NARRATIVE REVIEW

Hepcidin: A key regulator of iron

Syeda Saneela,[1] Razia Iqbal,[2] Ali Raza,[3] Muhammad Fiaz Qamar[4]

Abstract

Hapcidin is the central regulator of iron homeostasis in the body. Primarily it is extracted from urine. Hepcidin is a 25 amino acid long chain peptide. Inflammation or iron overload greatly stimulate production of hepcidin by hepatocytes. Recent evidences have revealed that mutations in the human haemochromatosis (HFE) gene lead to deficiency of hepcidin which is responsible for iron overload and contributing to haemochromatosis. Moreover, hepcidin plays a key role in different types of anaemia, mainly anaemia of inflammation in which concentration of hepcidin increases up to 100 folds. Its contribution to renal disease, heart diseases, cancer and obesity-related disorders are also observed. On the other hand, its role is quite inevitable in understanding metastasis in certain cancers. By understanding the mechanism of hepcidin and its pathological roles in blood and iron diseases could lead to new therapies.

Keywords: Hepcidin, Anaemia, Iron metabolism, Iron, Inflammation.

Introduction

Iron is an essential element for life, as it modulates oxidative energy metabolism, proliferation and respiration of cells, oxygen transportation, synthesis of haemoglobin, myoglobin, cytochromes and many other enzymes which are all basic functions of the body.[1,2] In host-pathogen interactions, iron is also involved as a critical mediator. Approximately 4g of iron is present in an average adult male, 2g of which is in haemoglobin. Almost 1g is in stored form in the liver and the rest is used as part of iron carriers. Daily loss of iron occurs through the blood-loss in menstruating women, about 1-2mg, and by gastrointestinal tract (GIT) and skin.[2] However, vulnerability to bacterial, protozoan and viral infections become greater by elevated iron status.[3] Moreover, excess iron is noxious due to its tendency to release electrons and generating reactive oxygen species.[1,4] Important controlling mechanisms have been settled in mammals for regulation of iron according to needs of the body, preventing iron overload and regulate iron uptake, consumption, release and storage. The well-known iron responsive elements — iron regulatory proteins (IRE-IRP) system is used for cellular regulation while expression of iron-regulatory hormone, hepcidin, is used for the status at systematic level.[1,2,4]

[1,2]Department of Zoology, University of Gujrat, Gujrat Pakistan, [3]Department of Zoology, Government College University Lahore, Pakistan. [4]College of Veterinary and animal Sciences Jhang, Pakistan

Correspondence: Muhammad Fiaz Qamar. Email: fiaz.qamar@uvas.edu.pk

Hepcidin

Hepatic bactericidal protein (Hepcidin)[5] is an iron regulatory hormone designed basically for the homeostasis of iron. It's a cysteine-rich, small cationic peptide produced by the hepatocytes. Hepcidin was extracted recently from human urine and ultrafiltration of plasma.[6,7] The hepcidin antimicrobial peptide (HAMP) gene, also known as HFE, for High Iron Fe, for human hepcidin is found on chromosome 19q13, having a length of 2637 base pairs and composed of two introns and three exons. The HAMP 19q13 gene has expression at multiple sites including brain, liver, spinal cord, lungs, heart, skeletal muscles, intestine, stomach, pancreas, testis, adipocytes and macrophages. The post-translational process of hepcidin is mediated by hepatic prohormone convertase furin. Initially, hepcidin is produced as a larger precursor protein, enduring two cleavages and quickly secreted from the cell. Use of chemical inhibitor decanoyl-Arg-Val-Lys-Arg-chloromethylketone (dec-RVKR-cmk) for inhibition of furin protein convertase or inhibiting the furin synthesis by small interfering ribonucleic acid (siRNA) results in blocking of second cleavage of the hepcidin precursor. But its release from the cell is not inhibited, representing that furin is the main enzyme involved in hepcidin maturation.[8]

The bioactive and predominant form of hepcidin is 25-amino acid long and contains four disulphide bonds. Hepcidin-22 and hepcidin-20, having two peptides shorter at the amino terminus, are also found[9] which are biologically less active.[9] Hepcidin in range of 5% to 95% in healthy volunteers has a concentration of 29-254 ng/mL in men (n=65) and 17-286 ng/mL in women (n =49).[10]

Park et al. isolated a new peptide from human urine during their studies on antimicrobial properties of human body fluids and named this peptide hepcidin, based on its site of production which is the liver, or hep, and

antibacterial properties in vitro called 'cidin'. The same peptide was separated by Krause et al. from plasma ultrafiltrate, and they titled it liver-expressed antimicrobial peptide (LEAP-1).[11] The molecule has a simple hairpin structure with the two arms linked across by four disulphide bridges in a way just like ladder. Near the turn of the hairpin, two adjacent cysteine residues have a unique disulphide linkage which possesses greater chemical reactivity;[12] species have conserved sequence of peptide. Due to spatial separation of positive hydrophilic and negative hydrophobic side chains of hepcidin, it gains antimicrobial ability to disrupt bacterial membranes.[6] Binding of hepcidin to the only iron export protein ferroportin (FPN) controls iron efflux in the cell[13] causing its internalisation and lysosomal degradation of duodenal enterocytes and macrophages.[1,14] This binding requires five N-terminal amino acids on hepcidin molecule, and absence of these amino acids makes another naturally occurring hepcidin-20, which is biologically inactive.[2,9] In this way, by negative feedback mechanism, both iron absorption in the intestine and iron release from macrophages into plasma are controlled by circulating hepcidin.[1]

Induction of Hepcidin

According to studies demonstrating its role as a down-regulator of iron absorption, induction of hepcidin occurs in response to iron loading and inflammation.[2,9,15] Pigeon et al. first studied the association between hepcidin and iron metabolism during hepatic responses to iron excess.[15] Regulation of hepcidin seems to focus on the bone morphogenetic protein (BMP) receptor, including the signalling pathway and its additional protein-6 (BMP6) from liver sinusoidal endothelial cells, in a paracrine manner, proposed as a main physiologic controller of hepcidin. Two transferrin receptors, TfR1 and TfR2, sense the plasma iron that convey the information to the BMP receptor complex via the additional proteins HFE and haemojuvelin (HJV).[2,7,16-18] BMP6 activates the intracellular S-mothers against decapentaplegic (SMAD) pathway, which in turn up-regulates the HAMP promoter to synthesise hepcidin. Excision of additional proteins HFE, TfR2, HJV or BMP6, or key component of the BMP receptor signalling pathway, excision of SMAD homolog 4 (SMAD4), results in poor and abnormal production of hepcidin.[19]

A study suggested that vegetarian children had a two-fold decrease in serum hepcidin level complemented by decreased ferritin level and small but statistically significant increase in concentration of soluble transferrin receptor (sTfR). But there are no differences in concentration of haemoglobin, mean corpuscular volume (MCV), iron, and transferrin compared to the omnivorous group. Furthermore, vegetarian children had comparable total iron intake, but consumed about 30% more ascorbic acid in food.[20] Increased sTfR reflects higher expression of TfR in erythrocyte precursors, permitting more effective iron uptake even when plasma iron concentrations are decreased. There is also evidence that increased TfR expression helps mediate suppression of hepcidin in the liver.[21] By degrading duodenal FPN, hepcidin is a key regulator of iron uptake from the diet.[22] Furthermore, habitual consumption of high-phytate foods may reduce the negative effect of phytate on non-heme iron absorption.[23]

Iron sensor cells, hepatocytes, produce hepcidin during iron-mediated regulation.[9,24] The blocking effect of hepcidin to regulate iron is observed at multiple sites, including macrophages, intestinal epithelium and placenta and many other sites. When the iron level is elevated, hepcidin is synthesised by liver which feeds back to placenta and GIT to prevent exogenous absorption of iron. The discharge of iron in circulating transferrin from reticuloendothelial system (RES) is also suppressed by hepcidin. It also performs role as negative controller of placental iron transport in the foetus.[25]

Kupfer cells in liver release interleukin-6 (IL-6) which in turn induces cytokine, and hepcidin activity is increased during inflammation or infection.[9] These processes show the phenomenon of correlation between acute phase reactants, ferritin and hepcidin. When iron release is prevented, it results in high serum ferritin and low transferrin saturation (TSAT) level.[26] In mice, it was observed that induction of hepcidin micro RNA (mRNA) increased 4-fold while serum iron decreased 2-fold when an inflammatory stimulus, turpentine, was given.[9] Urinary hepcidin secretion increases greatly by the elevated amount of iron. In patients with anaemia of inflammation caused by chronic infections or severe inflammatory diseases, a 100-fold increase in hepcidin excretion was observed due to 24 assayed urinary hepcidin peptides. Same results were also observed in patients who have transfusions for sickle cell anaemia or myelodysplasia and iron overload. Collectively, hepcidin plays key role in many types of iron disorders either iron-deficient or iron overload.[27]

Suppression of Hepcidin

Anaemia has a stronger effect for suppression of hepcidin than iron overload for the stimulation of hepcidin. Down-regulation of hepcidin is mainly caused by anaemia and hypoxia, and both factors reduce the inhibitory effect on absorption and release of iron from macrophages.[28]

Patients with complete iron-deficiency anaemia or erythropoiesis have very low concentrations of hepcidin.[29]

Greater iron release from stores and increased absorption occurs when hepcidin gets low. This additional iron supply increases the haemoglobin concentration. Marked decrease occurs in serum hepcidin of humans by a single injection of an erythropoietin-stimulating agent (ESA).[10,30,31]

Increased erythroid drive also suppresses hepcidin expression. Moreover, during ineffective erythropoiesis and observations on thalassemia patients the growth differentiation factor 15 (GDF15) and twisted gastrulation 1 (TWSG1) are two transforming growth factor-beta (TGF) family products produced and they likewise down-regulate hepcidin. Soluble HJV19, and transmembrane protease, serine 6 (TMPRSS6) also down-regulate hepcidin expression.[32,33]

Hepcidin disorders

Shifts in hepcidin concentrations results in many human diseases. One of the consequences is accumulation of iron in the parenchymal cells of liver which cause toxicity. Generally, iron deficiency is known as a foremost health problem recognised to be associated with serious neuro-developmental and cognitive deficits in low-resource settings.[34] Ambroszkiewicz et al. demonstrated the increased concentrations of sTfR and decreased hepcidin level in lacto-ovo-vegetarian children and suggested that the vegetarian children may suffer from subclinical iron deficiency.[20,35]

Suppression of hepcidin also leads to iron overload and excessive FPN function.[1] Fleming and Sly suggested that high levels of hepcidin should result generally in anaemia of inflammation, mainly reduction of circulating iron, rise of iron level in RES and lesser iron absorption.[36] Nicolas et al. revealed that inflammation, anaemia and hypoxia are associated with the regulation of gene encoding hepcidin. Hypoxia (2% oxygen) significantly suppresses hepcidin expression in hepatoma cells.[6,37,38]

Hepcidin synthesis is directed by numerous elements apart from inflammation, including iron stores, hypoxia and erythropoiesis, and hepcidin release into the peripheral circulation is regulated by other proteins, including HJV, hereditary haemochromatosis protein, transferrin receptor 2, matriptase-2 and neogenin.[39,40] Pathologic modifications of hepcidin regulation are dominant in many disorders of iron metabolism, together with iron-loading anaemia, hereditary haemochromatosis, and anaemia of inflammation.[2] Individuals having genetic defect in hepcidin feedback mechanism for the prevention of excessive iron absorption suffer with hereditary haemochromatosis. Haemochromatosis type 2B is caused by the mutations in HAMP gene, also called juvenile haemochromatosis, a disease resulting by severe iron excess that leads to cardiomyopathy, endocrine failure and cirrhosis.[24]

Anaemia of inflammation is a result of hypoferremia due to increased activity of hepcidin concentrations which results in sequestration of iron in macrophages. In transgenic mice, excessive hepcidin is the reason for iron-regulated erythropoiesis.[37] Prominent urinary hepcidin concentrations linked with serum ferritin were observed in patients suffering from anaemia of inflammation.[19] In anaemia of iron-loading (β-thalassemia and inherited dyserythropoietic anaemia), the suppression of hepcidin expression occurs due to erythropoiesis which leads to the high amounts of dietary iron absorption and thus causing iron overload which damage the liver and myocardium.[2]

Hepcidin regulation in cancer through BMPs

Many studies have documented that different BMPs control hepcidin expression in tumour tissues. BMP6 is positioned as the key BMP molecule that controls hepcidin expression in prostate cancer. The local BMPs, especially BMP4 and BMP7, are linked with prostatic hepcidin expression but might be influenced by BMP6 produced through signalling from bone stromal cells (BSCs).[41] Additionally, the high level of BMP7 causes hepcidin overexpression in prostate cancer, especially during its metastasis. Irrespective of androgen suppression therapy, prostatic hepcidin is considered a promoter of cancer cell survival.[42] A recent study on breast cancer patients demonstrated very low level of BMP6 in cancer tissue compared with non-cancerous tissues, attributing the local BMP6 as an unlikely inducer of hepcidin expression.[43] Although hepcidin production in breast cancer does not only originate from cancer tissue but liver is an important source of increased hepcidin levels in breast cancer.[44] Excessive iron significantly induces BMP6 production in cancerous breast tissues. Hence Iron, BMP6 and IL-6 mutually direct hepcidin in breast cancers.[45]

A recent study conducted for investigating the relationships of the hepcidin and ferroportin (fpn) expression in tissues and serum taken from breast cancer (bca) patients, and the relationship of hepcidin and fpn with anaemia. Expression of hepcidin in serum was high, suggesting that serum hepcidin plays a major role in anaemia.[46] and fpn was significantly lower, in non-

anaemic bca patients and in control subjects.[47] On the other hand it is also investigated that hepcidin level has a significant correlation with IL-6 and Hb levels in breast cancer patients with bone metastasis and is considered as an independent risk factor for breast cancer and its bone metastasis.[48]

Some studies also relate that BMPs are important inducers of hepcidin expression in lung cancer because of elevated serum hepcidin levels caused by up-regulation of BMP2 levels.[49,50] A clinical study evaluated and documented for the first time serum hepcidin level hepcidin as a predictor of disease outcome in Non-Small Cell Lung Cancer (NSCLC).[51,52] On the other hand, BMP4 has also been associated with metastatic forms of colon cancer.[53] In a recent study, it has demonstrated that hepcidin and ferroportin expressions are associated with prognosis of patients with pancreatic cancer.[54] There is another emerging interest that BMPs are suspected to be inducers of hepcidin expression in Non-Hodgkin Lymphoma (NHL) because of the strong correlation between hepcidin and ferritin observation in this cancer.[55]

Recommendations

Many studies, as cited above, have described detailed mechanisms of up- and down-regulation of hepcidin expression during various cellular iron levels. There is an established phenomenon relating the level of hepcidin expression with different BMPs. But many questions are just mysteries, such as why local BMP7 is able to induce hepcidin expression, provided the role of local BMP6 in hepcidin regulation in prostate cancer. Future studies should resolve this mystery. In addition, there is no certainty about the exact mechanisms of BMP2 regulation in lung cancer and its relationship with other BMPs. In future it might be possible to have an insight of BMP regulation and hepcidin expression in lung cancer. We recommend that the future studies should resolve the roles of BMPs in inducing local hepcidin expression in different cancers like BMP4 and BMP7 controlling colon cancer.

Conclusion

Hepcidin is a cysteine-rich, small peptide produced by hepatocytes. It is stimulated by iron overload and inflammation while hypoxia and anaemia significantly suppress expression of hepcidin. Hepcidin is the principal iron-regulatory hormone, having central role in anaemia of different types and erythropoiesis. On the other hand, its role is quite inevitable in understanding the cancers metastasis. By understanding the mechanism of hepcidin and its pathological roles in blood and iron diseases could lead to new therapies and ultimately great medical success.

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