Once iron has crossed the cell and reached the plasma basolateral membrane, it is exported into the plasma by ferroportin (official gene symbol *SLC40A1* gene), the only known cell iron exporter. Iron is subsequently re-oxidized by hephaestin (official gene symbol *HEPH* gene) so that iron can be taken up by transferrin, the plasma iron transporter. Most plasma iron (about 80%) targets the bone marrow, enters the erythroblasts (the red blood cell progenitors) through the transferrin receptor1 and transferrin cycle pathway. This iron contributes to the emergence of new red blood cells (also known as erythrocytes), being integrated within hemoglobin for oxygen transport and delivery purposes. At the end of their life, red blood cells are degraded within spleen macrophages, in a process which releases their iron content. This iron is recycled into the plasma through the ferroportin channels, then, is linked again to transferrin, thanks to the ferroxidase activity of ceruloplasmin –instead of hephaestin- for the required oxidation process. Transferrin iron is delivered to the bone marrow through an efficient recycling process. A small part of absorbed iron (20%) targets other organs and participates to multiple biological reactions. Indeed, inside those targeted cells, iron can be located within molecules of ferritin, which acts both as a storage protein –to protect the cytosol from the toxicity of "free" iron- and as a reservoir from which iron can be released depending on cellular and body iron needs. Finally, daily body iron losses are minimal through intestinal cell exfoliation, skin, biliary and urine losses, and are quantitatively equal to absorbed iron (1–2 mg per day).

1.2. Iron homeostasis

The vital necessity for the human body to maintain adequate iron stores explains a finely tuned regulation of iron. Two main complementary systems ensure this regulation [1]: a systemic regulation of iron that involves the hepcidin-ferroportin duo, and a cellular regulation of iron metabolism that relies on IRE/IRP system.

The hepcidin-ferroportin duo is crucial for systemic regulation of iron. Hepcidin, mainly produced by the liver, is the iron hormone [2–4]. Whenever plasma iron concentration or body iron stores decrease, hepcidin synthesis decreases in order to counteract this iron deficiency. This feedback mechanism consists of two main effects, which are both related to the "stimulation" of ferroportin. On the one hand, intestinal iron absorption is enhanced; on the other hand, there is an increased release by the spleen of the iron coming from the normal degradation of old red blood cells. As a global result, plasma iron increases in order to compensate the initial iron decrease. A reverse mechanism occurs in case of increased plasma iron concentration or body iron stores. It should be noticed that this systemic regulation does not significantly impact body iron losses that are known to be very poorly adaptable.

The IRE/IRP system is responsible for the local cellular regulation of iron metabolism [5]. When cellular iron content decreases, the physical interaction of IRP (iron regulatory protein) with IRE (iron responsive element), located at the 5′ non coding region of L-ferritin mRNA, is increased, leading to decreased ferritin translation. This leads to decrease the cellular iron storage capacity. Simultaneously, IRP interaction with IREs, located at the 3′ extremity of transferrin receptor1 mRNA, is increased leading to increased stability of transferrin receptor 1 mRNA. Therefore, it results in an increased capacity of the cell for taking up iron from the plasma. These two combined mechanisms concur to compensate the initial decrease of cellular iron content. The reverse mechanism occurs when cellular iron content increases. Altogether, the genome receives a feedback signal from the systemic iron status, leading to promotion of expression of genes that regulate iron metabolism.

1.3. Iron metabolism dysregulation

When dealing with the main clinical consequences of human iron dysregulation (other than those related to genotoxicity), three different cases of dysregulation have to be considered: iron deficiency, iron overload and iron maldistribution. Whatever the cause of body iron deficiency is –including poor dietary intake, intestinal malabsorption or increased blood losses-, the major consequence of body iron deficiency is anemia characterized by the anemic syndrome: fatigue, palor, decreased blood pressure, tachycardia [6]. Other complications can be however observed including hair loss, spoon nails and dry skin. Whatever the cause of body iron overload is –acquired (multiple transfusions in chronic anemia, excessive parenteral iron supplementation) or genetic (hemochromatosis, most frequently related to *HFE* gene mutations)-, the iron overload syndrome involves some common clinical consequences such as chronic fatigue, hyperpigmentation, liver, pancreas, pituitary, and heart damage [7,8]. Finally, even if total body iron is normal, iron tissue distribution may be