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IRON METABOLISM IN HEMATOPOIESIS: IMPLICATIONS FOR ANEMIA, BONE MARROW FAILURE, AND THERAPEUTIC TARGETING

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ABSTRACT

Iron is a vital micronutrient that is important in normal hematopoiesis especially erythropoiesis and hemoglobin production. Its macro and cellular homeostasis is highly coordinated with mechanisms that include intestinal absorption, recycling with the help of macrophages and hormonal control; hepcidin being the major hormone to maintain homeostasis. Iron imbalance, both deficiency and overload, have a dramatic negative effect on hematopoietic processes and has been implicated in an extensive repertoire of hematologic conditions, including iron-deficiency anemia, anemia of inflammation and iron overload syndromes. New developments have emphasized the expanded role of iron beyond the synthesis of hemoglobin, such as iron being involved in the maintenance of hematopoietic stem cell and cellular proliferation, mitochondrial activity, and redox regulation. The interaction of iron metabolism and hematopoiesis is conditioned by multimodular molecular mechanisms that guarantee the sufficient supply of iron and avoid toxicity. This review emphasizes the existing knowledge regarding the molecular pathways through which iron homeostasis is connected with hematopoietic control with emphasis on the iron transport, hepcidin regulation, and erythroid differentiation. Moreover, it addresses the pathological implications of iron metabolism dysregulation and dwells upon the new therapeutic approaches aimed at addressing the iron-mediated pathways in hematologic disorders.

Keywords: *Iron Metabolism, Hematopoiesis, Erythropoiesis, Hepcidin Regulation, Iron Homeostasis, Iron-Deficiency Anomie, Hematopoietic Stem Cells*

INTRODUCTION

Iron is an essential micronutrient that forms the basis of many body processes particularly oxygen delivery, cellular respiration and DNA replication.(Chen & Elowitz, 2021).Of these biological processes, the most important and closely connected with hematopoiesis is iron metabolism because of which hematopoietic stem cells (HSCs) produce all the lineages of circulating blood cells (Juarez-Vazquez et al., 2002). Specialized hematopoiesis, erythropoiesis, which produces red blood cells (RBCs) is extremely dependent on iron due to the hemoglobin production and appropriate maturation of erythroid (Kafina & Paw, 2017).Due to the high demand, systemic and cellular iron homeostasis is highly coordinated with erythropoiesis to ensure that the production of blood cells and iron-related toxicity are avoided (Chen & Elowitz, 2021; Juarez-Vazquez et al., 2002).

Iron deficiency and iron overload can be considered as a major contributor to hematologic aberrations and iron imbalance, which is a crucial global public health concern.

The commonest type of anemia in the globe is iron deficiency anemia (IDA), which is a prevalent condition affecting over 1.2 billion people and a significant percentage of the world anemic population of about 2 billion individuals with a significant proportion of children and women of reproductive age (Kassebaum et al., 2014).The iron deficiency affects the formation of hemoglobin and erythropoiesis, causing a decrease in oxygen-carrying capacity and morbidity of patients with the corresponding vulnerability (Kassebaum et al., 2014).

Alongside nutritional deficiency, hereditary iron-related disease burden is also caused by inherited anemias like thalassemia. The maladaptive erythropoiesis in patients with the β-thalassemia group promotes increased iron absorption in the intestine and causes iron overload on the body system despite the absence of the transfusion treatment. The iron build-up in the vital organs, such as liver, heart, and endocrine glands is further worsened by chronic blood transfusion administered to treat severe cases of thalassemia and other hematologic disorders (Camaschella, 2015).

In addition, secondary iron overload is often linked to such disorders as myelodysplastic syndromes (MDS) and other anemias that are caused by transfusion. Abnormal iron facilitates oxidative stress and tissue damage, which may aggravate hematopoietic dysfunction and cause the likelihood of organ failure (Ganz & Nemeth, 2012).

Iron deficiency as well as excess iron interfere with normal hematopoiesis and underscore the significance of having iron homeostasis under strict control to ensure that blood cells are produced by the system and the system is in good condition. Iron is also the central element of the process of erythropoiesis as it allows the production of heme, which is one of the main components of hemoglobin, the oxygen carrier in the red blood, or erythrocytes. The growing erythroblasts absorb large amounts of iron during erythroid differentiation to form hemoglobin and so erythropoiesis is the greatest iron consumer in the human body. The body uses about 2 out of every 3 of iron to make hemoglobin which is in red blood cells. Iron availability thus has a direct effect on the erythroid proliferation, differentiation, and maturation in the bone marrow (Ginzburg et al., 2023; Kafina & Paw, 2017).

Additionally to erythropoiesis, iron plays a role in the control of the hematopoietic stem cell activity. Iron plays roles in transcriptional regulation, mitochondrial metabolism and oxidative balance of HSCs. The right amount of iron is required to sustain self-renewal and differentiation of the stem cells, and iron deficiency or excessive iron build-up may disrupt the processes and cause replacement of hematopoietic homeostasis. The regulatory processes of the iron regulatory protein (IRP) system and hepcidin ferroprotein axis are among other molecular pathways that play a critical role in regulating the availability of iron in hematopoietic tissues and balancing iron supply with the erythropoietic requirement (Coates & Cazzola, 2019).

There are disruption of these regulatory pathways, which may lead to hematological disorders such as inflammatory anemia, ineffective erythropoiesis, and iron overload syndromes. Therefore, the interaction between iron metabolism and hematopoiesis needs to be investigated to develop particular treatment methods toward iron-related hematologic diseases (Ganz & Nemeth, 2012; Ginzburg et al., 2023).

Hematopoiesis and iron metabolism are the processes that are closely related and which ensure efficient production of red blood cells and oxygen delivery. Erythropoiesis is the most important consumer of iron in the body because it requires iron in hemoglobin production and mitochondrial processes of erythroid cells (Hentze et al., 2010). Recent research has determined the key regulators as hepcidin, ferroprotein, transferrin receptors and erythroferrone which mediate the systemic iron homeostasis and the erythropoietic demand. These molecules control the uptake, transport, and discharge of iron to maintain a sufficient amount of iron needed to formulate erythroblasts (Kautz et al., 2014).

Since the interplay between iron metabolism and hematopoietic control is fundamental, there is a need to take a deeper assessment of such interaction to further clinical and fundamental research in the field of hematology. The purpose of this review is to provide an overview of the existing knowledge on the mechanisms that

connect iron homeostasis and the hematopoietic stem cell biology and erythropoiesis. The underlying physiology of iron metabolism and systemic control will be initially discussed in the review. It will then discuss the molecular processes that regulate iron use in the erythropoiesis process and the hematopoietic stem cell functionality of iron. Lastly, some pathological conditions of interrupted iron-hematopoiesis interactions will be emphasized in the review and emerging therapeutic interventions of iron metabolism in hematologic disease would be discussed (Ganz & Nemeth, 2012; Ginzburg et al., 2023).

2. Overview of Hematopoiesis

Hematopoeisis can be described as the highly regulated biological process which all circulating blood cells are continually produced as a result of the hematopoietic stem cells (HSC) that are present in the bone marrow (Orkin and Zon, 2008). This mechanism is important because it guarantees the production of erythrocytes, leukocytes, and platelets lifelong to carry out their functions to transport oxygen, defend the body, and control the hemostasis (Morrison and Scadden, 2014). The regulation of hematopoiesis is achieved by a complicated network of cytokine, transcription factor, and bone marrow microenvironment interactions (Orkin & Zon, 2008; Morrison & Scadden, 2014).

In their normal physiological state, the hematopoietic stem cells balance between self-renewal and lineage differentiation so that they can maintain a constant production of blood cells and at the same time avoid depletion of the stem cells (Orkin & Zon, 2008). The multipotent progenitor cells derived out of these stem cells eventually lose their self-renewal ability and become limited to particular hematopoietic lineages (Seita & Weissman, 2010). One of the many types of hematopoietic procedures that is particularly more iron-sensitive is erythropoiesis, as it is required by growing erythroblasts in the synthesis of heme and hemoglobin (Ganz et al., 2012; Muckenthaler et al., 2017). In turn, iron metabolism should be well regulated to ensure successful hematopoiesis and avoid hematologic disease (Camaschella, 2015).

2.1 Hematopoietic Stem Cells (HSCs)

The hematopoietic stem cells are extremely rare multi-potential cells that can self-renew long-term as well as differentiate into all the mature cell lineages of the blood (Orkin and Zon, 2008). The majority of cells reside in particular niches of the bone marrow and are mostly in the quiescent state in steady-state conditions to maintain their regenerative ability (Morrison & Scadden, 2014). Intrinsic transcriptional programs and external signals provided by the microenvironment closely control the balance between the stem cell quiescence, proliferation and differentiation (Seita & Weissman, 2010).

A number of transcription factors such as RUNX1, GATA-2, and TAL1 are necessary to regulate the lineage commitment and preserve the identity of hematopoietic stem cells (Orkin and Zon, 2008). Along with genetic control, such factors as metabolism, including the activity of the mitochondrion and iron availability have been identified as significant determinants of hematopoietic stem cell activity (Muckenthaler et al., 2017). There is need of sufficient iron supply to aid cellular metabolism and proliferation in hematopoietic progenitors (Ganz & Nemeth, 2012).

2.2 Lineage commitment in Hematopoiesis

In the hematopoeisis, multipotent progenitor cells differentiate into myeloid and lymphoid lineage stages (Seita & Weissman, 2010). Myeloid lineage gives rise to erythrocytes, megakaryocytes, granulocytes, and monocytes; the lymphoid lineage produces B cells, T cells and natural killer cells which play an important part in adaptive and innate immunity (Orkin and Zon, 2008).

One of the most active and iron-dependent hematopoiesis pathways is called erythropoiesis (Ganz & Nemeth, 2012). The synthesis of heme and hemoglobin, which takes place in the mitochondria to a large extent, requires large amounts of iron to develop erythroblasts (Chiabrando et al., 2014). This is because iron is transported to erythroid precursors using the process of transferrin-mediated uptake via transferrin receptor-1, which guarantees that iron is delivered to synthesize hemoglobin (Muckenthaler et al., 2017). A defective delivery of iron or mismanagement of iron metabolism may hence interfere with the erythroid

maturation and lead to either anemia or ineffective erythropoiesis (Camaschella, 2015).

2.3 Bone marrow Microenvironment

A key component of the regulation and differentiation of the hematopoietic stem cells involves the hematopoietic niche or the bone marrow microenvironment (Morrison & Scadden, 2014). The specialized environment includes stromal cells, endothelial cells, osteoblasts, macrophages, and extracellular matrix components to supply the hematopoietic regulatory structural and biochemical cues (Morrison & Scadden, 2014; Seita and Weissman, 2010).

Macrophages in the bone marrow also play a role in erythropoiesis building the structure called erythroblastic islands, in which the developing erythroblasts are enclosed by the central macrophage (Klei et al., 2017). These macrophages are essential in the disposal of iron in the senescent erythrocytes and supply the growing erythroid cells (Klei et al., 2017). Effective iron recycling of the bone marrow is thus critical to adequate supply of iron to support erythropoiesis and the normal activity of hematopoiesis (Ganz & Nemeth, 2012).

3. Systemic Iron Metabolism

Iron metabolism is a highly regulated physiological process that ensures adequate supply of iron to support the important cellular processes, and eliminate iron toxicity that arises due to excessive supply of free iron (Ganz & Nemeth, 2012). Among the biological functions of iron, there are oxygen transportation, respiration in the mitochondrion, and DNA replication and cell proliferation (Muckenthaler et al., 2017). Since the human body does not have an active mechanism of iron excretion, the systemic iron balance is mainly regulated at the intestinal absorption and iron recycling of senescent erythrocytes (Camaschella, 2015).

Hemoglobin in erythrocytes absorbs about two-thirds of the total body iron, and therefore erythropoiesis is the most iron-demanding process in the body (Muckenthaler et al., 2017). The rest of iron is accumulated primarily in liver, spleen and bone marrow as ferritin or hemosiderin which forms are intracellular storage proteins of iron (Hentze et al., 2010). Iron homeostasis is a systemic process that is carefully regulated by ensuring that iron absorption, transport, storage, and recycling processes occur in balance (Ganz & Nemeth, 2012).

The peptide hormone hepcidin is a major systemic iron metabolism regulator that is primarily synthesized by hepatocytes located in the liver (Camaschella, 2015). Hepcidin controls the levels of iron by binding to ferroportin, a sole cellular engineer of iron and subsequently causing its intracellular assimilation and degradation that subsequently decreases the amount of iron to be expelled to the circulation (Ganz & Nemeth, 2012). In this way, hepcidin is also very important in terms of iron regulation and the prevention of iron deficiency and iron overload (Muckenthaler et al., 2017).

Failure to regulate iron in the body may cause a number of hematologic diseases, such as iron-deficiency anemia, anemia of inflammation, and hereditary hemochromatosis (Camaschella, 2015). Knowing how iron metabolism in the body is regulated is thus paramount in the explanation of how iron homeostasis is related to hematopoiesis.

3.1 Dietary Iron Absorption

The absorption of dietary iron is mainly done in the duodenum and the upper jejunum parts of the small intestine (Hentze et al., 2010). Dietary iron is available in two forms heme and non-heme, respectively, where heme iron is found in animal products and non-heme iron in plant foods (Abbaspour et al., 2014). Heme iron can be transported more effectively with the help of special methods, but non-heme iron needs to be reduced to ferrous (Fe 2 +) before the intestinal enterocytes can absorb it (Hentze et al., 2010).

Ferrous iron intake into enterocytes is facilitated by divalent metal transporter 1 (DMT1) which helps to move iron across the apical membrane of intestinal epithelial cells (Muckenthaler et al., 2017). The iron may either be stored in ferritin or released to the bloodstream via ferroportin on the basolateral membrane once it is within the enterocyte (Ganz and Nemeth, 2012). Ferroportin activity is under strict control of hepcidin, which regulates the level of released dietary iron entering the circulation (Camaschella, 2015).

3.2 Iron Transport and Storage

The absorption of iron after the intestines involves transporting it in the blood as a complex of iron and a carrier protein known as transferrin that supplies iron to other tissues within the body (Hentze et al., 2010). Transferrin has great affinity to ferric iron and conveys it to the cells that have transferrin receptors on the surface, more specifically, the erythroid precursor cells present in the bone marrow (Muckenthaler et al., 2017). The cellular uptake of transferrin iron-bound is done through receptor-mediated endocytosis by using transferrin receptor-1 (TfR1) (Ganz & Nemeth, 2012).

Iron that is not immediately needed by the cellular processes is stored in the cell through the use of ferritin, a protein complex that has the capacity to safely store thousands of iron atoms in the forms of a soluble and non-toxic form (Hentze et al., 2010). In iron overload conditions, further iron can be stored as an insoluble storage form hemosiderin, which is typical of macrophages and hepatocytes (Abbaspour et al., 2014). Correct control of iron absorption and retention plays the key role in iron homeostasis and preventing oxidative injury of free iron (Muckenthaler et al., 2017).

3.3 Iron Recycling

Recycling of iron is the primary source of iron in erythropoiesis and it is mainly facilitated by the macrophages within the reticuloendothelial system especially in the spleen, liver, and bone marrow (Ganz & Nemeth, 2012). Macrophages identify and ingest senescent/damaged erythrocytes in a process called erythrophagocytosis (Klei et al., 2017).

In macrophages, hemoglobin is broken down, heme is broken down by an enzyme heme oxygenase and releases iron which may be stored in ferritin or returned to the circulation via ferroportin (Hentze et al., 2010). The transferrin carries the recycled iron to the bone marrow where it is used in the production of new hemoglobin during the erythropoiesis (Muckenthaler et al., 2017). Recycling of iron renders most of the required iron in erythropoiesis to be obtained internally and not through dietary intake (Ganz & Nemeth, 2012).

3.4 Iron Homeostasis Molecular Regulation

An intricate system of hormonal signals in the body and intracellular regulatory mechanisms control iron homeostasis (Muckenthaler et al., 2017). Hepcidin-ferroportin axis is the key regulatory process that monitors the iron in the body (Ganz and Nemeth, 2012). The hepcidin production in the liver is stimulated by increased levels of iron or inflammatory signals and results in a reduction in iron absorption and in the release of iron by macrophages (Camaschella, 2015).

On the cellular level, the metabolism of iron is further regulated by the iron responsive element/iron regulatory protein (IRE/IRP) complex that controls the expression of genes that play a role in iron uptake, storage as well as its utilization (Hentze et al., 2010). The IRE/IRP system enables cells to rapidly vary iron metabolism in response to intracellular iron content using post-transcriptional regulation of proteins (transferrin receptor and ferritin) (Muckenthaler et al., 2017).

Collectively, these control processes promote systemic and cellular iron homeostasis, which is not only critical in facilitating the hematopoiesis process, but also iron-related diseases (Fig. 01).

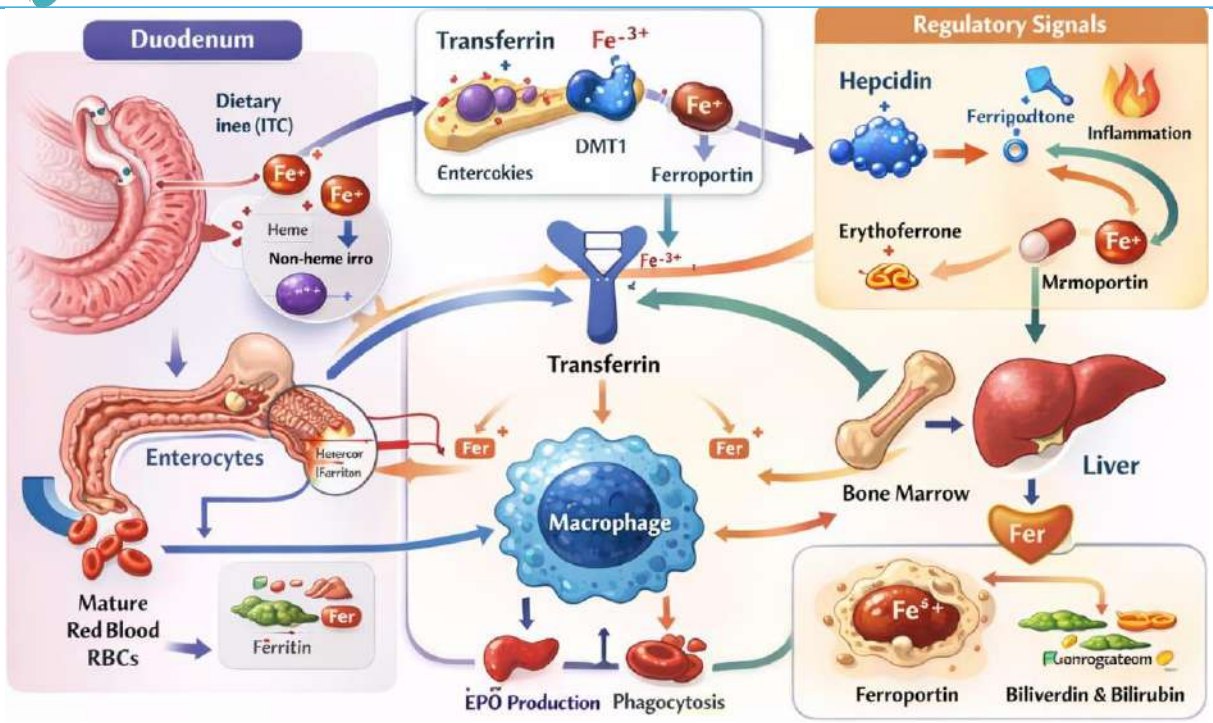

Fig. 01. Systemic Iron Metabolism and regulation

4. Molecular Role of Iron in Erythropoiesis

Iron is a key element in the erythropoiesis process as the essential element of heme, which is the prosthetic group of hemoglobin that carries oxygen to the red blood cells (Ganz and Nemeth, 2012; Muckenthaler et al., 2017). The differentiation of erythroblasts in the bone marrow needs a lot of iron to maintain the hemoglobin production and mitochondrial metabolism in the erythroblasts (Chiabrando et al., 2014; Camaschella, 2015). Erythropoiesis in adults needs about 2025mg/day of iron; the majority of this iron is recycled via the spleen by the senescent erythrocytes and not via dietary absorption (Hentze et al., 2010; Ganz & Nemeth, 2012).

The transferrin-loaded with iron in plasma reaches the bone marrow through the erythroid precursor cells and feeds iron to the bone marrow (Muckenthaler et al., 2017). High concentrations of transferring receptor-1 (TfR1) are found in erythroblasts; the process through which transferrin-bound iron is picked up with the help of receptor-mediated endocytosis (Hentze et al., 2010). After internalization, transferrin is depleted of iron in endosomes and moves to the cytoplasm where iron can be used in heme production, as well as in other metabolism (Ganz and Nemeth, 2012).

In erythroid cells, the iron is carried into mitochondria where it is involved in the production of heme, which is a critical process in the formation of hemoglobin (Chiabrando et al., 2014). During erythropoiesis, iron usage is closely regulated with the erythroid differentiation signals to maintain sufficient hemoglobin synthesis and red blood cells maturation (Camaschella, 2015). The disturbance in the delivery of iron or mitochondrial iron metabolism may hamper the development of erythroid and lead to inefficient erythropoiesis or anemia (Muckenthaler et al., 2017).

4.1 Heme Biosynthesis and Hemoglobin Production

Heme biosynthesis is a complex biochemical pathway that takes place partially in the mitochondria and partially in the cytosol of the erythroid precursor cells (Chiabrando et al., 2014). It starts with the condensation of glycine and succinyl-CoA catalyzed by the enzyme δ-aminolevulinic acid synthase (ALAS2) being the rate-limiting enzyme in erythroid heme synthesis (Muckenthaler et al., 2017).

The mitochondrial ferrochelatase enzyme includes iron in protoporphyrin IX to create heme, which is paired to globin chains to form hemoglobin (Chiabrando et al., 2014). A

sufficient amount of iron is thus required in order to sustain normal hemoglobin production during erythropoiesis (Ganz & Nemeth, 2012). Iron deficiency interferes with the production of heme and causes a decrease in the synthesis of hemoglobin, which causes microcytic and hypochromic anemia (Camaschella, 2015).

Heme synthesis is closely controlled in relation to globin production in erythroid cells to avoid the buildup of toxic products (Muckenthaler et al., 2017). This regulation makes sure that the assembly of hemoglobin is very efficient in the maturation of erythroblasts.

4.2 Iron-Regulatory proteins and Cellular Iron Control

Iron metabolism in the cell is regulated at the cellular level by the iron-responsive element/iron-regulatory protein (IRE/IRP) system that regulates the translation and stability of mRNAs coding iron uptake, storage, and utilization proteins (Hentze et al., 2010). Iron-controlling proteins (IRP1 and IRP2) interact with iron-sensitive areas in the un-translated segments of target mRNAs and regulate gene expression in accordance with the intracellular iron condition (Muckenthaler et al., 2017).

In case of low cellular iron status, the IRPs interact with IREs in transferrin receptor mRNA, stabilizing the transcript and enhancing the uptake of iron (Hentze et al., 2010). Simultaneously, the binding of IRP to the mRNA of ferritin suppresses ferritin translation and, consequently, iron storage and enhances the provision of iron to vital metabolic activities (Ganz & Nemeth, 2012). On the other hand, IRPs lose the ability to bind RNA and achieve a reduction in iron uptake and increase iron storage when iron levels are adequate (Muckenthaler et al., 2017). This post-transcriptional regulatory process enables the erythroid cells to respond quickly to changes in intracellular iron and ensure adequate supply of iron to generate hemoglobin (Hentze et al., 2010).

4.3 Iron Usage in Erythroblasts in Mitochondria

Mitochondria are the key players in the erythropoiesis process as they are the major location of heme production and iron use in immature erythroid cell development (Chiabrando et al., 2014). Iron can be imported into mitochondria with the help of specialized mitochondrial transport proteins that assist in the inclusion of iron into heme and iron-sulfur complexes that are utilized in various metabolism processes (Muckenthaler et al., 2017).

A number of enzymes that participate in cellular respiration and DNA synthesis rely on iron-sulfur clusters, which underscores the significance of iron metabolism in erythroid cells performed by mitochondria (Hentze et al., 2010). Effective erythropoiesis and maturation of red blood cells can only be supported by proper control of mitochondrial iron use (Chiabrando et al., 2014). Abnormal accumulation of iron in erythroblast mitochondria is the characteristic of sideroblastic anemia caused by defects in mitochondrial iron metabolism (Camaschella, 2015). These diseases demonstrate how essential the iron regulation in the mitochondrion is in the physiological hematopoiesis and erythroid differentiation (Fig 02).

5. Iron during Non-Erythroid Hematopoiesis

Even though most of the systemic iron use is erythropoiesis, non-erythroid hematopoietic lineage proliferation, differentiation, and functional maturation also require iron. Iron controls the DNA synthesis, mitochondrial respiration, redox signaling pathways, and immune signaling pathways. Both iron deficiency and iron overload interrupt non-erythroid hematopoiesis, and lead to immune dysfunction and hematologic pathways (Ganz & Nemeth, 2012; Wessling-Resnick, 2010).

5.1 Iron and Myelopoiesis

Myeloid progenitor proliferation and differentiation needs iron since it is a cofactor of ribonucleotide reductase, the rate limiting enzyme in DNA production. It is especially in rapid division of granulocyte and monocyte progenitors that sufficient intracellular iron supply is relied upon (Cassat & Skaar, 2013).

Neutrophil activity is closely associated with the metabolism of iron. Enzymes with iron e.g. myeloperoxidase (MPO) play a vital role in the production of reactive oxygen species (ROS) during the oxidative burst, which is a major antimicrobial response. Iron deficiency was

found to cause a decrease in neutrophil bactericidal function and diminish the capability of oxidative burst (Ganz, 2018).

In myelopoiesis and systemic iron homeostasis macrophages are placed on a dual role. Macrophages break down iron in senescent erythrocytes as main facilitators of erythrophagocytosis and control iron export by ferroprotein. Inflammation leads to the degradation of ferroprotein under the influence of hepcidin which encourages intracellular iron sequestration, which causes anemia of inflammation and limits the supply of iron to the pathogen (Ganz & Nemeth, 2012). Therefore, the iron status has a direct effect on the development of the myeloid cells and innate immune response.

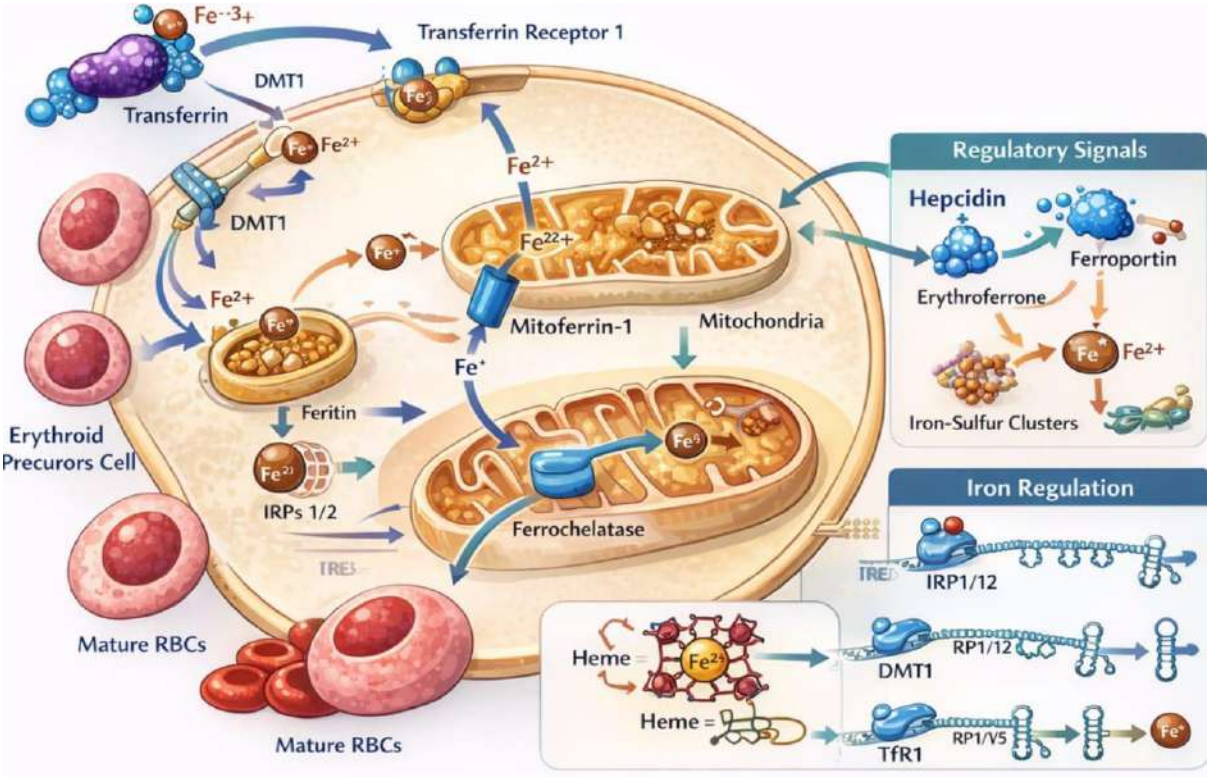

Fig. 02. Molecular Role of Iron in Erythropoiesis

5.2 Iron in Lymphopoiesis

The metabolic reprogramming and high levels of iron uptake are needed to activate and expand clones. When activated, T lymphocytes increase the expression of transferring receptor 1 (TFR1) so that transferrin-mediated iron uptake can be intensified (Sanchez et al., 2011). Iron facilitates replication of DNA by means of ribonucleotide reductase activity, and maintains mitochondrial respiration that is required to allow proliferative expansion.

Iron deficiency suppresses T-cell growth, interleukin-2 (IL-2) generation and cell-mediated immunity. In experimental systems, it is proven that interference with transferrin receptor signaling impairs the process of maturation of thymocytes and peripheral T-cell homeostasis (Sanchez et al., 2011).

The iron also regulates cytokine signaling and immune cell differentiation. Oxidative stress, changes in redox-sensitive transcription factor like NF-KB and defects in adaptive immune response are induced by excess iron. Iron overload disorders clinical effect is linked to the imbalance of the lymphocyte subsets and their increased susceptibility to infections (Ganz, 2018). Thus, iron homeostasis, in general, and iron equilibrium, in particular, is essential to lymphopoiesis and immune competence.

5.3 Production of Iron and Platelets

The iron status has a great impact on megakaryopoiesis and platelet output. The iron deficiency anemia is clinically accompanied by reactive thrombocytosis, and the mechanism of the latter is not yet fully studied (Karakantza et

al., 2000). A theory has been suggested that competition between erythroid and Megakaryocytic progenitors in the bone marrow niche where iron limitation inhibits erythropoiesis and differentiation changes to Megakaryocyte lineage commitment.

Iron can also regulate thrombopoiesis by regulating erythropoietin (EPO) and hypoxia-inducible factor (HIF) signaling pathways, which also regulate common progenitor populations. There is experimental evidence that changed iron metabolism impacts the maturation of megakaryocytes and the formation of proplatelets (Ginzburg et al., 2018).

Excessive ROS production in the state of iron overload can damage platelet membrane integrity and stimulate abnormal platelet activation, which leads to the occurrence of thrombotic risk. Therefore, the availability of iron does not only regulate the quantity of the platelets but also the functioning of the platelets.

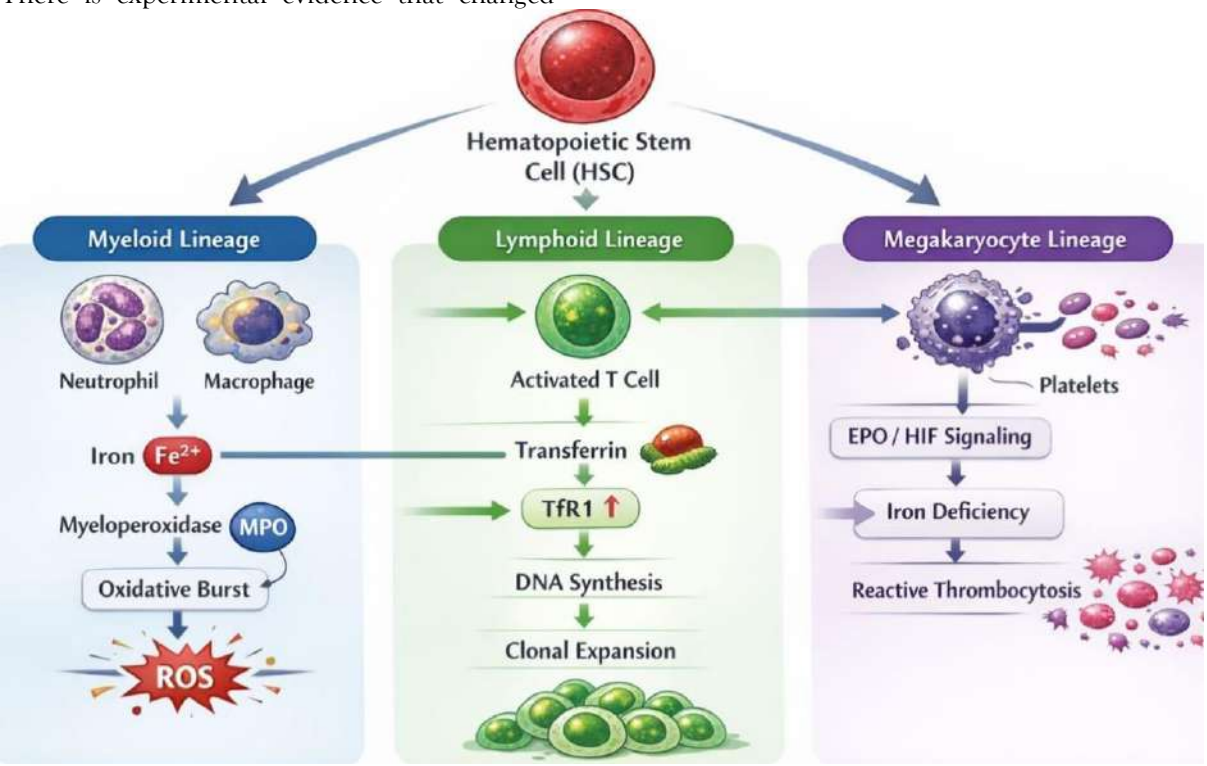

Fig. 03. Role of Iron in Non-Erythroid Hematopoietic Lineages

6. Diseases associated with Iron Metabolism and Hematopoiesis

Appendage of iron homeostasis has a devastating influence on hematopoiesis. Iron deficiency and iron overload both modify the erythroid proliferation, bone marrow microenvironment dynamics and systemic inflammatory signaling. Hepcidinferroportin axis dysregulation is a key pathogenic process of connecting iron metabolism and hematologic disease (Ganz and Nemeth, 2012; Camas Chella, 2015).

6.1 Iron Deficiency Anemia

Iron deficiency anemia (IDA) is the most common nutritional deficiency in all countries of the world with more than 1.2 billion people having this disorder (Camas Chella, 2015). It occurs when there is a deficiency in iron to satisfy the erythropoietic needs.

Pathophysiology

Iron deficiency decreases the synthesis of hemoglobin, which causes the production of hemoglobin to be low and the development of microcytic, hypochromic erythrocytes. On the molecular level, iron-restricted erythropoiesis stimulates iron regulatory proteins (IRPs), which stimulate the expression of transferrin receptor but inhibit ferritin translation in order to optimize cellular uptake of iron (Camaschella, 2015). Constant deficiency inhibits the erythroid progenitor growth and enhances the degradation of bone marrow leading to low production of red cells.

Impact on Marrow Function

Iron deficiency not only restricts the erythropoiesis process, but it might also affect other hematopoietic processes. IDA is often associated with reactive thrombocytosis which implies a defect in lineage commitment in common megaloblastic anerythrocyte progenitors (Karakantza et al., 2000). Prolonged iron deficiency can also interfere with the working of immune cells because of the limited intensity of DNA synthesis and mitochondrial metabolism.

6.2 Anemia of Inflammation

Some causes of autoimmune disorders, chronic infections, malignancies, and chronic kidney disease are some causes of anemia of inflammation (AI) or anemia of chronic disease.

Hepcidin Overexpression

The characteristic of AI is the elevated hepcidin secretion caused by inflammatory cytokines, especially interleukin-6 (IL-6). Hepcidin is binding to ferroportin, which facilitates its internalization and degradation, thus reducing the intestinal intake of iron and iron retention in macrophages (Nemeth et al., 2004; Ganz and Nemeth, 2012). High levels of hepcidin cause hypoferremia although total body iron stores are adequate or even excessively large.

Iron Sequestration by Cytokines

Pro-inflammatory cytokines repress erythropoietin (EPO) synthesis and block erythroid progenitor receptiveness. The presence of iron in macrophages limits the supply of iron to hemoglobin production to cause normocytic or mildly microcytic anemia (Ganz & Nemeth, 2012). Therefore, the redistribution of iron that is caused by inflammation is an adaptive host defense mechanism, but maladaptive in chronic disease.

6.3 Iron Overload Disorders

Iron overload disorders are caused by the excessive absorption of iron or frequent transfusion which causes a buildup of iron in the tissues, causing oxidative damage.

Hereditary Hemochromatosis

The most frequently mutated gene that leads to hereditary hemochromatosis (HH) is the HFE gene that disrupts the control of hepcidin. Lower amounts of hepcidin enhance the activities of ferroportin and intestinal iron uptake leading to progressive liver, heart, pancreatic, and endocrine accumulation of iron (Pietrangelo, 2010). Iron-causing oxidative stress helps in the hepatocellular injury, cirrhosis, cardiomyopathy and endocrine dysfunction.

Transfusion-Related Hemosiderosis

Chronic transfusion dependence (2 -thalassemia major, myelodysplastic syndromes) patients develop iron buildup, since every unit of transfused blood has about 200 -250 mg of iron. Humans do not have a controlled excretion route of iron; therefore, repeated transfusion cause secondary iron overload and toxicity in organs (Camas Chella, 2015). Cardiac and hepatic complications are thus necessary to be prevented by iron chelation therapy.

6.4 Myelodysplastic Syndromes (MDS)

Myelodysplastic Syndromes (MDS) are a group of non-malignant bone marrow disorders characterized by pathophysiological abnormalities in bone marrow, typically resulting in bone marrow failure, bone defects, and abnormal bone development. The myelodysplastic syndromes are clonal hematopoietic stem cell diseases whose pathogenesis is ineffective hematopoiesis and cytopenias. The dysregulation of iron is a factor in the disease progression and morbidity. Iron overload is common in patients with MDS because of transfusion-dependent and inefficient erythropoiesis. Increased labile plasma iron increases oxidative stress, propagates the damage of DNA, and can increase genomic instability (Ganz & Nemeth, 2012).

In addition, abrogated hepcidin in MDS has been detected and it further interferes with the national iron distribution. The cardiac complications, which are also related to iron overload, lead to higher mortality.

6.5 Thalassemia and Ineffective Erythropoiesis

The defective production of 2hd -globin in 2hd -thalassemia results in ineffective production of erythropoiesis and chronic anemia. Increased and nonfunctional erythroid precursors generate erythroferrone which inhibits

production of hepcidin, increasing intestinal iron absorption (Camas Chella, 2015).

Patients acquire systemic iron overload in the presence of anemia caused by inhibition of hepcidin and frequent transfusion. The deposition of iron in the vital organs causes a significant portion of morbidity and mortality. Therefore, thalassemia is an exemplar of impaired cross-talk between the erythropoietic driver and iron homeostasis.

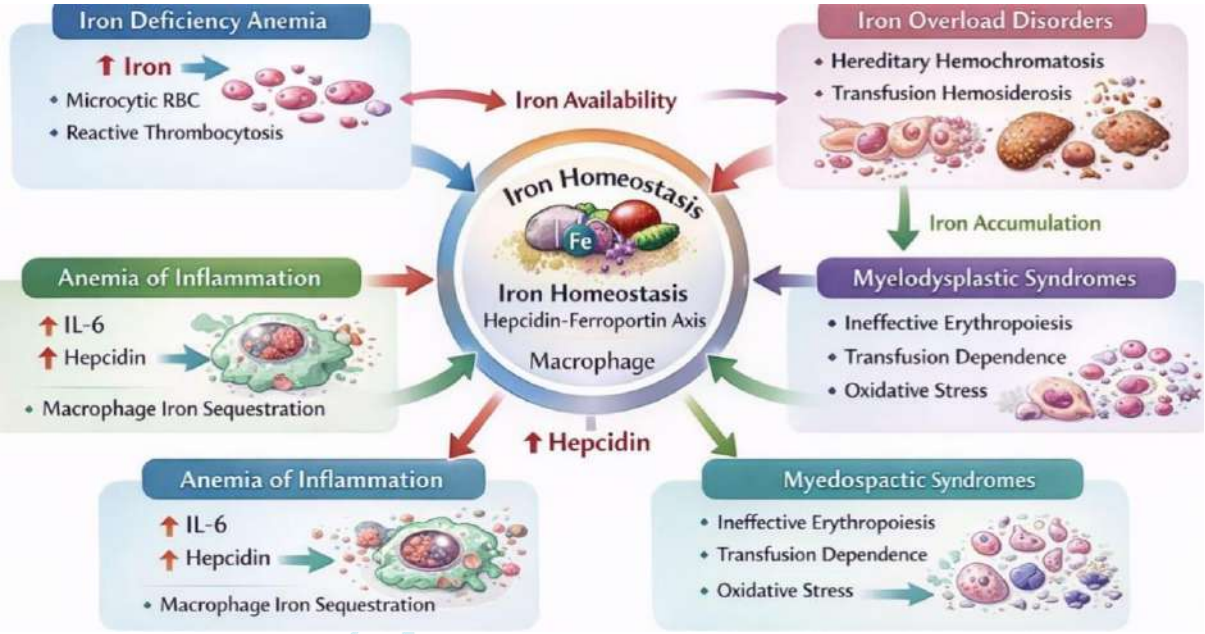

Fig. 04. Disorders of Iron Homeostasis Affecting Hematopoietis

7. Iron, Oxidative Stress, and the Fate of Hematopoietic Stem Cell

Iron plays a critical role in the metabolism of hematopoietic stem cell (HSC), though the excess of free iron stimulates oxidative stress and cellular damage. Due to the fact that HSCs dwell in a highly controlled bone marrow niche and rely on regulated redox homeostasis to self-renew, iron miss regulation produces strong influences on stem cell fate choice. The most significant processes that link iron homeostasis to the biology of hematopoietic stem cells include reactive oxygen species (ROS), ferroptosis, and iron-induced genomic instability (Rouault, 2015; Ganz & Nemeth, 2012).

7.1 ROS Generation

Iron also serves in the production of reactive oxygen species by the Fenton reaction where ferrous iron (Fe^{2+}) is used to catalyze the hydrogen peroxide into highly reactive hydroxyl radicals. Although the physiological levels of ROS have been shown to mediate signaling during the growth and differentiation of the HSCs, high levels of ROS interfere with the stem cell quiescence and induce exhaustion (Ghaffari, 2008).

The HSCs naturally have low-ROS level to sustain the self-renewal ability in a long-term basis. High intracellular iron augmentation of oxidative pressure stimulates the p38 MAPK and various stress-induced pathways, which induce differentiation or apoptosis (Ghaffari, 2008). Persistent oxidative stress is a cause of defective hematopoietic regeneration and age related stem cell dysfunction.

It is linked to transfusion-dependent anemias and myelodysplastic syndromes, which are conditions of iron overload that are accompanied by elevated labile plasma iron and oxidative stress throughout the body, further impairing the functioning of the bone marrow (Ganz & Nemeth, 2012).

7.2 Ferroptosis in Hematopoietic

Cells the ferroptosis of hematopoietic cells occurs in Hematopoietic cells and is not readily suppressed by iron. Ferroptosis is an iron-regulated form of cell death that is regulated, involves lipid peroxidation, and the buildup of reactive oxygen species. In contrast to apoptosis or necrosis, ferroptosis is caused by iron-

catalyzed oxidative damage of membrane phospholipids in particular (Dixon et al., 2012). Ferroptosis is especially more sensitive to hematopoietic cells because of their high iron flux and metabolic activity. One important antioxidative protector is the glutathione peroxidase 4 (GPX4) that inhibits lipid peroxidation; functional degradation of GPX4 or an excess of labile iron can cause ferroptosis cell death in progenitor cell populations.

New evidence indicates that ferroptosis is an inner cause of the bone marrow failure syndromes and perhaps the leukemic stem cell survival. Attack on ferroptosis pathways is also considered as a possible approach to therapy in hematologic malignancies (Dixon et al., 2012).

7.3 Iron-Induced DNA Damage

Overload of intracellular iron favors oxidative DNA damage by hydroxyl radical generation. Oxidative stress mediated by iron can lead to the alteration of the base, the breakage of single-strands and the destruction of the two-strand DNA. Clonal evolution and mutagenesis are caused by persistent genomic injury in hematopoietic stem and progenitor cells (Rouault, 2015).

Under iron overload conditions, high labile plasma iron promotes oxidative damage of the DNA in the bone marrow microenvironment. This can enhance the progression of the disease in conditions like myelodysplastic syndromes and the risk of leukemic transformation (Ganz & Nemeth, 2012). Also, redox balance is closely connected with DNA damage response pathways. Prolonged oxidative stress affects the stability of the genome, epigenetic regulation, and HSC lineage commitment.

8. Therapeutic modulation of Iron in hematological disorders

Iron metabolism Therapeutic agents: Iron metabolism is essential to the treatment of hematologic diseases such as iron deficiency anemia (IDA), iron overload syndromes, as well as hematologic malignancies. These modalities consist of iron supplement, the regulation of the vital regulatory blocks like the hepcidinferroportin axis, iron chelation treatment, and iron-directed frameworks in cancers. Both the modalities impact the process of hematopoiesis by modifying the availability of iron systemically and in cells, thus curing anemia or eliminating iron toxicity (Mansour et al., 2025; Zhao & He, 2025).

8.1 Iron incorporation procedures

The oral and intravenous (IV) iron supplementation has been broadly utilized in the treatment of IDA, a prevalent hematologic disorder that affects erythropoiesis. Even though oral iron preparations are both cheap and widely available, they usually lead to serious gastroenteric side effects and are less effective in inflamed patients or in those with malabsorption (Zhao & He, 2025).

Recent systematic reviews and meta-analyses prove that IV iron is typically better than oral iron in raising hemoglobin and ferritin in diseases like chronic kidney disease, inflammatory bowel disease, cancer induced anemia and general populations of IDA. The IV iron also has a more rapid correction of the anemia and has superior toleration and fewer gastrointestinal side-effects (Alharbi et al., 2025; Zhao & He, 2025).

In addition, such studies demonstrate the benefit of IV iron in clinical situations where quick correction is needed or in which the oral absorption of iron is impaired. Nevertheless, oral iron can still be used in mild and moderate IDA when the patient does not need a rapid fixation (Zhao & He, 2025).

8.2 Hepcidin modulator

The hepatic peptide hormone (hepatic iron) governing the iron levels in the blood stream by enhancing ferroportin internalization, called hepaticidin, has become a major target of therapy. Hepcidin is dysregulated in anemia of inflammation and iron overload in conditions such as 2-thalassemia and thus its regulation has clinical potential (Mansour et al., 2025).

Recent literature mentions a number of possible interventions that may increase the production of hepcidin (hepcidin agonists or mimetics) in order to reduce iron overload or prevent hepcidin (hepcidin inhibitors) in order to enhance iron delivery to erythropoiesis in inflammatory anemia. The agents in preclinical trials are recombinant hepcidin, hepcidin inductive BMP analogs, TMPRSS6 inhibitors, and anti-hemojuvelin antibodies aimed at optimizing the distribution of iron based on clinical requirements (Mansour et al., 2025).

Moreover, hepcidin signaling has broad applications in other diseases other than traditional anemia, and it has been shown that it can be involved in cancer and metabolic diseases, which suppress iron sequestration and tumor microenvironment interactions in case of a modified hepcidin expression (Lin et al., 2023). The therapeutic changing in the iron metabolism in hematological disorders explained in the figure (Fig 05).

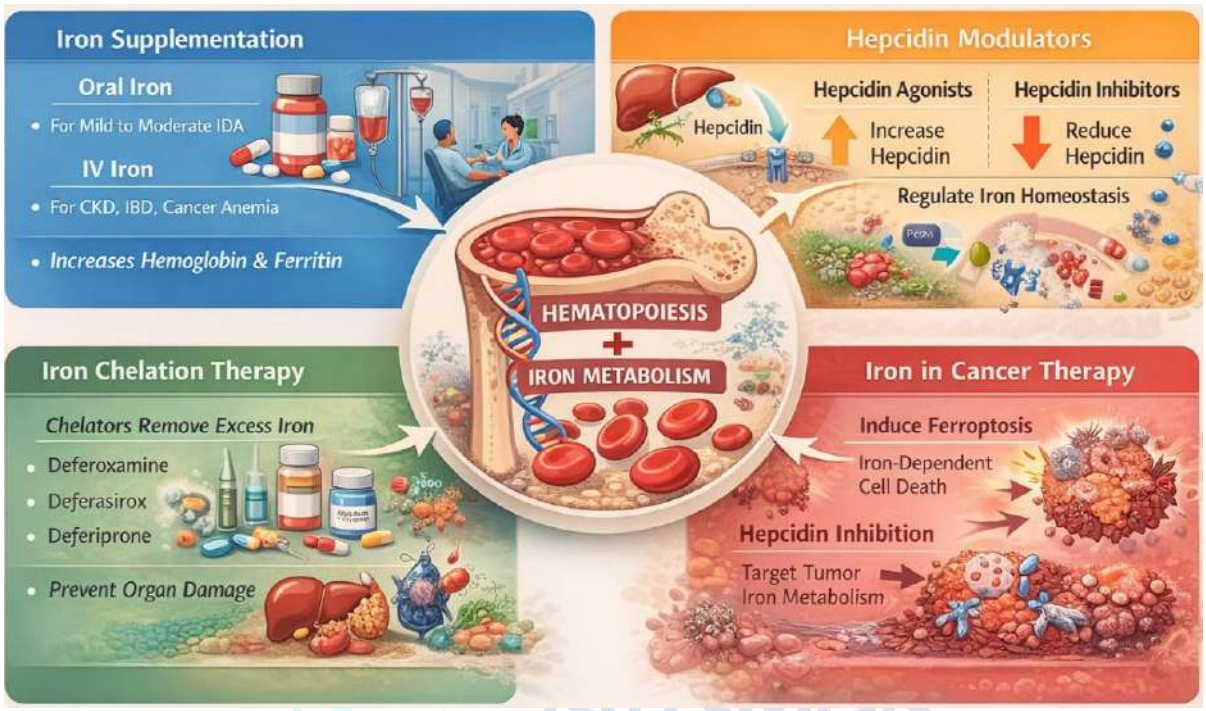

Fig. 05. Therapeutical modulation of iron in hematological disorders

8.3 Iron chelation therapy

The corner stone mode of treatment in the prevention of organ damage in iron overload diseases caused by chronic transfusions or ineffective erythropoiesis is iron chelation. The excess iron is captured by chelators and excreted to eliminate iron toxicity and oxidative stress that disrupts the hematopoietic activity (Entezari et al., 2022). Popular chelators are deferoxamine (DFO), deferasirox and deferiprone. Parenterally used, deferoxamine is still effective but has administration drawbacks (Temraz et al., 2014). Oral chelator deferasirox is highly plasma protein bound and lowers serum ferritin and liver iron levels providing a more convenient and better patient adherence than DFO (Entezari et al., 2022). There is also an emerging evidence that chelation could alter the gut microbiome of thalassemia patients to influence immune regulation, systemic inflammation and subsequently hematopoiesis (Deumić et al., 2025).

8.4 Iron in Malignancies Targeting.

It is also common to observe abnormal iron metabolism in cancer cells such as the elevated iron intake and accumulation in the cells to promote rapid proliferation. Manipulating iron metabolism by iron deprivation model or using ferroptosis or hepcidin activity inhibition has been demonstrated to be effective in preclinical and early clinical trials (Bu & Wang, 2024). Ferroptosis is a type of iron-dependent regulated cell death, which is a new therapeutic pathway in blood cancers. Ferroptosis modulation makes cancerous cells susceptible to treatment and takes advantage of their embarrassment to oxidative damage caused by iron (Liu et al., 2025). Moreover, the most recent study points to the role of hepcidin and its dysregulation in cancer not only in the distribution of iron throughout the body but also in the local management of the iron in the tumor microenvironment, which has implications on tumor growth and treatment response (Lin et al., 2023).

9. Emerging Concepts and Research Gaps in Iron Metabolism and Hematopoises

A. Iron Metabolism in leukemic stem cells

Newer reports suggest that iron metabolism is crucial to the existence and operation of hematopoietic stem cells (HSCs) and leukemic stem cells (LSCs). It has been experimentally determined that mitochondrial functions are compromised, and HSCs have a lower repopulating capacity in the absence of ferritin-mediated iron storage, proving intracellular iron homeostasis is a condition of stem cell viability (Yi et al., 2024).

There is also the disturbed iron metabolism in leukemic stem cells as opposed to normal HSCs. As an illustration, elevated iron absorption via transferrin receptor systems and inhibition of iron export processes are involved in the accumulation of iron in cells, which facilitates the proliferation and survival of leukemic cells (Liu et al., 2025). Nevertheless, major gaps in knowledge persist on the specific aspects by which iron regulatory pathways regulate the self-renewal and differentiation of leukemic stem cells, and whether the iron regulatory pathways are safe to target in the treatment.

B. Ferroptosis as an Iron-Dependent Cell Death Pathway in Hematologic Disease

Ferroptosis is a newly established type of controlled cell death that is mediated by iron-dependent lipid peroxidation. In contrast to apoptosis, ferroptosis is associated with the oxidative destruction of membrane lipids and changes in mitochondria, which eventually cause cell death (Li et al., 2020).

Hematologic malignancies like the acute myeloid leukaemia (AML) often display an augmentation of the iron uptake, augmentation of reactive oxygen species, and a shift in the antioxidant defences among leukemic cells. The latter aspects predetermine their high risk of ferroptosis-inducing treatments (Liu et al., 2026). Even though ferroptosis has become an effective potential therapeutic approach, a lot of questions still remain open, such as how ferroptosis pathways relate to normal hematopoietic stem cell survival and how ferroptosis-inducing drugs can safely be used in clinical practice.

C. Iron Regulation of Hematopoietic Stem Cell Fate

Accumulating body of evidence indicates that iron stature has the effect of modulating the lineage commitment of the hematopoietic stem and progenitor cells (HSPCs). It is experimentally proven that the increase or decrease of iron levels enhances or inhibits the erythroid or megakaryocytic lineage commitment, respectively (Xavier-Ferrucio et al., 2024).

Moreover, the iron homeostasis can be disturbed by iron imbalance. Extreme iron deficiency can disrupt the hematopoiesis, and iron overload may result in the mitochondrial damage, a state of oxidative stress, and the loss of HSPCs (Xavier-Ferrucio et al., 2024). Nevertheless, the molecular processes governing iron signalling pathways in governing the decisions of lineage of HSPCs are not yet fully understood, which constitute a significant research gap.

D. Ferritinophagy and Iron Recycling in Hematopoietic Cells

The selective autophagy process of degrading ferritin to release stored iron, known as ferritinophagy, has recently become a significant process that controls cellular iron supply. This is mediated by the cargo receptor, NCOA4, and it is important to ensure that intracellular iron balance is maintained (Liu et al., 2025). Ferritinophagy can also be part of controlling intracellular iron levels and determine vulnerability to ferroptosis and oxidative stress in leukemic stem cells. Blockage of ferritinophagy was also proven to raise the intracellular amount of iron and make ferroptosis more sensitive, which may find therapeutic uses (Liu et al., 2025).

E. Iron-Directed Therapeutic Approaches

It is becoming a more common area of research to focus on iron metabolism as a treatment of hematologic malignancies. Iron chelation, iron transport proteins modulation, and ferroptosis induction are strategies that are under investigation to kill malignant hematopoietic cells (Li and Zhang, 2022). Such strategies are based on the reliance of most cancer cells on iron as a metabolic activity and proliferation

factor. Nevertheless, the difficulty in conveying these strategies in clinical treatments is that it is potentially toxic and may cause hematopoietic functions to be normal (Li & Zhang, 2022).

10. Future Directions in Iron Metabolism and Hematopoiesis

A. Development of Hepcidin-Targeted Therapies

The development of therapeutic approaches to iron metabolism disorders in the future is devoted to the increasing attention to hepcidin, which is the primary regulator of iron homeostasis in the body. Hepcidin regulates the levels of iron by binding to an iron exporter called ferroportin that makes ferroportin internalize and degrade, which lowers the release of iron by enterocytes and macrophages (Ganz & Nemeth, 2012). The recent studies have touched on the design of hepcidin agonists and antagonists as possible treatment of iron-related hematologic disorders. Hepcidin agonists could be useful in the treatment of iron overload diseases like hereditary hemochromatosis, transfusion-induced siderosis, and hepcidin inhibitors could be beneficial in iron-destitute anaemia of chronic disease (Camaschella, 2015). Some of the drugs that have been developed as hepcidin-modulating agents are still under development and their impact on the long-term functioning of the hematopoietic stem cell and systemic iron homeostasis is yet to be sufficiently tested.

B. Precision Medicine Approaches to Iron Disorders

The development of the genomic technologies is likely to facilitate the realization of the precision medicine approach in the treatment of the iron-related hematologic diseases. Genetic variations of the principal controllers of iron metabolism, such as HFE, TFR2, HAMP, and SLC40A1 have been found to be a significant factor in iron overburden conditions (Camaschella, 2015). It is possible that the future studies combining genomic data and clinical biomarkers will enable the personalization of therapeutic approach according to the genetic profile of a patient. This form of personalized therapy can enhance results of diagnosis, prognosis, and treatment in hereditary hemochromatosis, iron-refractory iron deficiency anaemia, and myelodysplastic syndromes (Muckenthaler et al., 2017).

C. Targeting Iron Metabolism in Hematologic Malignancies

There is a growing evidence that malignant hematopoietic cells often have defective iron metabolism with an augmented intake of iron and reliance on iron-driven metabolic pathways. Such metabolic properties can offer new targets of therapy to leukaemia and other cancers of the hematologic system (Torti & Torti, 2013). Iron chelators, iron transport protein inhibitors, and ferroptosis-inducing compounds are some of the possible approaches that can be used to kill malignant cells selectively. Nevertheless, additional studies are required to reveal how these therapies may be used without impairing normal hematopoiesis, which also involves a strictly controlled iron homeostasis (Torti & Torti, 2013).

D. Role of Iron in the Bone Marrow Microenvironment

The research on the effects of iron metabolism on the bone marrow microenvironment, which is of paramount importance in the regulation of hematopoietic stem cell maintenance and differentiation, should also be addressed in the future. The macrophages found in erythroblastic islands reuse iron of the senescent erythrocytes and supply iron to the developing erythroblasts, creating a critical enabling system of erythropoiesis (Klei et al., 2017). The mechanisms by which iron availability is involved in the actions between hematopoietic stem cells, the stromal cells, and the immune cells within the bone marrow niche have however not been fully understood. The consideration of these questions could give new knowledge about the pathophysiology of the hematologic diseases related to the iron imbalance.

E. Advances in Biomarkers of Iron Status

The other direction of importance in the future is the creation of more precise biomarkers to determine the iron status and erythropoietic activity. Conventional diagnostic indicators serum ferritin and transferrin saturation may be affected by inflammation or liver disease and are not as diagnostic as they could be (Ganz &

Nemeth, 2012). New biomarkers, such as hepcidin values, soluble transferrin receptor, and reticulocyte hemoglobin, have been prospective in offering better diagnosis of iron deficiency and anemia of inflammation (Muckenthaler et al., 2017). Further studies are needed to confirm the validity of these biomarkers and make them a part of the common practice in the clinic.

Iron metabolism and hematopoiesis are tightly interconnected physiological processes that ensure efficient oxygen transport and maintenance of blood cell homeostasis. Iron serves as a critical cofactor for hemoglobin synthesis, mitochondrial respiration, and DNA replication, making it indispensable for erythropoiesis and the proper functioning of hematopoietic stem and progenitor cells. The regulation of systemic and cellular iron homeostasis is achieved through coordinated mechanisms involving intestinal iron absorption, macrophage-mediated recycling of senescent erythrocytes, and hormonal control by the hepcidin–ferroportin axis, which maintains a balance between iron availability and protection from iron-induced toxicity (Ganz & Nemeth, 2012; Camaschella, 2015).

Disturbances in iron metabolism profoundly affect hematopoiesis and contribute to the pathogenesis of several hematologic disorders, including iron-deficiency anemia, anemia of inflammation, transfusion-related iron overload, myelodysplastic syndromes, and thalassemia. Both iron deficiency and iron excess disrupt erythroid maturation, alter bone marrow microenvironment dynamics, and impair immune cell development through mechanisms involving oxidative stress, ferroptosis, and genomic instability (Rouault, 2015; Dixon et al., 2012). Moreover, iron availability plays an important role not only in erythropoiesis but also in non-erythroid hematopoiesis, influencing myelopoiesis, lymphopoiesis, and megakaryopoiesis.

11. Conclusion

Recent advances have expanded our understanding of molecular pathways linking iron metabolism with hematopoietic regulation, including the iron-responsive element/iron regulatory protein system, ferritinophagy, erythroferrone signaling, and iron-dependent epigenetic regulation within the bone marrow niche. Emerging evidence also highlights the role of iron metabolism in leukemic stem cell biology and the potential of ferroptosis-based therapeutic strategies in hematologic malignancies. Future research should focus on clarifying the molecular mechanisms that regulate iron-dependent lineage commitment, identifying reliable biomarkers of iron status, and developing targeted therapies such as hepcidin modulators, iron chelators, and ferroptosis-inducing agents. A deeper understanding of iron-hematopoiesis interactions will not only improve the management of iron-related hematologic disorders but also open new avenues for precision medicine in hematology.

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