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The iron-regulatory hormone hepcidin: A possible therapeutic target?

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ABSTRACT

The maintenance of stable extracellular and intracellular iron concentrations requires the coordinated regulation of iron transport into plasma. Iron is a fundamental cofactor for several enzymes involved in oxidation–reduction reactions. The redox ability of iron can lead to the production of oxygen free radicals, which can damage various cellular components. Therefore, the appropriate regulation of systemic iron homeostasis is decisive in vital processes. Hepcidin has emerged as the central regulatory molecule of systemic iron homeostasis. It is synthesized in hepatocytes and in other cells and released into the circulation. It inhibits the release of iron from enterocytes of the duodenum and from macrophages by binding to the iron exporter protein, ferroportin (FPN). FPN is a transmembrane protein responsible for iron export from cells into the plasma. Hepcidin is internalized with FPN and both are degraded in lysosomes. The hepcidin–FPN axis is the principal regulator of extracellular iron homeostasis in health and disease. Its manipulation via agonists and antagonists is an attractive and novel therapeutic strategy. Hepcidin agonists include compounds that mimic the activity of hepcidin and agents that increase the production of hepcidin by targeting hepcidin-regulatory molecules. The inhibition of hepcidin could be a potentially attractive therapeutic strategy in patients suffering from anaemia or chronic inflammation. In this review, we will summarize the role of hepcidin in iron homeostasis and its contribution to the pathophysiology of inflammation and iron disorders. We will examine emerging new strategies that modulate hepcidin metabolism.

Contents

Abbreviations: AA, amino-acid; ABCA1, ATP binding cassette transporter A1; ABCB, ATP binding cassette (ABC) transporter; AKI, acute kidney injury; AMI, acute myocardial infarction; ARE, antioxidant response element; ATP, adenosine triphosphate; CHD, coronary heart disease; CKD, chronic kidney disease; CHF, chronic heart failure; CO, carbon monoxide; COX, cyclooxygenase; CPB, cardiopulmonary bypass; CREBH, cyclic AMP response element-binding protein-H; CRP, C-reactive protein; DMT1, divalent metal transporter 1; EAM, experimental autoimmune myocarditis; EPO, erythropoietin; ER, endoplasmic reticulum; ESAs, erythropoietin-stimulating agents; FPN, ferroportin; GDF-15, growth differentiation factor-15; hHepc, human hepcidin; HIF, hypoxia-inducible factor; HJV, haemojuvelin; HMGB1, high mobility group protein B1; HO, haem oxygenase; H_2S, hydrogen sulphide; HSP, heat shock protein; IL, interleukin; IREs, iron-responsive elements; IRPs, iron-regulatory proteins; JAK, Janus kinase; Keap, Kelch-like ECH-associated protein 1; LPS, lipopolysaccharide; Lrp1, lipoprotein receptor-related protein-1; α2M, α2-macroglobulin; MAL, MyD88 adapter-like; NO, nitric oxide; NOS, nitric oxide synthase; NOX, nicotinamide adenine dinucleotide phosphate oxidase; Nrf2, nuclear factor erythroid-related factor 2; PEG, polyethylene glycol; RNOS, reactive nitrogen and oxygen species; RNS, reactive nitrogen species; ROS, reactive oxygen species; sHJV.Fc, soluble HJV-Fc fusion protein; SOD, superoxide dismutase; STAT, signal transducer and activator of transcription; SR, sarcoplasmic reticulum; Tf, transferrin; TfR, Tf receptors; TLRs, toll-like receptors; TPP, thiamine pyrophosphate; TRAM, TLR4–TRIF-related adapter molecule; TTFD, thiamine tetrahydrofurfuryl disulphide.

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1. Introduction

Iron is a fundamental cofactor for several enzymes involved in oxidation–reduction reactions due to its ability to exist in two ionic forms: ferrous (Fe + 2) and ferric (Fe + 3) iron. However, the redox ability of iron can lead to the production of oxygen free radicals, which can damage various cellular components. For this reason, iron levels in tissues must be tightly regulated (Ganz, 2013). Various molecules are involved in iron uptake and storage by hepatocytes and its export from hepatocytes, and systems describing the iron cycle have evolved. The discovery of the iron-regulating role of the hormone hepcidin, followed by the elucidation of its mechanism of action has led to better understanding of the physiopathology of human iron disorders (Munoz-Bravo et al., 2013; Waldvogel-Abramowski et al., 2014) and offers new clinical potential in terms of diagnosis and therapy. Hepcidin has emerged as the central regulatory molecule of systemic iron homeostasis. Knowledge on how hepcidin exerts its regulatory function and on the molecular processes that regulate hepcidin production is largely based on animal and in vitro studies. Hepcidin is a peptide secreted predominantly from hepatocytes. It down-regulates ferroportin, the only known iron exporter, and therefore inhibits iron efflux from duodenal enterocytes, macrophages and hepatocytes into the bloodstream (Ganz & Nemeth, 2012). Hepcidin expression is regulated positively by body iron load. Although the underlying mechanism of iron-regulated hepcidin expression has not been fully elucidated, several proteins have been identified that participate in this process. In this review, we will summarize the role of hepcidin in iron homeostasis and its contribution to the pathophysiology of inflammation and iron disorders. We will examine emerging new strategies to modulate hepcidin metabolism. The therapeutic manipulation of hepcidin activity may become an important approach in cardiovascular and metabolic disorders.

2. Systemic iron metabolism and the importance of iron storage

2.1. Iron distribution

The total amount of iron in a 70-kg adult is approximately 4 g, of which two thirds is the iron in red blood cells and 300 mg is in the myoglobin of muscles. The majority of this iron comes from the recycling of senescent erythrocytes by macrophages of the reticulo-endothelial system (about 20 mg/day) (Gudjoncik et al., 2014). Most of the iron in plasma is directed to the bone marrow for erythropoiesis. More than 2 million new erythrocytes are produced every second by the bone marrow, requiring a daily supply of at least 20–30 mg of iron. Only 1 to 2 mg of the daily iron supply is derived from intestinal absorption, which, under a steady state, is sufficient only to replace insensible iron loss. Significant amounts of iron are also present in macrophages (up to 600 mg) whereas excess body iron (~1 g) is stored in the liver. Each erythrocyte contains a billion atoms of iron; at normal rates of turnover, this concentration corresponds to the incorporation of 2×10^{20} atoms of iron per day. Consequently, anaemia is the cardinal sign of iron deficiency. The best characterized syndrome of iron overload is hereditary haemochromatosis (Vujic, 2014). The acquisition, transport, utilization and storage of iron are tightly controlled to meet physiological needs and prevent excessive accumulation of the metal within cells. Mammals utilize distinct mechanisms to regulate iron homeostasis at the systemic and cellular levels (Lawen & Lane, 2013).

2.2. Proteins that exert crucial functions in the maintenance of systemic iron homeostasis

2.2.1. A range of regulatory mechanisms: general regulation

Several proteins, such as transferrin, ferritin, hemosiderin, hepcidin and ferroportin, exert crucial functions in the maintenance of systemic iron homeostasis. Macrophages play an important role in executing the regulatory events that lead to changes in systemic iron levels (Gammella et al., 2014). Schematically, the main site of iron absorption is the small intestine, but most iron is recycled by the monocyte–macrophage system via phagocytosis of senescent erythrocytes. In the circulation, iron is usually bound to transferrin (Tf), and most of the Tf-bound iron is utilized for bone marrow erythropoiesis (Gudjoncik et al., 2014). Within cells, iron is stored in the proteins ferritin or hemosiderin. Iron is the only micronutrient known to have a regulatory hormone, hepcidin, which responds to both nutrient status and infections. Hepcidin is mainly synthesized in the liver. It is a negative regulator and its production is increased during iron overload and inflammation. Intracellular iron is released into the circulation via ferroportin (FPT). The iron is donated to Tf and reutilized for bone marrow erythropoiesis. Hepcidin binds to the iron exporter FPT and leads to its degradation, thereby inhibiting intestinal iron absorption, cellular export and reticulo-endothelial iron release (Munoz et al., 2011).

2.2.2. Role of ferritin

Multiple physiological processes are involved in maintaining iron homeostasis. These include iron storage at the intracellular and extracellular levels. Ferritin is the major iron-storage protein. Typical ferritins are composed of 24 subunits, which fold into a 4-helix bundle and form an almost spherical protein shell. There is a strong equilibrium between ferritin-bound iron (Fe^{3+}) and the labile iron pool in cells (Fe^{2+}), by which ferritin prevents the formation of reactive oxygen species mediated by the Fenton reaction (Alkhateeb & Connor, 2013). Various cell types contain a transient cytosolic pool of iron, presumably bound to low-molecular-mass intracellular chelates, such as citrate, various peptides, ATP, AMP or pyrophosphate. This labile iron pool is redox-active and its concentration is determined by the rates of iron uptake, utilization for incorporation into iron enzymes, storage in ferritin and export from the cell (Cabantchik, 2014).

There are two functionally and genetically distinct ferritin subunits: L-ferritin and H-ferritin (also known as light-chain and heavy-chain ferritin). Ferritin is found in the cytoplasm, nucleus and mitochondria of cells. Serum ferritin has been thought to reflect iron stores in the body and to increase as a secreted by-product of intracellular ferritin synthesis. Cellular iron is stored primarily in the cytoplasm, but organelles such as mitochondria are the main users of metabolically active iron (MacKenzie et al., 2008).

The regulation of ferritin synthesis by iron is mainly due to post-transcriptional regulation through the binding of IRP1 and IRP2 to iron-responsive elements (IRE) located in the 5′ UTR of ferritin mRNA. Both IRP1 and IRP2 are expressed ubiquitously in most tissues. In