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IRON DEFICIENCY AND GENETIC REGULATION IN TUBERCULOSIS THROUGH MOLECULAR HOST-PATHOGEN INTERACTIONS

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ABSTRACT

Background: Anemia is a frequent comorbidity in tuberculosis (TB), often driven by chronic inflammation and dysregulated iron metabolism. Elevated hepcidin levels limit iron availability by suppressing ferroportin, leading to functional iron deficiency and impaired erythropoiesis. **Objective:** This review discusses the molecular mechanisms linking iron metabolism, host immune response, and *Mycobacterium tuberculosis* persistence, particularly in the context of drug-resistant TB**. Content: W**e summarize current knowledge on the hepcidin–ferroportin axis, siderophore-mediated iron acquisition by *M. tuberculosis*, and the diagnostic value of biomarkers such as ferritin, transferrin saturation, and soluble transferrin receptor. Considerations for iron therapy, including its risks during active inflammation and emerging targeted treatments, are also addressed. **Conclusion:** Anemia in TB requires a selective, biomarker-guided approach. While iron supplementation may benefit those with true deficiency, improper use can worsen infection. Targeted modulation of iron pathways offers promising therapeutic alternatives.

INTRODUCTION

Tuberculosis (TB) remains a major global health concern, with Indonesia ranking second worldwide in incidence and contributing approximately 10% of the global burden. The emergence of multidrug-resistant TB (MDR-TB) has compounded these challenges, leading to prolonged treatment duration, increased healthcare costs, and lower success rates[1]. Anemia is frequently observed in TB patients, affecting over half of cases, and is predominantly classified as iron deficiency anemia (IDA) or anemia of chronic disease (ACD). Both types are associated with impaired immune responses and poorer clinical outcomes[2-5].

A key mechanism linking TB and anemia is inflammation-induced dysregulation of iron homeostasis. Chronic immune activation elevates hepcidin levels, which suppress the expression of ferroportin (FPN1), the only known iron exporter. This results in functional iron deficiency and iron-restricted erythropoiesis, despite adequate or even elevated body iron stores.[2,6] While anemia has been associated with delayed sputum conversion and poor treatment response, especially in MDR-TB, iron supplementation during active infection remains controversial[3]. Mycobacterium tuberculosis (M.tb) requires iron for replication and utilizes sophisticated mechanisms, including siderophore secretion and ATP-binding cassette (ABC) transporters such as IrtAB for iron acquisition. These systems are regulated by iron-sensitive transcriptional factors such as IdeR and WhiB7, the latter of which also contributes to drug resistance[7-9].

To our knowledge, this is the first comprehensive review to integrate molecular insights into host iron metabolism, including the hepcidin–ferroportin axis with M.tb's iron acquisition strategies and their clinical implications in TB-associated anemia. By synthesizing recent biomarker evidence, e.g., hepcidin, non transferin bound iron (NTBI), soluble transferrin receptor (sTfR) with emerging targeted therapies, this article aims to inform future directions in the management of anemia in TB, particularly in the context of MDR-TB.

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REGULATION OF IRON METABOLISM AND HOST IRON RECYCLING

Iron is a vital micronutrient required for oxygen transport, mitochondrial respiration, and enzymatic activity. Most of the body's iron is bound in hemoglobin and myoglobin, with smaller amounts stored in ferritin or transported via transferrin. Iron exists in two oxidative states, ferrous (Fe^{2+}) and ferric (Fe^{3+}), which enable it to function as a redox catalyst. While this redox activity is vital for life, it also renders iron potentially toxic through the generation of reactive oxygen species via Fenton reactions. Therefore, the body maintains a tightly regulated system to balance iron's biological necessity against its toxicity risk[10,11].

In the duodenum, dietary non-heme iron (Fe^{3+}) is reduced to Fe^{2+} by duodenal cytochrome b (DCYTB) and imported into enterocytes via divalent metal transporter 1 (DMT1). Heme iron, primarily found in animal products, is efficiently absorbed via the heme carrier protein-1 (HCP1). Once inside the cell, iron may be stored in ferritin or exported into circulation through FPN1[10].

Circulating iron binds to transferrin (Tf), the main iron-transporting protein in plasma. The transferrin–iron complex (Tf–Fe^{3+}) is recognized by transferrin receptor-1 (TfR1) on the surface of target cells such as erythroblasts. Upon receptor-mediated endocytosis, iron is released within the acidified endosome, reduced by six-transmembrane epithelial antigen of the prostate 3 (STEAP3), and transported into the cytosol via DMT1. Inside cells, iron is utilized for metabolic needs, stored in ferritin, or exported via FPN1. A small labile iron pool also exists in the cytoplasm to meet immediate demands[10,11].

Unlike other micronutrients, daily iron requirements (~20–25 mg) are met primarily through the recycling of senescent erythrocytes by macrophages, rather than through dietary absorption. Aged red blood cells are phagocytosed by macrophages in the bone marrow, liver, and spleen. Following erythrophagocytosis, hemoglobin is degraded and heme is released into the phagolysosome. Heme is then exported into the cytosol by heme-responsive gene 1 (HRG1), a transmembrane transporter that facilitates heme translocation across the phagosomal membrane. HRG1 is highly expressed in iron-recycling macrophages and is essential for efficient mobilization of heme-derived iron. Once in the cytosol, heme is degraded by heme oxygenase-1 (HMOX1), which releases free iron from the protoporphyrin ring. This iron is subsequently stored in ferritin or exported back into the circulation through FPN1[10,11].

At the cellular level, iron metabolism is governed primarily through post-transcriptional mechanisms involving iron regulatory proteins (IRP1 and IRP2) and iron-responsive elements (IREs) located in the untranslated regions of mRNAs encoding proteins involved in iron uptake (such as TfR1 and DMT1), storage (ferritin), and export (FPN1). Under iron-deficient conditions, IRPs bind to IREs, stabilizing mRNAs that promote iron uptake while repressing the translation of mRNAs encoding ferritin and FPN1. Conversely, when intracellular iron levels are sufficient, IRPs dissociate from IREs, allowing translation of ferritin and FPN1 while downregulating iron import[12].

Systemically, iron homeostasis is primarily controlled by hepcidin, a liver-derived peptide hormone encoded by the HAMP gene. Hepcidin expression is modulated through two key pathways: one responsive to systemic iron levels and the other to inflammation. The first regulatory pathway involves the bone morphogenetic protein (BMP)–SMAD signaling cascade. Under conditions of iron sufficiency or overload, BMP6 secreted by hepatocytes binds to BMP receptors (ALK2/ALK3–BMPR2) on the hepatocyte surface, in association with the co-receptor hemojuvelin (HJV). This complex activates intracellular SMAD1/5/8 proteins, which form a complex with SMAD4 and translocate into the nucleus to upregulate HAMP transcription[12].

The second pathway is triggered during inflammation and is mediated by the interleukin-6 (IL-6)/Janus kinase (JAK)/signal transducer and activator of transcription 3 (STAT3) signaling cascade. Inflammatory stimuli increase circulating IL-6, which binds to IL-6 receptors and the gp130 co-receptor on hepatocytes, leading to STAT3 activation and nuclear translocation. Activated STAT3 promotes HAMP gene expression independently of iron status. In chronic infections like TB, inflammation-driven hepcidin elevation results in functional iron deficiency.

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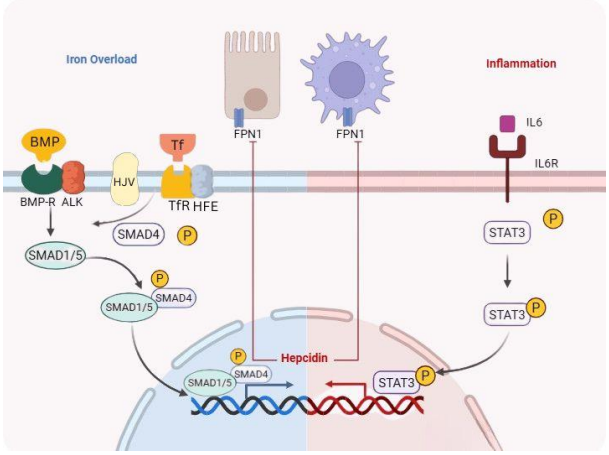

Figure 1. Regulation of Hepcidin Expression via Iron Sensing and Inflammatory Pathways
Left: under conditions of iron overload, transferrin-bound iron (Tf) binds to transferrin receptor (TfR) and HFE on hepatocyte membranes, promoting the BMP (bone morphogenetic protein) signaling cascade. BMP binds to BMP receptors (BMP-R) in the presence of the co-receptor HJV (hemojuvelin), leading to phosphorylation of SMAD1/5 and its complex with SMAD4. This complex translocates into the nucleus and induces HAMP (hepcidin) gene transcription. **Right:** inflammatory stimuli such as IL-6 bind to their receptor (IL-6R), activating the JAK–STAT3 pathway. Phosphorylated STAT3 also translocates into the nucleus, independently upregulating HAMP transcription. The resultant hepcidin acts systemically to degrade ferroportin (FPN1), the only known iron exporter, on enterocytes and macrophages, thereby limiting iron absorption and release into the circulation.

Conversely, hepcidin suppression occurs during active erythropoiesis, mediated by erythroferrone (ERFE) and transmembrane protease serine 6 (TMPRSS6), to enhance iron availability. Erythropoietin (EPO) stimulates the production of erythroferrone (ERFE) by maturing erythroblasts, which suppresses hepcidin synthesis by antagonizing the BMP–SMAD pathway. Additionally, transmembrane protease serine 6 (TMPRSS6), or matriptase-2, inhibits hepcidin production by cleaving membrane-bound HJV, thereby preventing BMP-mediated signaling.[12,13]

IRON ACQUISITION AND PERSISTENCE MECHANISMS OF *MYCOBACTERIUM TUBERCULOSIS*

Mycobacterium tuberculosis (M.tb) depends on iron for key metabolic functions, including DNA synthesis, respiration, and oxidative stress defense. During infection, the host limits extracellular iron availability through nutritional immunity. To overcome this, M.tb produces siderophores, lipophilic mycobactin and hydrophilic carboxymycobactin encoded by the mbtA–J operon. These molecules capture ferric iron (Fe^{3+}) and import it into the bacterial cytoplasm via the IrtAB transporter, which reduces Fe^{3+} to the more bioavailable Fe^{2+}.[8,9,14]

Iron regulation in M.tb is controlled by IdeR, under iron-replete conditions, Fe^{2+}-bound IdeR represses the transcription of iron uptake genes such as mbtB and irtAB, while simultaneously upregulating iron storage genes including bfrA and bfrB. In contrast, during iron deficiency, inactive IdeR allows for derepression of siderophore biosynthesis and transport pathways, thereby enhancing iron acquisition. A key adaptive feature of M.tb is its ability to persist within macrophages. Hepcidin-induced FPN1 suppression traps iron intracellularly, creating a favorable environment for M.tb replication.[7,9]

M.tb responds to environmental stressors, including iron deprivation and antibiotic exposure by inducing the transcriptional regulator WhiB7, which contains an iron–sulfur (Fe–S) cluster. WhiB7 modulates the expression of several genes associated with intrinsic drug resistance. Among these are:

- tap (transporter associated with antibiotic persistence), which encodes an ABC transporter involved in drug efflux and reduced intracellular antibiotic accumulation;
- eis (enhanced intracellular survival), which encodes an acetyltransferase capable of inactivating aminoglycoside antibiotics through enzymatic acetylation;
- Rv2688c, which encodes a putative major facilitator superfamily (MFS) efflux pump associated with fluoroquinolone resistance and general multidrug tolerance.[9]

In severely iron-deprived environments, such as the necrotic centers of granulomas, M.tb transitions into a quiescent, non-replicating state. This physiological shift is accompanied by reduced metabolic activity and increased tolerance to antibiotics. A critical factor in this tolerance is the downregulation of KatG (catalase-peroxidase), a heme-containing enzyme responsible for activating isoniazid (INH), a first-line anti-TB prodrug. When katG expression is suppressed under iron-starvation, INH activation is impaired, contributing to M.tb's survival. Furthermore, inhibition of the electron transport chain due to reduced iron availability limits the proton motive force needed for aminoglycoside

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uptake, enhancing drug tolerance. This quiescent state, together with the induction of drug resistance genes, mirrors the microenvironment of latent TB and underscores the role of iron starvation in promoting long-term persistence of M.tb within the host.[9]

ANEMIA IN TUBERCULOSIS: CLINICAL IMPLICATIONS AND BIOMARKER PROFILES

Anemia is a frequent complication in TB and is most often classified as either IDA or ACD, with ACD being predominant. Chronic systemic inflammation associated with TB suppresses erythropoiesis through cytokine-mediated mechanisms, including reduced erythropoietin (EPO) activity, impaired iron utilization, and shortened erythrocyte lifespan.[3]

IL-6 plays a key role by stimulating hepatic hepcidin production, leading to the degradation of ferroportin and subsequent iron sequestration in macrophages and hepatocytes. This results in functional iron deficiency, characterized by low serum iron despite normal or increased total body iron stores. Ferritin, an acute-phase reactant, is often elevated in TB patients, reflecting inflammation rather than adequate iron reserves. CRP (C-reactive protein) is similarly elevated. In contrast, transferrin, a negative acute-phase protein, decreases during inflammation due to suppressed hepatic synthesis.[3,15]

Biomarkers such as sTfR remain relatively unaffected by inflammation and rise in IDA, making them useful in distinguishing IDA from ACD. The sTfR/log ferritin index, decreased in ACD and increased in IDA, facilitating accurate differentiation. Thus, a combination of ferritin, sTfR, transferrin saturation (TSAT), and CRP is recommended to accurately differentiate anemia subtypes in TB.[15]

Hepcidin is markedly elevated in ACD and may serve as a discriminating marker. Vyas et al. found that a plasma hepcidin cut-off >72.93 ng/mL was associated with high diagnostic accuracy for ACD.[16] Notably, hepcidin can also be measured in urine, offering a non-invasive and practical alternative with diagnostic performance comparable to plasma assays. Urinary hepcidin reflects systemic iron status and may facilitate early detection of iron deficiency, even in asymptomatic individuals. The urinary hepcidin assay holds promise for integration into point-of-care (POC) diagnostics. This approach is particularly valuable in low-resource settings where conventional laboratory infrastructure is limited, supporting timely and targeted management of anemia in high-risk populations.[17]

The sTfR to hepcidin (sTfR/hepcidin) ratio has emerged as a promising biomarker for the early detection of absolute iron deficiency. In a study by Tarancon-Diez et al., this ratio was shown to correlate significantly with iron status when serum ferritin levels dropped below 50 ng/mL, indicating the onset of functional iron deficiency even in individuals without anemia. Clinically, the sTfR/hepcidin ratio offers greater sensitivity than ferritin alone, especially in the context of inflammation, and supports the use of a ≤50 ng/mL ferritin threshold for early diagnosis and targeted intervention.[18]

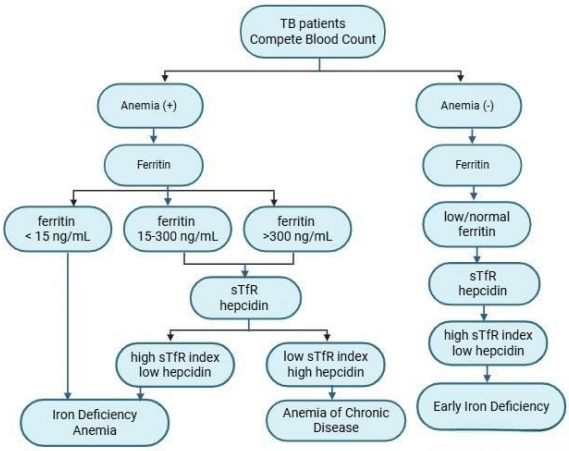

Figure 2. Diagnostic Algorithm for Differentiating Anemia Types in Tuberculosis Patients.

Clinically, anemia in TB is associated with delayed sputum conversion, increased risk of relapse, and higher mortality, particularly in MDR-TB. A cohort study on MDR-TB patients showed significantly prolonged time to culture conversion among anemic individuals.[4,19] In contrast, another study reported no significant association between anemia and sputum conversion during the first six months of treatment.[20] Despite these discrepancies, certain hematologic parameters such as hemoglobin levels below 9.75 g/dL, low total leukocyte count (TLC) (<8.45 × 10^9/L), and low neutrophil count (<1.59 × 10^9/L) have been identified as predictors of poor outcomes, including 90-day post-discharge mortality.[4] These findings highlight the need to

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evaluate and monitor anemia in TB patients, not only as a common comorbidity but also as a potential prognostic marker.

THERAPEUTIC CONSIDERATIONS IN MANAGING TB-ASSOCIATED ANEMIA

Recent studies have provided valuable insights to guide iron supplementation in tuberculosis (TB)-associated anemia. A major clinical challenge lies in determining whether, and at what point, anemic TB patients should receive additional iron. While iron deficiency can impair immune function and reduce treatment efficacy, premature supplementation during active TB may increase morbidity by promoting bacterial growth through elevated levels of NTBI.[3] A 26-week prospective study by Cercamondi et al., which employed oral and intravenous iron tracers, demonstrated that IL-6 and hepcidin levels declined significantly within two weeks of initiating anti-TB therapy. This reduction facilitated the mobilization of stored iron and triggered reticulocytosis, with hemoglobin levels rising substantially by week 4. Notably, ERFE and EPO levels remained elevated until weeks 6 to 8. Throughout therapy, ERFE levels were inversely correlated with hepcidin and positively associated with reticulocyte counts, indicating a sustained role for ERFE in overcoming functional iron deficiency and restoring iron homeostasis.[6]

During active TB, dietary iron absorption was nearly abolished and remained reduced even after the intensive treatment phase. Nevertheless, iron mobilized from macrophage stores, combined with the resolution of inflammation, was generally sufficient to support hemoglobin recovery without the need for supplementation. A significant increase in fractional iron absorption was observed only after treatment completion, suggesting that iron supplementation may be more appropriate for patients with persistent anemia at that stage.[6]

Intravenous (IV) iron formulations, which bypass intestinal absorption, are rapidly cleared by macrophages. However, the release of iron from these cells requires export via FPN1, a process that is inhibited by hepcidin. In inflammatory conditions where hepcidin is elevated, this blockade leads to intracellular iron sequestration, reducing iron bioavailability and necessitating higher IV iron doses and ferritin targets to achieve therapeutic efficacy.[21] This sequestration also increases the risk of NTBI accumulation, which may contribute to oxidative stress, impair innate immune defenses, and promote microbial proliferation. Such risks are especially relevant in TB, as *M. tb* resides within macrophages and relies on intracellular iron for survival and replication.[3,6]

Given these challenges, iron supplementation should be reserved for patients with confirmed absolute iron deficiency. Ideal candidates present with low ferritin (<30–50 ng/mL), high sTfR, low transferrin saturation (<20%), and reduced hepcidin, typically in the absence of systemic inflammation (CRP <10 mg/L).[3,15,18,21] In such cases, alternate-day low-dose oral iron is preferable to minimize transient hepcidin surges.[22] If oral iron is poorly tolerated or ineffective, intravenous iron may be considered cautiously, only after inflammatory markers improve.[3,6,21]

Emerging therapies offer new directions by targeting the hepcidin–ferroportin axis. Hepcidin antagonists, such as NOX-H94 (lexaptepid pegol) and PRS-080, bind and neutralize circulating hepcidin, restoring iron export. Early-phase trials have shown safety and increased serum iron parameters. Additionally, therapies targeting upstream hepcidin regulators are under investigation. Tocilizumab, a monoclonal antibody against the IL-6 receptor, inhibits the IL-6/STAT3 pathway and has been shown to reduce hepcidin levels and improve anemia in chronic inflammatory conditions. Although not yet approved for TB-related anemia, its potential role is under active exploration.[13]

In parallel, BMP–SMAD pathway inhibitors such as soluble hemojuvelin–Fc fusion protein (sHJV-Fc) and LDN-193189 (a BMP type I receptor kinase inhibitor) have shown efficacy in reducing hepcidin expression in preclinical models. These targeted strategies highlight the need for personalized anemia management in TB, guided by iron biomarkers and inflammatory status. Integrating these tools into clinical decision-making may improve outcomes while minimizing the risk of infection reactivation or iron overload.[13]

CONCLUSION

Anemia is a prevalent comorbidity in tuberculosis, especially in MDR-TB, and contributes to delayed treatment response and worse clinical outcomes. The

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predominant mechanism involves hepcidin-mediated iron restriction driven by chronic inflammation, which impairs erythropoiesis and favors M.tb persistence. Iron therapy should not be used routinely but reserved for patients with confirmed iron deficiency, guided by laboratory parameters such as ferritin, soluble transferrin receptor (sTfR), transferrin saturation (TSAT), and hepcidin. Novel strategies, including hepcidin inhibitors and drugs targeting upstream regulators like IL-6/STAT3 and BMP–SMAD pathways, are being investigated and may provide more specific options for treating anemia in TB patients in the future.

ETHICAL APPROVAL

There is no ethical approval.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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AUTHOR CONTRIBUTIONS

The author is solely responsible for the conception, literature review, analysis, writing, and final approval of this manuscript.

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