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Review

Role of Iron Metabolism in Anemia

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Abstract:
Anemia remains one of the most prevalent hematological disorders worldwide, affecting nearly two billion individuals. Central to its pathophysiology is iron metabolism, which underpins hemoglobin synthesis, mitochondrial energy production, and diverse enzymatic functions. Because unbound iron catalyzes reactive oxygen species formation, its regulation is tightly controlled through absorption, transport, storage, and recycling. Hepcidin, the master regulator of ferroportin, orchestrates systemic iron balance, and disturbances in this network give rise to distinct clinical phenotypes. Iron deficiency anemia commonly results from inadequate intake or chronic blood loss, whereas anemia of chronic disease reflects inflammatory upregulation of hepcidin. Genetic mutations in iron transport proteins further contribute to hereditary anemias. Recent advances emphasize the roles of hypoxia-inducible factors, erythroferrone, and immune signaling in adjusting iron availability during hypoxia and increased erythropoietic demand. Oxidative stress and ferroptosis exacerbate ineffective erythropoiesis and premature red cell destruction, linking iron imbalance to cellular injury. Macrophage-mediated recycling and hepatic storage normally buffer systemic fluctuations, but these mechanisms are impaired in chronic inflammation, thalassemia, and hemochromatosis. Clinically, precise diagnosis integrates conventional markers such as serum ferritin, transferrin saturation, and soluble transferrin receptor with emerging assays for hepcidin, which help distinguish iron deficiency anemia from anemia of chronic disease. Therapeutic innovation increasingly focuses on modulating hepcidin activity, targeting erythroferrone pathways, and developing safer iron formulations. Collectively, these insights highlight iron metabolism as a mechanistic cornerstone of anemia, bridging molecular regulation, oxidative stress, and biomarker development while guiding strategies for diagnostic accuracy and therapeutic progress.

Keywords: Anemia; Iron metabolism; Hepcidin; Erythroferrone; Hypoxia-inducible factors; Ferroptosis; Oxidative stress; Diagnostic biomarkers

INTRODUCTION

Anemia is one of the most prevalent hematological disorders worldwide, affecting nearly two billion individuals and posing a major public health challenge across both developed and developing nations [1]. Anemia, marked by low hemoglobin or erythrocyte mass, impairs oxygen delivery; iron metabolism disturbances dominate its diverse etiological spectrum [2].

Iron supports hemoglobin, energy, DNA, and enzymes, yet excess causes oxidative stress. Regulation via DMT1, ferroportin, transferrin, ferritin, and hepcidin preserves systemic balance and cellular protection [3].Together, these molecular players maintain iron equilibrium under physiological conditions. Thus, iron metabolism is not merely a nutritional concern but a mechanistic cornerstone in diverse anemic conditions [4].Iron regulation remains complex; new studies highlight immune interplay, hypoxia-inducible factors,

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and genetic diversity shaping individual susceptibility to iron imbalance [5].

Dysregulation of iron metabolism—particularly involving hepcidin activity, iron absorption, and mobilization from storage sites—contributes directly to the onset and progression of anemia by impairing erythropoiesis and limiting hemoglobin synthesis. Therefore, targeting key regulators of iron homeostasis may provide novel therapeutic strategies for anemia management

IRON METABOLISM : PHYSIOLOGICAL OVERVIEW

Physiological Overview of Iron Metabolism

Iron metabolism maintains balance by regulating absorption, distribution, storage, and recycling, ensuring essential functions while preventing harmful accumulation [6]. Iron absorption occurs mainly in the duodenum, involving heme and non-heme forms. Uptake, storage, and export via DMT1, ferritin, and ferroportin are tightly regulated by hepcidin to maintain systemic balance [7]. Most iron supports hemoglobin synthesis; surplus stored in ferritin and hemosiderin, while macrophages recycle iron from senescent red cells [8].

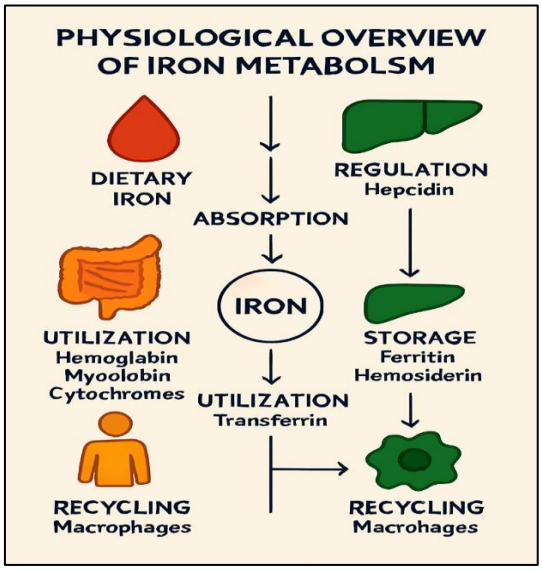

Fig 1: Physiological overview of iron metabolism

Absorption and Transport

Iron absorption in the duodenum involves heme and non-heme forms, differing in bioavailability and uptake, ensuring balance without toxicity [9].Non-heme iron, ingested as ferric (Fe^{3+}), is reduced by Dcytb to ferrous (Fe^{2+}), absorbed via DMT1, with vitamin C enhancing and phytates, tannins, calcium inhibiting uptake [10].Heme iron, highly bioavailable, enters enterocytes via HCP1 without reduction. Heme oxygenase liberates ferrous iron, enabling utilization or storage, explaining superior absorption from animal sources [11]. Iron is oxidized to ferric (Fe^{3+}) by hephaestin and ceruloplasmin, then bound to transferrin, enabling safe transport, tissue delivery, and regulated uptake via transferrin receptors [12].Iron absorption is tightly regulated since mammals lack excretion. Homeostasis relies on absorption and recycling; imbalance causes deficiency anemia or overload disorders, emphasizing coordinated intestinal, systemic, and hormonal control [13].

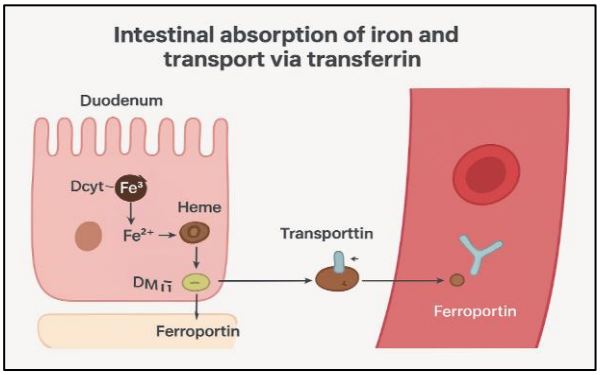

Fig 2: Intestinal absorption of iron and transport via transferrin

Cellular Regulation

Cellular iron uptake relies on transferrin receptor-mediated endocytosis. Acidic endosomes release ferric iron, reduced to ferrous by ferrireductases, then transported into the cytosol through divalent metal transporter [14].Cytosolic iron is directed to mitochondria for heme and Fe-S cluster synthesis, supporting metabolism. Excess iron is sequestered in ferritin, preventing oxidative stress and maintaining cellular stability [15].Ferritin and iron-related proteins are post-transcriptionally regulated by IRPs binding IREs. Low iron enhances uptake, while high iron promotes ferritin synthesis, ensuring cellular homeostasis [16]. Disrupted iron metabolism causes deficiency or overload, impairing mitochondria, inducing oxidative stress, and promoting ferroptosis linked to disease [17].

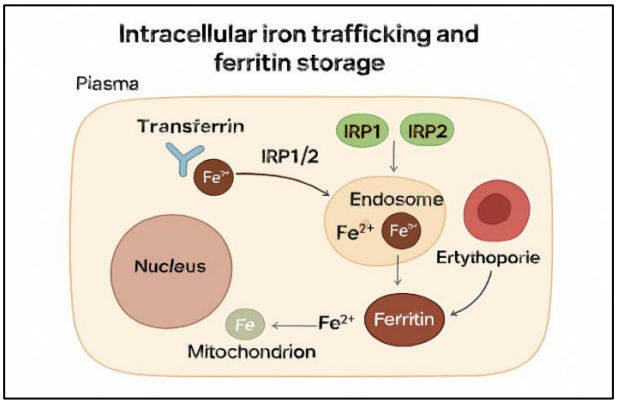

Fig 3: Intracellular iron trafficking and ferritin storage

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Hormonal Control: Hepcidin

Iron supports hemoglobin, respiration, and enzymes; excess causes toxicity. Hepcidin, liver-derived hormone, regulates systemic iron balance to maintain homeostasis [18].

Regulation of Hepcidin Expression

Hepcidin synthesis is tightly regulated by multiple physiological signals:

- **Iron overload:** High plasma iron activates the BMP/SMAD signaling stimulating hepcidin transcription to prevent further absorption.
- **Inflammation:**Cytokines, particularly interleukin-6 (IL-6), upregulate hepcidin, contributing to anemia of chronic disease.
- **Erythropoietic demand:** Conditions such as anemia or hypoxia suppress hepcidin to ensure iron availability for hemoglobin synthesis [19].

Role of Erythroferrone

Erythroferrone, secreted by erythroblasts under erythropoietin stimulation, suppresses hepatic hepcidin, sustaining ferroportin activity, enhancing iron mobilization, and serving as biomarker and therapeutic target in iron-related disorders [20].

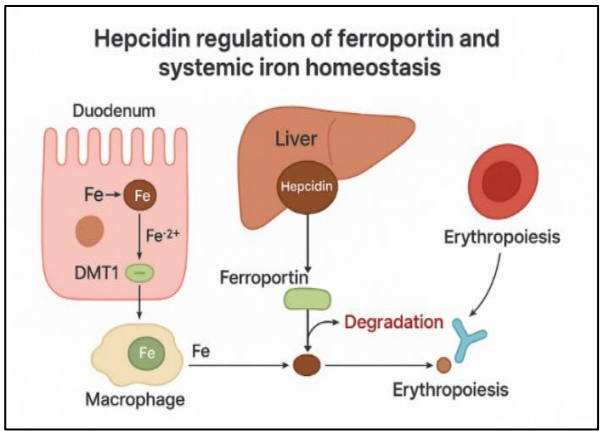

Fig 4: Hepcidin regulation of ferroportin and systemic iron homeostasis

Recycling Pathways

Macrophages recycle iron by engulfing aged erythrocytes, degrading hemoglobin, releasing heme, and exporting liberated iron via ferroportin, sustaining erythropoiesis and essential metabolic functions [21].The liver stores iron in ferritin and hemosiderin, releasing it during deficiency. Along side macrophages, hepatic reserves regulate absorption, storage, and utilization, maintaining systemic iron balance [22].

Table 1: Types of Iron-Related to Anemia

Type of Anemia	Mechanism	Key Features
Iron Deficiency Anemia (IDA)	Absolute lack of iron due to poor intake, malabsorption, or chronic blood loss	Microcytic, hypochromic RBCs; low ferritin; high TIBC [23]
Functional Iron Deficiency	Iron stores present but unavailable for erythropoiesis (often due to inflammation or hepcidin excess)	Normal/high ferritin but low transferrin saturation [24]
Anemia of Chronic Disease (ACD)	Cytokine-driven iron sequestration and reduced erythropoietin response	Normocytic or mildly microcytic; high ferritin; low serum iron [25]
Sideroblastic Anemia (Iron-loading anemia)	Defective incorporation of iron into heme	Ring sideroblasts in bone marrow; high serum iron [26]

Molecular Mechanism and Pathophysiology

a. Hepicidin regulation

Iron supports hemoglobin, respiration, and enzymes but excess is harmful. Hepcidin regulates ferroportin, coordinating absorption, storage, and mobilization to maintain systemic iron homeostasis [27].

- **BMP/SMAD Pathway: Primary Iron Sensing Mechanism** HJV, HFE, or TFR2 mutations lower hepcidin, elevate ferroportin, driving hereditary hemochromatosis with iron overload, cirrhosis, diabetes, cardiomyopathy, pigmentation [28].
- **JAK/STAT3 Pathway: Hepcidin in Inflammation** Interleukin-6 stimulates hepcidin transcription through JAK/STAT3 signaling. IL-6 activates JAKs, phosphorylating STAT3, which enters the nucleus, binds HAMP promoter, and enhances hepcidin gene expression [29].Anemia of chronic disease arises from high hepcidin, causing macrophage iron sequestration, reduced absorption, functional deficiency with low serum iron yet elevated ferritin [30].
- **Suppression of Hepcidin: Hypoxia and Erythropoietic Demand** Erythroferrone from erythroblasts and hypoxia-inducible factors suppress hepcidin, sustaining ferroportin activity and iron mobilisation. This regulation supports erythropoiesis, while persistent suppression in

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thalassemia promotes pathological iron overload [31].

- **Pathophysiological Consequences** Elevated hepcidin traps iron causing deficiency; reduced hepcidin overloads tissues, leading organ damage and disease [32].
- **Therapeutic Modulation of Hepcidin** Hepcidin agonists reduce iron absorption in overload, while antagonists alleviate inflammatory anemia. Therapeutic strategies also target BMP/SMAD and JAK/STAT3 pathways, offering promising avenues for regulating systemic iron homeostasis [33].

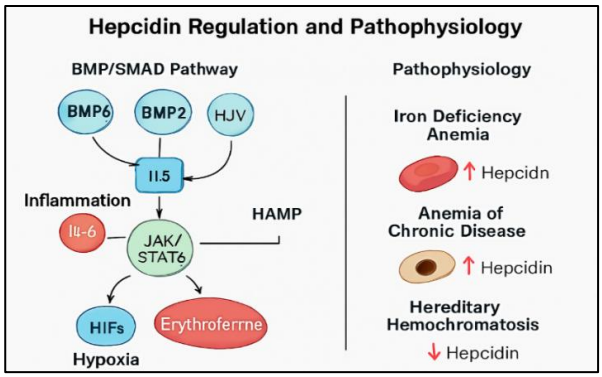

Figure 5: Hepicidine Regulation and Pathophysiology

b. Role of hypoxia-inducible factors (HIFs)

Hypoxia-inducible factors link oxygen sensing with iron metabolism; stabilized HIF-2α enhances erythropoiesis by boosting erythropoietin, iron uptake, hepcidin suppression, and macrophage recycling, regulated via PHD-dependent oxygen-sensitive degradation [34]. A critical downstream target is erythropoietin (EPO). HIF-2α induces EPO transcription in renal interstitial fibroblasts, stimulating erythropoiesis in the bone marrow. This mechanism compensates for hypoxic stress and is particularly relevant in anemia associated with chronic kidney disease, where impaired EPO production is a major contributor [35,36].HIF-2α enhances intestinal iron absorption by inducing DMT1 and DCYTB. DMT1 transports ferrous iron, while DCYTB reduces ferric, ensuring bioavailability and meeting erythropoietic demand through increased uptake [37]. Hepcidin limits iron by degrading ferroportin. HIFs suppress hepcidin via erythroferrone and BMP modulation, enhancing plasma iron. In chronic disease anemia, cytokine-driven hepcidin elevation overrides suppression, restricting iron availability despite physiological demand [38,39].Finally, HIFs regulate macrophage iron recycling by modulating polarization and erythrophagocytosis. Efficient recovery sustains erythropoiesis, while dysfunction under hypoxia or inflammation impairs recycling, worsening anemia [40].

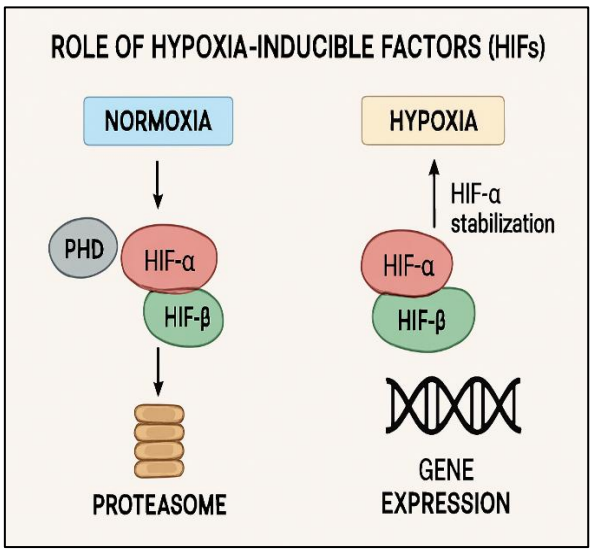

Figure 6: Role of HIF s

c. Erythropoiesis

- **EPO–JAK2–STAT5 Signaling** Erythropoietin drives erythropoiesis through EPOR–JAK2–STAT5, but anemia's inflammation and iron limits hinder output [41].
- **Iron Restriction and Hepcidin** Iron supports erythroblast heme synthesis. Hepcidin degrades ferroportin, restricting iron release. In chronic disease, cytokine-driven hepcidin elevation induces functional deficiency despite sufficient iron reserves [42].
- **Erythroferrone (ERFE) Crosstalk** Erythroferrone from EPO-stimulated erythroblasts suppresses hepcidin, enhancing iron for hemoglobin; chronic elevation in ineffective erythropoiesis causes overload despite anemia [43].
- **Hypoxia–HIF Pathway** Hypoxia stabilizes HIF-2α, enhancing EPO transcription and iron transporter expression. Iron deficiency disrupts HIF-2α via IRPs, diminishing EPO production and aggravating anemia through impaired oxygen–iron regulation [44].
- **Chromatin Remodeling in Erythroblasts** Terminal erythropoiesis requires chromatin condensation and enucleation; impaired heterochromatin remodeling disrupts maturation, causing anemia [45].
- **Macrophage Recycling** Macrophages recycle iron from aged erythrocytes, but inflammation-induced hepcidin blocks ferroportin, trapping iron and restricting erythropoiesis, causing anemia of chronic disease [46].

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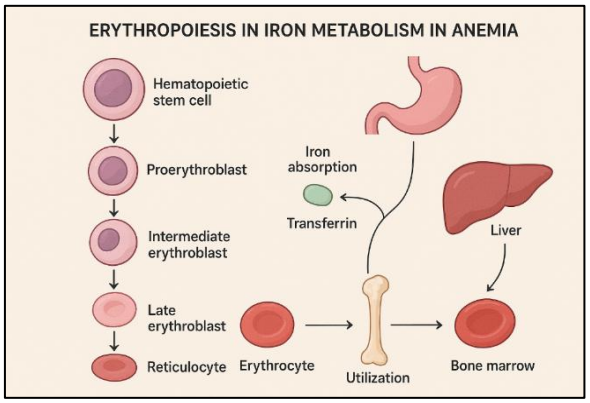

Fig 7: Erythropoiesis in Iron Metabolism in Anemia

d. Oxidative Stress

- **Iron as a Catalyst of ROS** Iron's redox cycling (Fe^{2+}/Fe^{3+}) drives Fenton/Haber–Weiss reactions, producing hydroxyl radicals that trigger oxidative damage—lipid peroxidation, protein oxidation, DNA injury—compromising erythrocyte viability [47].
- **Disruption of Iron Homeostasis** Iron homeostasis relies on ferritin, transferrin, and ferroportin. Oxidative stress disrupts them, releasing free iron, suppressing export, and elevating hepcidin, causing intracellular accumulation and impaired erythropoiesis [48].
- **Oxidative Damage to Erythrocytes** Reactive oxygen species damage erythrocyte membranes via lipid peroxidation and cytoskeletal injury, inducing eryptosis with shrinkage, blebbing, phosphatidylserine exposure, ultimately reducing lifespan and promoting anemia [49].
- **Mitochondrial Dysfunction in Erythropoiesis** Erythroblast mitochondria synthesize heme and iron–sulfur clusters; oxidative stress disrupts enzymes, impairing hemoglobin, leading to thalassemia and sideroblastic anemia [50].
- **Ferroptosis and Iron-Driven Cell Death** Ferroptosis via iron-driven lipid peroxidation impairs erythroid precursors, aggravating ineffective erythropoiesis and anemia progression [51].

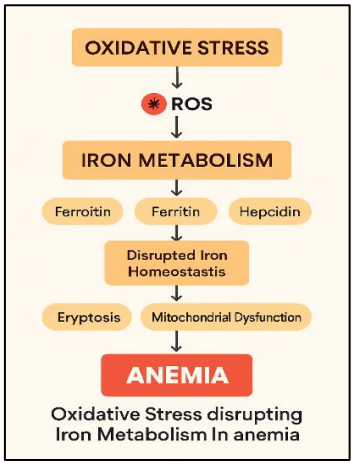

Fig 8: Oxidative Stress disrupting Iron Metabolism In Anemia

1) Diagnostic markers

Table 2: Diagnostic markers and their Role

Marker	Physiological Role	Diagnostic Utility	Limitations
Serum Ferritin	Storage protein for iron; reflects body iron reserves	Low ferritin (<30 ng/mL) is highly specific for IDA	Elevatedin inflammation, liverdisease, and malignancy (acute-phase reactant) [52]
Transferrin Saturation (TSAT)	Ratio of serum iron to totaliron-binding capacity	TSAT<20% suggests iron deficiency; useful for iron overload	Fluctuates with diurnal variation, inflammation, malnutrition [53]
Soluble Transferrin Receptor (sTfR)	Circulating fragment of transferrin receptor; reflects erythropoietic iron demand	Elevatedin IDA; unaffectedby inflammation; sTfR/log ferritin index distinguishes IDA vs ACD	Limited availability, higher cost, assay variability [54]

- **Emerging biomarkers:**

Hepcidin assays Hepcidin controls iron via ferroportin degradation; high restricts absorption, low enhances uptake, aiding anemia management [55].

Types of Hepcidin Assays

1.Mass Spectrometry (MS) Assays 2. Immunoassays (ELISA, RIA)3.Novel Immunological Assays

2) Therapeutic strategies: oral/parenteral iron, erythropoiesis-stimulating agents, hepcidin modulators.

- **Oral Iron Therapy**

Recent Oral Formulations

- Ferric maltol: improved bioavailability and tolerability.

- Sucrosomial iron: encapsulated formulation with better GI tolerance, useful in patients intolerant to ferrous salts [56].

    - **Parenteral (Intravenous) Iron Therapy**

Formulations

- Iron sucrose
- Ferric carboxymaltose (FCM) – allows high-dose single infusions.
- Ferumoxytol – rapid infusion, lower hypersensitivity risk.
- Iron dextran – older, associated with higher risk of allergic reactions [57]**.**

    - **Recent Drugs in Anemia Therapy**

Beyond traditional iron supplementation, new pharmacological agents have emerged:

Hypoxia-Inducible Factor Prolyl Hydroxylase Inhibitors (HIF-PHIs)

- Daprodustat (Jesduvroq) – FDA-approved (2023) for CKD-related anemia.
- Roxadustat – approved in Asia and Europe; lowers hepcidin, improves iron mobilization.
- Vadadustat – approved in Japan/EU; oral alternative to ESAs.
- Mechanism: Stabilize hypoxia-inducible factors → increase endogenous erythropoietin, enhance iron metabolism [58].

Novel Iron Formulations

- Ferric carboxymaltose (FCM) – high-dose IV iron, fewer infusions.
- Ferumoxytol – rapid infusion, safer profile.
- Sucrosomial iron – oral, better GI tolerance [59].

Hepcidin Modulators

- **LY2787106 (anti-hepcidin antibody)** – restores iron availability in anemia of inflammation.
- **PTG-300 (rusfertide)** – hepcidin mimetic, under trial for iron overload but with anemia potential.
- **Spiegelmers (NOX-H94)** – oligonucleotide-based hepcidin antagonists [60].

Recent Advance Treatments

Nanomedicine in iron delivery Nanomedicine in iron therapy employs nanoparticles to enhance absorption, distribution, and efficacy, addressing limitations of conventional formulations like poor bioavailability, gastrointestinal discomfort, and oxidative stress, thereby improving therapeutic outcomes in anemia management[61].

Gene therapy for iron metabolism disorders

Gene therapy revolutionises iron disorder treatment by correcting genetic defects in hepcidin–ferroportin, transferrin signaling, and hemoglobin synthesis, offering lasting cures beyond conventional symptom management through precise gene editing or replacement [62]**.** Iron metabolism disorders stem from genetic mutations; gene therapy provides curative potential by correcting molecular defects beyond conventional treatments [63].

Methods of Gene Therapy in Iron Metabolism Disorders

1) **Gene Addition (Replacement Therapy)** Functional copies of defective genes are introduced using viral vectors such as lentiviruses or adeno-associated viruses. Example: Adding normal *HAMP* or *TFR2* genes to restore hepcidin regulation and iron sensing [64].
2) **Gene Editing (Correction Therapy)** CRISPR-Cas9, TALENs, and zinc finger nucleases enable precise correction of mutations. In β-thalassemia, CRISPR-mediated editing of *BCL11A* enhances fetal hemoglobin, indirectly balancing iron metabolism [65].
3) **Gene Silencing (Downregulation Therapy)** RNA interference and antisense oligonucleotides are used to silence pathogenic gene expression. Silencing *HAMP* in conditions of excessive hepcidin may restore iron availability [66].
4) **Ex Vivo Stem Cell Editing** Hematopoietic stem cells are harvested, genetically corrected outside the body, and reinfused into patients. This approach is being tested in clinical trials for β-thalassemia and sickle cell disease [67].
5) **In Vivo Delivery Systems** Nanoparticle-based CRISPR delivery and improved viral vectors are being developed to directly target hepatocytes and bone marrow cells. This method aims to bypass the need for stem cell transplantation [68].

Novel hepcidin antagonists and agonists Hepcidin modulators adjust iron balance through ferroportin and BMP pathways, offering therapeutic potential in diverse anemias [69].

Hepcidin Antagonists Hepcidin antagonists block hepcidin-ferroportin interaction, enhancing iron availability for erythropoiesis, treating anemia of chronic disease, IRIDA, and β-thalassemia [70].

- **Monoclonal Antibodies Against Hepcidin** Neutralizing antibodies block hepcidin-ferroportin binding, restoring iron and hemoglobin in inflammatory anemia models; ongoing trials assess efficacy in chronic kidney disease and cancer-related anemia patients [71].
- **Ferroportin Stabilizers** Small molecules inhibit hepcidin–ferroportin binding, stabilizing ferroportin, sustaining iron export, and offering therapeutic potential for IRIDA and inflammatory anemia [72].
- **BMP/SMAD Pathway Inhibitors** BMP6-SMAD signaling drives hepcidin transcription; inhibitors of BMP receptors or SMAD reduce synthesis, enhancing iron absorption. Dorsomorphin derivatives and anti-BMP6 antibodies are currently under investigation [73].
- **TMPRSS6 Agonists** TMPRSS6 cleaves hemojuvelin, reducing hepcidin transcription; pharmacological activation enhances iron absorption, offering therapeutic relevance for IRIDA linked to TMPRSS6 mutations [74].
- **RNA-Based Therapies** Antisense oligonucleotides and siRNAs suppress HAMP mRNA, lowering hepcidin, enhancing iron availability, and showing promise for treating anemia of inflammation [75].

Hepcidin Agonists Hepcidin agonists aim to increase hepcidin activity or mimic its function, thereby reducing iron overload. They are particularly useful for hereditary hemochromatosis, transfusional iron overload, and β-thalassemia with ineffective erythropoiesis [76].

- **Synthetic Hepcidin Peptides** Engineered analogs of hepcidin can directly bind ferroportin, mimicking natural hormone activity. These peptides reduce serum iron and tissue iron deposition in animal models of hemochromatosis [77].
- **Mini-Hepcidins** Mini hepcidins, stable peptide derivatives with improved bioavailability, ease administration, reduce iron overload in preclinical models, and are currently undergoing clinical trials for human safety and efficacy [78].
- **Gene Therapy Approaches** Viral vector delivery of the *HAMP* gene or CRISPR-based upregulation of hepcidin expression in hepatocytes offers durable correction. This strategy could provide long-term control of iron overload in hereditary hemochromatosis [79].
- **Small-Molecule Inducers** Compounds that activate BMP6/SMAD signaling increase endogenous hepcidin production. These agents are being explored as oral therapies for iron overload disorders [80].
- **Hepcidin Mimetics** Engineered antibodies or fusion proteins that replicate hepcidin's ferroportin-binding effect are being developed as long-acting agonists. These mimetics may provide sustained iron regulation with fewer dosing requirements [81].
- **Systems Biology Approaches** Systems biology integrates computational modeling, high-throughput omics technologies, and network analysis to understand complex biological processes at a holistic level [82].

Conclusion

Anemia continues to represent a global health challenge, with iron metabolism at the core of its pathophysiology. Iron is indispensable for hemoglobin synthesis, cellular respiration, and enzymatic activity, yet its dual nature—as both essential and potentially toxic—necessitates precise regulation. The interplay of absorption, transport, storage, and recycling, coordinated by hepcidin and ferroportin, ensures systemic balance under normal conditions. Disruption of this network manifests in diverse clinical forms, ranging from iron deficiency anemia to anemia of chronic disease and genetic iron-loading disorders. Recent advances have expanded our understanding of iron biology, highlighting the roles of hypoxia-inducible factors, erythroferrone, and immune signaling in modulating iron availability. Oxidative stress and ferroptosis further illustrate how iron imbalance contributes to ineffective erythropoiesis and premature erythrocyte destruction. These mechanistic insights not only deepen our comprehension of anemia but also reveal novel therapeutic targets. Hepcidin modulation, erythroferrone regulation, and innovative iron formulations exemplify translational strategies aimed at restoring iron equilibrium and improving patient outcomes. From a clinical perspective, integrating conventional markers such as ferritin, transferrin saturation, and soluble transferrin receptor with emerging

hepcidin assays enhances diagnostic precision, particularly in distinguishing iron deficiency anemia from anemia of chronic disease. This diagnostic refinement is critical for guiding appropriate therapy and avoiding mismanagement. In summary, iron metabolism is a mechanistic cornerstone in anemia research and clinical practice. Continued exploration of its regulatory pathways and pathological consequences will not only advance scientific knowledge but also foster innovative interventions to alleviate the global burden of anemia.

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