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Review

An overview of molecular basis of iron metabolism regulation and the associated pathologies

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ABSTRACT

Iron is essential for several vital biological processes. Its deficiency or overload drives to the development of several pathologies. To maintain iron homeostasis, the organism controls the dietary iron absorption by enterocytes, its recycling by macrophages and storage in hepatocytes. These processes are mainly controlled by hepcidin, a liver-derived hormone which synthesis is regulated by iron levels, inflammation, infection, anemia and erythropoiesis. Besides the systemic regulation of iron metabolism mediated by hepcidin, cellular regulatory processes also occur. Cells are able to regulate themselves the expression of the iron metabolism-related genes through different post-transcriptional mechanisms, such as the alternative splicing, microRNAs, the IRP/IRE system and the proteolytic cleavage. Whenever those mechanisms are disturbed, due to genetic or environmental factors, iron homeostasis is disrupted and iron related pathologies may arise.

1. Introduction

The central role of iron in cells and organisms is widely known, as many branches of essential metabolisms, encompassing a full range of cellular processes, energy production, biosynthesis, replication and locomotion, require iron in order to occur.

Despite being so important, it has toxic properties when presented on its free form. Its regular ability to mediate electron transfer, changing between the +2 and +3 oxidation states, may elicit the production of reactive oxygen species responsible for cellular and tissue damage. To avoid those negative effects, iron is usually found coupled with other proteins. In serum, it is mainly associated with transferrin, while within the cells it is driven by chaperones or stored within ferritin.

In humans, erythropoiesis is the biological process with the highest demand for iron atoms because of its requirement to heme synthesis and subsequent incorporation into hemoglobin molecules. Circulating erythrocytes consist mainly of hemoglobin containing four heme groups that temporarily binds to oxygen molecules in the lungs and release them throughout the body. When senescent, erythrocytes are phagocytized by macrophages and iron becomes available to be reutilized. Consequently, an organism needs to absorb from diet only the amount of iron strictly necessary to overcome the nonspecific body iron losses. The control of dietary iron absorption by enterocytes and its release from macrophages and from storing hepatocytes are the main examples of mechanisms through which iron homeostasis is maintained. Commonly, these processes are regulated by hepcidin, a liver-derived hormone (Fig. 1). Hepcidin gene (*HAMP*) transcription is up-regulated by high iron levels, infection and inflammation, while anemia and erythropoiesis inhibit its expression. Hepcidin acts by binding to the cell surface ferroportin-1 (Fpn1), the only known iron exporter, inducing its internalization and degradation. As a consequence, iron release from enterocytes, macrophages and hepatocytes is prevented. Besides the systemic regulation of iron homeostasis provided by hepcidin, cells enclose both general and specific mechanisms to regulate themselves the expression levels of iron metabolism-related genes. For instance, the iron regulatory protein (IRP)/iron responsive element (IRE) system controls both mRNA stability and translation of transcripts coding for proteins involved in iron uptake, export, transport and

Abbreviations: β2M, beta 2-microglobulin; aa, amino acid; ACD, anemia of chronic diseases; BMP, bone morphogenetic protein; BMPR, bone morphogenetic protein receptor; CD, cluster of differentiation; Cp, ceruloplasmin; DcytB, duodenal cytochrome b; Dmt1, proton-coupled divalent metal transporter 1; Epo, erythropoietin; ER, endoplasmic reticulum; Fe^{2+}, ferrous iron; Fe^{3+}, ferric iron; Fpn1, ferroportin-1; Ft, ferritin; Ft-H, ferritin heavy chain; Ft-L, ferritin light chain; GDF-15, growth differentiation factor 15; Gpi, glycosylphosphatidylinositol; *HAMP*, hepcidin gene; HCP1, heme-carrier protein 1; Heph, hephaestin; HH, hereditary hemochromatosis; HIF, hypoxia inducible factor; Hjv, hemojuvelin; HO1, heme oxygenase 1; HRE, hypoxia-response element; IDA, iron deficiency anemia; IL, interleukin; IRE, iron responsive element; IRIDA, iron-refractory iron deficiency anemia; IRP, iron regulatory protein; ISC, iron–sulfur cluster; JH, juvenile hemochromatosis; MT2, matriptase-2; Neo, neogenin; NTBI, non-transferrin bound iron; PC, proprotein convertase; ROS, reactive oxygen species; sCp, serum ceruloplasmin; sFt, serum ferritin; sHFE, soluble HFE; sHJV, soluble hemojuvelin; Stat, signal transducer and activator of transcription; Steap, six transmembrane epithelial antigen of the prostate; sTFR1, soluble transferrin receptor 1; TBI, transferrin-bound iron; Tf, transferrin; TfR, transferrin receptor; TfSat, transferrin saturation; TWSG-1, twisted gastrulation 1; UPR, unfolded protein response; UTR, untranslated region.

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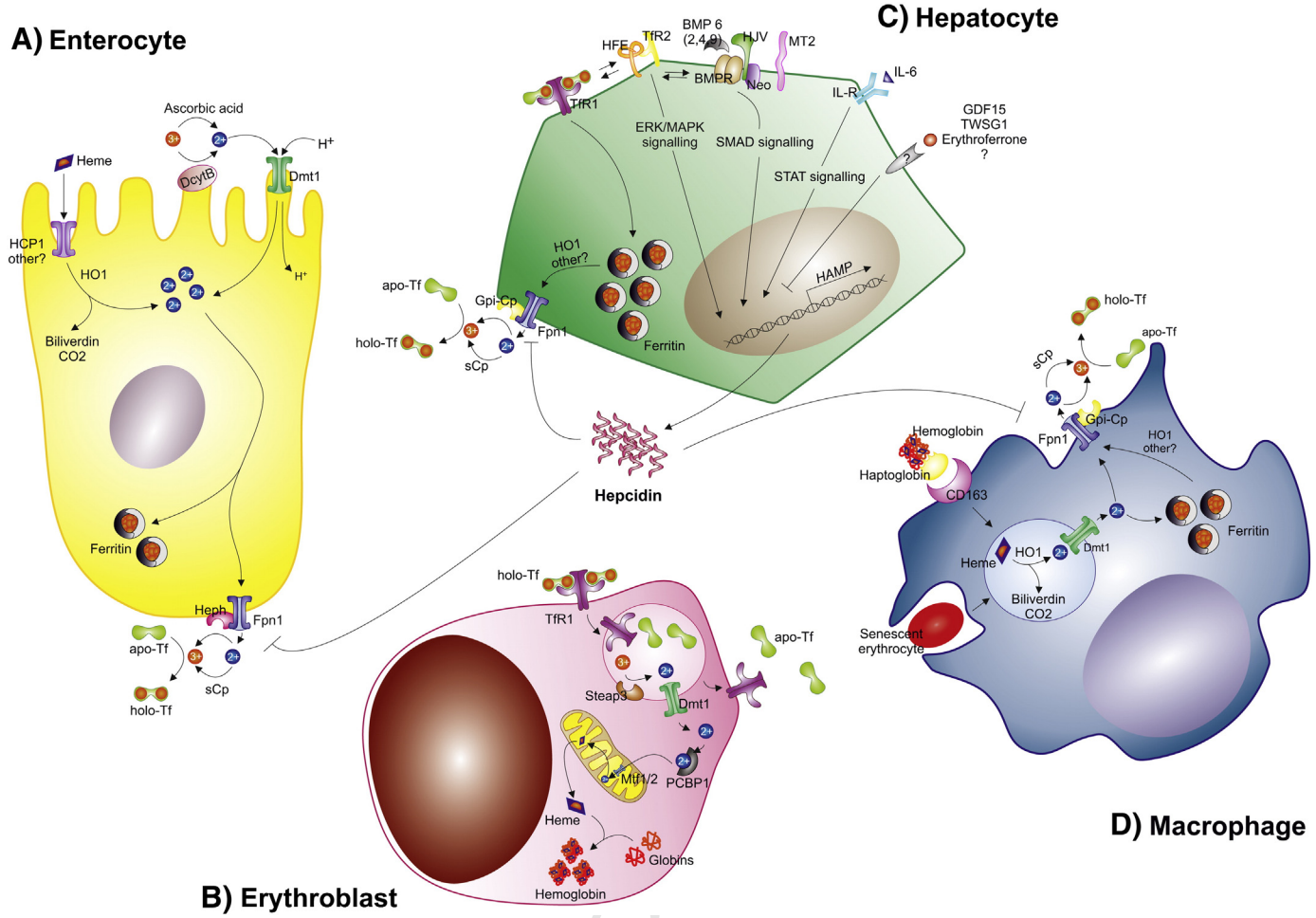

Fig. 1. Systemic iron metabolism regulation. The maintenance of iron homeostasis is a complex process that encompasses the regulation of (A) dietary iron by the duodenum enterocyte, (B) usage by erythroblasts, (C) storage by hepatocytes and (D) recycling by splenic macrophages. After being reduced by ascorbic acid and Dcytb at the apical membrane of enterocytes, dietary iron is absorbed by Dmt1 and driven to the basolateral membrane of these cells where it is exported by Fpn1 to circulation in association with transferrin (holo-Tf). Erythrocytes, which are the cells that require the major amounts iron, capture holo-Tf through the membrane-associated TfR1. After being endocytosed, iron is used by the mitochondria in the synthesis of heme, which will be incorporated in the hemoglobin, functioning as a transporter of oxygen. Whenever the organism absorbs more iron than the required, it is stored within ferritin, mostly at the hepatocytes. The most common source of iron are the macrophages, as they phagocyte the senescent erythrocytes, releasing iron from heme through the HO1, rendering it available to be re-utilized by the cells. In the control of all of these processes we find hepcidin, a circulatory protein synthesized in the liver accordingly to iron levels. Hepcidin acts by binding to membrane-associated Fpn1, inducing its internalization and degradation and, consequently, preventing dietary iron absorption and release from storing hepatocytes and recycling macrophages.

storage. Whenever these mechanisms are perturbed, due to genetic or environmental factors, iron overload or iron deficiency pathologies may arise. This manuscript will provide a general view of the iron metabolism regulatory mechanisms required to maintain homeostasis and the causes and consequences of their deregulation.

2. Inorganic and organic iron

2.1. The origin of life

The ability to complex with organic ligands is one of the reasons why iron is a co-factor of several enzymes. In nature, it can be found in eight oxidation states, ranging from −2 to +6 [1]. This redox property makes iron useful for electron transfer reactions. Recently, it has been hypothesized that, iron could have a crucial role on the origin of life. It is supported that it was an essential element for the development of the primordial membrane bioenergetics [2]. The process of serpentinization at alkaline thermal vents generates natural proton gradients similar to the ones used by modern cells [3]. Briefly, at high pressures and temperatures, iron-containing minerals, such as olivine, react with water to form serpentine and high concentrations of magnetite and H_2. The thin mineral walls would form osmotic barriers separating the warm H_2-rich alkaline fluids from the cold, Fe^{2+}-rich oxidized ocean. There, it would have been gathered the conditions for the formation of primordial natural proton gradients and, consequently, of the energy required for the reduction of CO_2, synthesis of complex organic compounds and the development of the first proto-cells.

2.2. Iron and evolution

Iron is an element required by almost all species within the six kingdoms of life. Before oxygenic photosynthesis, where O_2 and H_2O started cycled between photosynthesis and respiration, redox cycles took advantage of other elements in order to maintain microbial metabolism [4]. Some bacteria and archea retain the ability to extract energy from sources that are inaccessible to other organisms. For example, instead of acquiring electrons from water, some photosynthetic bacteria oxidize Fe^{2+} to promote CO_2 fixation (anoxygenic photosynthesis) while others transfer electron from organic carbon to Fe^{3+} (heterotrophic respiration) or obtain energy by oxidizing Fe^{2+} and reducing O_2 or NO_3 (lithotrophic respiration) [5].

Throughout evolution, and due to the increase of oxygen tension, redox properties of iron made it extremely useful, so that its usage in eukaryotes is focused on oxygen metabolism, both as an oxygen carrier or

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