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Review Article

Hepcidin and Disorders of Iron Deficiency Anemia and Metabolism

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ABSTRACT

The liver produces hepcidin which functions as the primary controller of body iron balance because it regulates the sole known iron transport protein called ferroportin. The body experiences two digestive issues which arise from hepcidin malfunction because it prevents proper iron absorption in iron-restricted erythropoiesis and it creates problems during iron overload because it activates both hereditary hemochromatosis and ineffective erythropoiesis syndromes. The study of hepcidin biology has led to advanced diagnostic methods and new treatment options which include hepcidin antagonists and mimetics and ferroportin pathway modulators. The review presents hepcidin structural information together with its regulatory mechanisms and its role in iron-related anemia and hepcidin biomarkers and assays and existing and developing hepcidin-targeted treatments and their clinical applications. The research agenda requires scientists to answer fundamental questions while making progress toward real-world applications.

INTRODUCTION

Humans need iron because it helps transport oxygen through their bodies while supporting their cellular breathing process and DNA creation, but unbound iron compounds create dangerous oxidative reactions thus requiring strict control of body iron levels. Hepcidin is a 25-amino-acid peptide that serves as the primary iron control mechanism because it binds to ferroportin proteins located in enterocytes and macrophages and hepatocytes to trigger their internalization and destruction which decreases iron discharge into blood and diminishes transferrin-associated iron levels. [1–3] The current understanding of hepcidin dysregulation shows that it serves as the fundamental cause behind multiple anemias which occur when hepcidin levels become too high and iron overload disorders that develop when hepcidin levels become too low. [1–5]

2. Overview of iron homeostasis .

Duodenal enterocytes absorb dietary iron which they export through ferroportin into plasma. In

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plasma iron binds to transferrin which delivers it to erythroid marrow and stores it in hepatocytes and macrophages. Splenic and hepatic macrophages phagocytose senescent erythrocytes and they use ferroportin to return recycled iron back to plasma. Ferroportin serves as the only cellular iron exporter which establishes the main control mechanism for systemic iron movement in the body. [2,6–8]

3. Hepcidin: structure, synthesis and multilayered regulation

3.1 Molecular form and biosynthesis

Hepcidin exists as a prepropeptide that contains 84 amino acids which gets transformed into its active form that exists as a 25-amino-acid peptide which enters the bloodstream. The peptide contains cysteine residues throughout its structure which enables it to maintain its essential binding properties with ferroportin through its highly conserved design. [3,9]

3.2 Hepatic regulation — core signaling pathways

Transcription of hepcidin in hepatocytes integrates several stimuli:

- **BMP6–HJV–SMAD pathway** : functions as the main mechanism which detects iron levels in the body. The liver sinusoidal cells together with hepatocytes produce BMP6 which activates the HJV-BMP receptor complex to initiate SMAD signaling that increases hepcidin transcription when the body has excess iron. [10–12]

- **IL-6–STAT3 inflammatory pathway**: Inflammatory activates hepcidin production during both infection and chronic inflammatory conditions, which leads to decreased iron levels that cause anemia of inflammation. [13,14]

- **Erythroferrone (ERFE)** : Functions as a biological response which erythroblasts produce when they detect erythropoietic stimuli that occur after erythropoietin treatment. The substance inhibits hepcidin production which results in higher iron availability for use during the process of producing new red blood cells. [15]

- **Hypoxia / erythropoietic drive** and the relationship between hepcidin and erythropoiesis requirements and iron requirements is controlled by hypoxia and erythropoietic drive and the regulatory proteins GDF15 and TMPRSS6 and matriptase-2. [7,16,17]

3.3 Hepcidin–ferroportin interaction

The process begins when mature hepcidin establishes a connection with ferroportin at the cell surface which activates the subsequent process of ferroportin being marked for degradation through ubiquitination to undergo lysosomal destruction. The mechanism provides an explanation for two conditions which occur during inflammatory states: hypoferremia and decreased capacity of the body to absorb dietary iron. [1,6,8]

4. Pathophysiological roles in specific anemia types

4.1 Anemia of inflammation / chronic disease

The body produces hepcidin when inflammation occurs through IL-6 and related cytokines which leads to iron being stored in macrophages and enterocytes while transferrin-bound iron decreases. The condition results in functional iron deficiency because there are sufficient iron reserves thus leading to problems in blood cell

production and subsequent development of anemia. This is the central mechanism of anemia of inflammation. [13,14,18]

4.2 Chronic kidney disease (CKD) associated anemia

CKD causes persistent high hepcidin levels because of ongoing inflammation and decreased kidney function. The elevated hepcidin levels lead to two medical problems which include impaired iron absorption through the gut and reduced effectiveness of erythropoiesis-stimulating agents thus requiring higher intravenous iron treatments and larger erythropoiesis-stimulating agent dosages. [19 20]

4.3 Cancer-related anemia

Tumor-driven cytokine production and systemic inflammation induce hepcidin, which restricts iron delivery to erythroid precursors; additionally, marrow suppression and nutritional factors compound anemia. Hepcidin-mediated iron withholding is thus central in many cancer-related anemias. [18,21]

4.4 Infections, immunity and iron withholding

In response to acute infection the body produces hepcidin as a defense mechanism which prevents pathogens from accessing iron through a process known nutritional immunity. The continuous production of hepcidin during chronic infections leads to the development of clinically important iron-restricted anemia. The medical doctors face a dual challenge of managing both infection control and anemia treatment in these situations. [13,22]

5. Diagnostic and biomarker landscape

5.1 Hepcidin assays and standardization

Direct serum hepcidin measurement through mass spectrometry and immunoassay methods provides valuable information for clinical application, but widespread clinical usage has been restricted because of problems with assay performance and absence of international testing standards. The organization is currently working to establish common testing methods which will improve standardization of laboratory results. [23,24]

5.2 Traditional iron indices and emerging biomarkers

The five tests ferritin, transferrin saturation (TSAT), soluble transferrin receptor, reticulocyte hemoglobin content (CHr), and the newer erythroferrone assay function as complementary tests. The combination of CRP and iron indices needs to be assessed because ferritin functions as an acute-phase reactant. The implementation of a biomarker panel that contains hepcidin helps to enhance both mechanistic diagnosis and the process of choosing appropriate treatments. [25–27]

6. Therapeutic approaches targeting hepcidin biology

Researchers can use hepcidin manipulation to create two different treatment approaches which involve decreasing hepcidin levels to improve iron availability for patients with iron-restricted anemia and increasing or simulating hepcidin levels to restrict iron in patients with iron overload conditions or those with abnormal blood cell production. The primary treatment methods consist of the following three main approaches:

6.1 Hepcidin antagonists (neutralizers)

- **Spiegelmers / aptamers**: The L-oligonucleotide spiegelmer Lexaptepid (NOX-H94) binds hepcidin) and blocks its

biological activity. The human volunteer studies showed that the experimental hypoferremia condition was reversed through testing. [9,28]

- **Antibodies / anticalins / decoy binders**: Monoclonal antibodies which can bind to hepcidin and engineered small protein binders. The preclinical models show promising results but the clinical data remains in its initial phase according to evidence from the study.[29 30]

6.2 Suppression of hepcidin expression (upstream pathway inhibitors)

- **IL-6 / inflammatory pathway blockade**: Tocilizumab has been reported to decrease hepcidin induction in inflammatory diseases and can also help alleviate anemia in which inflammation is the driver. [14, 31]

- **BMP pathway inhibitors / HJV modulators**: The research evidence shows that two methods of creating hepcidin transcription limitations through BMP6 neutralization and HJV co-receptor inhibition both lead to increased serum iron levels and enhanced iron mobilization according to preclinical studies. [10,11,32]

- **TMPRSS6 modulation**: TMPRSS6 (matriptase-2) operates as a hepcidin inhibitor because its TMPRSS6 suppression leads to increased hepcidin levels which researchers are developing to treat iron-overload and ineffective erythropoiesis disorders. The process of selecting specific targets must vary according to the particular disease being treated. [7,33]

6.3 Hepcidin mimetics and ferroportin inhibitors (agonists)

- Minihepcidins and synthetic hepcidin peptides replicate hepcidin functions to decrease iron levels which benefits people with hereditary hemochromatosis and conditions that cause abnormal red blood cell production. Recent structural studies of minihepcidin PR73 bound to ferroportin illuminate improved potency and design opportunities. [34,35]

- **Small-molecule ferroportin inhibitors:-** Inhibition of iron export is considered as a wide array of potential drug targets (e.g., VIT-2763) and has shown preclinical pharmacodynamic activities in phase I trials as the potential oral therapy for iron-loading diseases. [36]

7. Clinical evidence and translational highlights

7.1 Proof of concept: hepcidin neutralization

The anti-hepcidin spiegelmer NOX-H94 showed that it could reverse experimental inflammation-induced hypoferremia which existed in human subjects by demonstrating that hepcidin neutralization operates as an iron mobilization mechanism. This finding supports the need for clinical trials which will study patient populations that exhibit elevated hepcidin levels along with iron-restricted erythropoiesis. [9]

7.2 Hepcidin agonists in erythrocytosis

The hepcidin mimetic Rusfertide showed positive results in polycythemia vera treatment through its ability to reduce phlebotomy needs and maintain hematocrit levels which established a treatment area for hepcidin agonist drugs. [37]

7.3 Ferroportin inhibition and oral agents

VIT-2763 (oral ferroportin inhibitor) showed expected iron-lowering pharmacodynamics in

healthy volunteers and is being evaluated in relevant patient populations. [36]

7.4 RNA and antisense therapeutics

Scientists are developing liver-targeted siRNA and antisense agents which will target TMPRSS6 and HAMP mRNA as a platform to achieve long-lasting hepcidin modulation. The treatment must increase or decrease hepcidin levels according to the biological state of the disease according to therapeutic direction. [33,38]

8. Safety considerations and potential risks

Manipulating systemic iron flux carries real safety concerns:

- **Infection risk:** The research indicates that hepcidin reduction will increase serum iron levels which will subsequently create a favorable environment for particular pathogens to thrive. The research requires clinical trials to carry out continuous infection assessment throughout their operations. [22,39]
- **Iron overload and organ deposition:** The research demonstrates that hepcidin reduction will result in increased serum iron levels which will establish a favorable environment for specific pathogens to multiply. The research needs clinical trials to conduct ongoing assessment of infections during their entire study period.[22,39]
- **Immunogenicity and off-target effects:** Biologic agents (peptides, Spiegelmers, antibodies) can trigger immune reactions together with non-specific effects. The available research only provides limited information about long-term effects. [28,29,40]

9. Practical clinical applications and patient selection

The best results from hepcidin-focused treatments depend on understanding patient biology through mechanistic patient phenotyping which requires hepcidin and ferritin and TSAT and inflammatory marker assessment. Patients who have high hepcidin levels together with low TSAT levels which indicate functional iron deficiency represent suitable candidates for hepcidin reduction treatments. Patients who have low hepcidin levels together with iron overload conditions will likely derive benefits from hepcidin mimetics and ferroportin inhibitors. The decision-making process requires assessment of three factors which include the patient's current medical condition and their history of blood transfusions and their likelihood of developing iron overload. [23–27,33]

10. Research gaps and future priorities

1. **To standardize Hepepidin measurements and establish** clinical cutoffs for selecting therapies [23,24].
2. **The study involved large-scale randomized clinical trials** which investigated the effects of hepcidin-modulating treatments on patient outcomes that included hemoglobin response and transfusion avoidance and life quality and disease-related death rates.[37 41]
3. **Studies for the safety to determine infection risk** and iron accumulation in the course of chronic hepcidin suppression. [39,40]
4. **Strategies of combos** (e.g., hepcidin antagonist plus IV iron or ESAs) and an optimal approach to timing/dosing. [28,33,38]
5. **The research investigates** how companion diagnostics together with precision medicine

algorithms establish a treatment link between medical mechanisms and the patient's specific iron-regulatory genetic pattern.[31,33]

CONCLUSIONS

Hepcidin sits at the center of iron metabolism and constitutes a rational, mechanistic target for treating iron-related anemias and iron-overload disorders. Translational progress from molecular biology to early human trials has provided strong proof of concept: both hepcidin antagonists and mimetics can alter iron distribution in predictable ways. However, successful clinical implementation requires standardized diagnostics, careful patient selection, demonstration of patient-centered benefits in large trials, and long-term safety data. Continued development of peptides, small molecules, RNA therapies and companion diagnostics promises to broaden the therapeutic armamentarium for iron disorders over the next decade. [1–25]

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