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Impact of BMP-SMAD and JAK-STAT Signaling Pathways on Hepcidin Protein Expression and Iron Overloading in β-Thalassemia: A Review

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Abstract: ***Thalassemia represents an inherited blood disorder with a recessive genetic pattern that causes problems with hemoglobin production and leads to dysfunctional red blood cells and ongoing anemia. β-thalassemia patients show reduced levels of hepcidin hormone which controls iron homeostasis thereby leading to iron regulation problems. When hepcidin levels fall depleted, it raises the amount of iron that the intestines absorb while macrophages release too much iron which results in excessive iron accumulation throughout the body. β-thalassemia patients need blood transfusions face increased risks of endocrine disorders together with hepatic damage and heart complications owing to continued iron accumulation. Through its mechanism the protein hepcidin breaks down ferroportin which controls cell-based iron release thus restricting iron access from diet and stored reserves. The deregulation of hepcidin results in an abnormal iron imbalance where patients experience simultaneous iron deficiency anemia along with toxic iron buildup. Multiple signaling pathways control hepcidin regulation which includes bone morphogenetic protein/ small mothers against decapentaplegic (BMP/SMAD) as well as the Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway together with erythroferrone (ERFE) and growth differentiation factor 15 (GDF15). The treatment strategies for restoring iron equilibrium combine hepcidin agonists with BMP pathway activators alongside ERFE inhibitor administration to promote hepcidin production while stopping its suppression. The review establishes how hepcidin-associated signaling interacts with iron regulation within β-thalassemia while examining its importance for medical treatment approaches.***

Keywords: β-thalassemia, erythropoiesis, hepcidin, iron overloading, JAK/STAT, BMP/SMAD

1. Background

β-thalassemia, a genetic blood disorder is caused by anomalies in the expression of the β-globin chain. Different beta gene mutations result in a spectrum of clinical severities, from asymptomatic carriers to severe transfusion-dependent anemia[1]. More than 300 globin chain mutations have been identified, and β-thalassemia is caused by point mutations in the splicing site and promoter region of the chromosome 11 β-gene[2]. Free heme molecules are bound by unbound α-globin to create soluble, toxic aggregates called hemichromes that damage the erythroblast[3]. This results in ineffective erythropoiesis, which is distinguished in β-thalassemia patients by anemia and increased apoptosis of developing RBCs[4]. This disorder affects people of all genders, which is extremely prevalent (10%) in Asian, Mediterranean, and African populations but just 1.5% worldwide[5]. Intramedullary hemolysis, accelerated destruction of existing red blood cells, and decreased RBC survival are the causes of β-thalassemia, one of the most prevalent hereditary forms of chronic anemia[6]. Frequent blood transfusions and increased iron absorption cause iron overload, which worsens the condition. Thus, iron-induced damage to key organs including the liver and heart is the main cause of morbidity and death in transfusion-dependent β-thalassemia[7]. Stress increases iron absorption, but the iron is deposited in the organs rather than being used to produce erythrocytes, which can cause systemic problems[8]. Moreover, it induces reactive oxygen species (ROS) to develop, which results in oxidative stress and erythroid cell death[9]. In this review, we discuss the key signaling mechanisms that disrupt iron homeostasis in β-thalassemia, focusing on includes bone morphogenetic protein/small mothers against decapentaplegic (BMP/SMAD) and erythropoietin (EPO)-driven Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathways. We also examine the effect of hepcidin and erythroferrone (ERFE) in the development of iron overload. To effectively manage iron-related problems in β-thalassemia, a thorough understanding of these molecular pathways is necessary.

Hepcidin as an iron regulator

A 25-amino-acid peptide hormone, hepcidin is essential for maintaining iron homeostasis. Four disulphide bonds anchor this small, cysteine-rich molecule, giving it a strong structural foundation[10]. Encoding hepcidin, the hepatic antimicrobial peptide (HAMP) gene is found on chromosome 19q13 and has three exons that are necessary for its regulatory activity[11]. By inhibiting the absorption of iron from the duodenum and release of recovered iron from macrophages, while controlling the mobility of iron reserves in hepatocytes, hepcidin influences iron homeostasis in three distinct ways[12]. To maintain the plasma iron level within the normal range, they lead to a decrease in the outflow of iron from its store and its enclosing inside cells. Iron and hepcidin regulate each other through a classical endocrine feedback loop. A higher

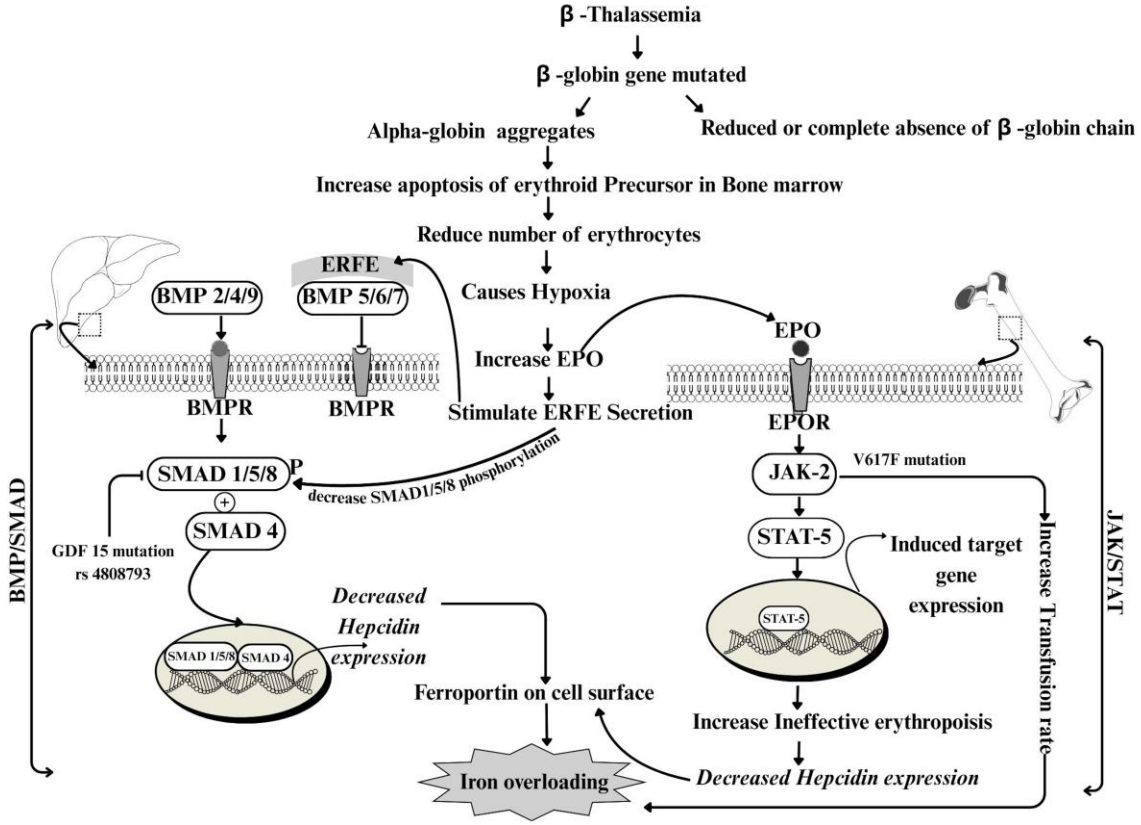
iron concentration in the body induces hepatocytes to produce more hepcidin that reduces the amount of available iron for absorption and storage release. Hepatocytes produce decreased amounts of hepcidin during periods of low iron which enables additional iron to reach plasma. The homeostatic function of hepcidin depends on three biological variables together with hepatic and extracellular iron distribution: erythropoiesis, inflammation and oxygen availability[13]. During the process of active erythropoiesis hepcidin formation remains suppressed to allow for increased iron availability that supports hemoglobin synthesis. Hepcidin (erythroid factor) is primarily suppressed by ERFE, a hormone released by EPO-stimulated erythroblasts that acts on the liver to reduce hepcidin synthesis[14]. The loss of iron efflux into plasma from enterocytes, hepatocytes, and macrophages causes hypoferremia in vivo due to the ongoing consumption of plasma iron, mostly for erythrocyte precursor hemoglobin production[15].

Hepcidin ferroportin complex and iron overloading

Hepcidin controls iron metabolism by interacting with ferroprotein, the only known iron exporter presents on the surface of enterocytes, macrophages, and hepatocytes. Iron levels in the blood decline as a result of ferroportin's internalization and breakdown upon binding, which also limits iron release from storage sites and reduces intestinal absorption of iron[12]. Through DMT1, a divalent metal transporter, in the gut, iron is absorbed, and ferroportin carries it into the bloodstream. It subsequently attaches itself to the transport protein transferrin and is transported via transferrin receptor 1 (TfR1) to different cells, such as macrophages and hepatocytes[16]. Most iron is stored in the liver in a ferritin-bound form. Plasma receives its iron supply through intestinal iron absorption of dietary inputs (1–2 mg per day) alongside senescent erythroblasts removed by the reticuloendothelial system (20-25 mg per day) [17]. Cellular iron egress in both cases is achieved through the only known iron export protein, ferroportin. Through its receptor ferroportin, the hepatic-derived hormone hepcidin modulates plasma iron levels and inhibits iron access to plasma[18]. By directly binding to ferroportin, blocking it, and causing a conformational shift by tyrosine phosphorylation, hepcidin prevents cellular iron efflux. This leads to ferroportin ubiquitination, endocytosis of both molecules, and their lysosomal breakdown. Mutations preventing these modifications can lead to hepcidin resistance and contribute to iron overload disorders. Hepcidin binding causes the hepcidin-ferroportin complex to be internalized and degraded by lysosomes, preventing iron delivery from the intracellular to the extracellular milieu[19].

Suppression of hepcidin

Due to inefficient erythropoiesis and altered signaling pathways, β-thalassemia substantially disrupts the control of iron homeostasis. The BMP-SMAD and JAK-STAT pathways, in particular, are intricate signaling pathways that affect hepcidin production and regulate iron homeostasis in β-thalassemia. Intracellular hepatic iron levels and extracellular iron-transferrin tightly regulate hepcidin production through the BMP pathway[20]. At the same time, high EPO levels from chronic anemia led to sustained JAK/STAT pathway activation. Increased erythropoietic activity, especially in the spleen, can arise from this prolonged activation, which could exacerbate splenomegaly[21].



EPO=erythropoietin, EPOR=erythropoietin receptor, ERFE=erythroferrone, BMP=bone morphogenetic protein, BMPR=bone morphogenetic protein receptor, SMAD=small mothers against decapentaplegic, JAK2=janus kinase 2, STAT-5=signal transducer and activation of transcription 5

Figure 1

Figure 1 The illustration shows the cellular process causing iron-overload in β-thalassemia. A mutation in the β-globin gene causes β-globin chains to be reduced or absent, which leads to α-globin chain aggregation and increased bone marrow erythroid precursor apoptosis. This causes tissue hypoxia and reduction in erythrocytes, which raises erythropoietin (EPO) synthesis. Increased EPO levels, further promote the release of erythroferrone (ERFE), which suppresses the liver's BMP/SMAD signaling. Hepcidin expression is lowered as a result of this inhibition. Simultaneously, EPO triggers the JAK2/STAT5 signaling, which further lowers hepcidin expression and encourages ineffective erythropoiesis. Low level of hepcidin allows over-expressed ferroportin on cell surfaces, which enhance iron captivation and release into circulation, resulting iron overloading.

BMP/SMAD Pathway

In thalassemia, ineffective erythropoiesis leads to a paradoxical decrease in hepcidin despite elevated iron in the body. This malfunction is largely caused by the BMP pathway, which controls the expression of hepcidin. Figure-1 shows BMP2/4/9 and BMP5/6/7 activate BMP receptors (BMPR) which phosphorylates SMAD1/5/8 proteins leading to the formation of SMAD4 complexes that migrate to the nucleus for hepcidin induction[22].

Thalassemia leads to excessive erythroblasts which release the inhibitory factor ERFE that blocks BMP signaling to prevent hepcidin production. The inhibitory effects of ERFE are specific to the BMP5/6/7 signaling pathway so it reduces phosphorylation of SMAD1/5/8 proteins thus decreasing hepcidin expression. Multiple experimental approaches have validated the specific inhibitor effect observed during these experiments. Experimental data demonstrate that ERFE fails to block BMP2-mediated signals effectively which precludes full inhibition of hepcidin gene expression[23]. Reduced amounts of hepcidin make ferroportin proteins more abundant on cell surfaces to support increased iron absorption followed by bloodstream entry that causes systemic iron overload[24]. The pathogenesis of thalassemia along with hereditary hemochromatosis worsens through gene mutations affecting hepcidin regulation factors such as BMP6 along with additional proteins HFE (homeostatic Fe regulator) and TFR2[25].

The transforming growth factor-beta (TGF-β) class of ligands together with their receptors participate in abnormal signaling pathways in thalassemia. The Activin A Receptor Type 2A (ACVR2A) together with Activin A Receptor Type 2B (ACVR2B) enables the binding of TGF-β-like ligands including GDF11 and activin in addition to BMP ligands in this pathway[26]. The combination of β-thalassemia with excessive iron and inefficient erythropoiesis activates Type Ireceptors in the path to disrupt SMAD signaling functions and triggers hepcidin regulatory abnormalities[27]. The accumulation of iron in tissues worsens damages in liver, heart and endocrine organs while paradoxically decreasing hepcidin levels. The regulation of iron absorption through this mechanism remains ineffective[28]. The pathophysiology of iron overload in thalassemia occurs from dysregulation of the BMP pathway and alongwith genetic iron-regulatory dysfunctions and abnormal response of erythroferrone pathway.

JAK/STAT pathway

Jak2 acts as an essential signal molecule which governs erythroid progenitor cell proliferation together with differentiation and survival in EPO-dependent cells. EPO production from hypoxic conditions enables this hormone to connect with EPOR receptors on erythroid cells to foster cellular multiplication and sustain their survival. After binding EPO to its receptor Jak2 becomes phosphorylated leading to subsequent phosphorylation of the signal transducer and activator of transcription-5 (STAT5) [29] as shown in figure 1. The EPO signaling pathway activates JAK2/STAT5 to induce both anti-apoptotic proteins Bcl-xL (B-cell lymphoma extra-large) and enhance transferrin receptor-1 expression for erythropoiesis-mediated iron uptake[30]. The Jak2 signaling cascades also promote erythropoietic cell survival via phosphoinositol-3-kinase (PI3K)-AKT signaling which enables activation of key erythroid transcription factors GATA-1 and Forkhead box O3 (FoxO3) for expression of genes related to globin chain synthesis and heme biosynthesis[31]. The pathophysiology of β-thalassemia features ineffective erythropoietic processes that generate excessive erythroblasts even though red blood cell production remains inadequate. EPO triggers erythropoiesis but RBCs fail to produce properly together with persistent low oxygen levels which keep activating hypoxia induced factor 2-alfa (HIF2α) [32]. The expression of hepcidin decreases when HIF2α activates while iron absorption increases. The upregulation of iron transporters DMT1 and DCYTB (duodenal cytochrome b) together with ferroprotein occurs in response to HIF2α regulation[33]. Excessive ferroprotein activity combined with deficient hepcidin levels within the duodenal tissue leads to prolonged import of iron which accumulates progressively throughout β-thalassemia. In β-thalassemia inadequate erythropoiesis combined with decreased oxygen levels together with disrupted signaling networks lead to an intricate iron dyshomeostasis. Failures in hepcidin regulation together with iron overloading result in continuous iron absorption that progresses into long-term organ damage specifically affecting the liver and heart as well as the endocrine system[34].

Other factors in β-Thalassemia pathophysiology

Research has demonstrated that ERFE-deficient mice fail to downregulate hepcidin following haemorrhage or EPO stimulation. Chromatin immunoprecipitation studies indicate that EPO administration reduces the binding of CCAT enhancer-binding protein (C/EBPα) to the hepcidin promoter[27], suggesting its role in hepcidin transcriptional regulation in response to enhanced erythropoiesis. New evidence demonstrates that EPO regulates TFR1expression on erythroblasts in patients with β-thalassemia major and intermedia by influencing liver hepcidin mRNA levels which inversely connect to soluble transferrin receptor and EPO concentrations instead of iron storage[35]. This, in turn, depletes diferric transferrin from plasma, a key regulator of hepcidin synthesis through its interaction with transferrin receptors (TFR1 and TFR2) on hepatocytes[12]. The impairment of SMAD signaling because of reduced diferric transferrin levels leads to decreased hepcidin synthesis. The elevated expression of ERFE together with hypoxia-induced factors

that enhance ferroportin activity and suppress hepcidin results in increased iron absorption in β-thalassemia. The excessive iron accumulation within thalassemia patients elevates their risk of infections thus becoming a principal reason for death in this condition[36]. Persistent erythropoietin stimulation of the JAK2 pathway occurs in patients with β-thalassemia due to their chronic anemia. Moreover, on the other hand, JAK2V617F, a mutation in JAK2 gene, is a gain-of-function mutation which further over activate this pathway. In case of β thalassemia, this mutation exacerbate the problem of ineffective erythropoiesis. It leads to enhanced proliferation and survival of hematopoietic cells, especially erythroid precursors, but these cells are often defective and fail to mature properly[37].

The differentiation process of erythroblasts releases several hepcidin-blocking substances including growth differentiation factor 15 (GDF15). The β-thalassemia major and intermedia patients show elevated serum ferritin combined with an increased iron overload risk associated with rs4808793 polymorphism of the GDF-15 gene. Increased GDF-15 expression associated with this variant causes the suppression of hepcidin and enhanced intestinal iron absorption resulting in iron accumulation[38]. GDF11 shows elevated expression in erythroid progenitors that matches disease progression levels. The excessive iron levels accentuate the condition of anemia by triggering premature destruction of erythroid precursors. Iron overload develops through GDF11-mediated suppression of hepcidin in liver cells which makes more iron available for erythropoiesis[39].

In β-thalassemia excessive iron absorption results from the feedback mechanism where EPO-induced erythropoiesis interacts with ERFE-mediated suppression of hepcidin and HIF2α stabilization. The disease leads to chronic anemia and iron overload because of impaired iron regulation along with deficient erythropoiesis ultimately presents complex issues for disease management and organ protection[40].

2. Conclusion

In view of iron overload, hepcidin suppression, and inefficient erythropoiesis, β-thalassemia severely disrupts the regulation of iron metabolism. Despite systemic iron overload, increased iron absorption results from the inhibition of the BMP signaling pathway, which typically controls hepcidin production, by ERFE and other erythropoietic factors. Additionally, EPO stimulated pathways and HIFs further contribute to hepcidin suppression and increased iron transport[41]. β-thalassemia patients experience a pathological condition due to improper erythropoiesis regulation causing continued iron absorption alongside tissue iron overload accumulation. The iron dysregulation becomes worse for transfusion-dependent patients who develop severe risks from chronic iron overload that can lead to organ failure and increased infection risks. Future scientific investigations should work on treatments that reduce iron toxicity and fix erythropoietic abnormalities in β-thalassemia patients to enhance their clinical outcomes.

Author's Contributions

Rajinder Kaur: Writing – review & editing, Supervision, Project administration, Investigation, Conceptualization. **Kanchan Bhardwaj:** Visualization, Supervision. Aarti Saini: Writing – original draft, Methodology, Formal analysis, Figure Construction, Data Curation, Conceptualization.

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There are no conflict of interest to declare**.**

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