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REVIEW ARTICLE

Insight to the Biochemical Mechanism of the Bone Morphogenetic Protein (BMP6) as an Iron-Regulatory Protein in Iraqi Patients with Iron Deficiency Anemia

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ABSTRACT

Liver has emerged as the major site of systemic iron regulation, being the location where the iron regulatory hormone hepcidin is produced. Hepcidin is a negative regulator of iron absorption and recycling, achieving this by binding to the only known cellular iron exporter ferroportin and causing its internalization and degradation, thereby reducing iron efflux from target cells and reducing serum iron levels. Bone morphogenetic proteins (BMPs) are members of the transforming growth factor-beta (TGF-β) superfamily of signaling molecules. It has a central role in iron homeostasis. Specifically, BMP6 serves to relate hepatic iron stores to the hepatocellular expression of the iron regulatory hormone hepcidin. Systemic iron regulation maintains a stable concentration of iron transferrin in plasma and extracellular fluid. Therefore, this review was aimed to tracking the biochemical mechanism of the BMP6 as an iron-regulatory protein to provide further insight into their clinical applications, also to suggest areas where further research is needed, either to deal with gaps in the knowledge related to their important roles in a wide array of processes.

INTRODUCTION

"Anemia is defined as a diminution in the count of circulating red blood cells (RBCs). It is a globally main reason for morbidity and mortality. In medical contexts, this definition is rarely considered. World Health Organization (WHO) defined anemia as a disorder in which the count of RBCs, and, as a result, their oxygen-carrying capacity is inadequate to provide its physiologic requirements".[1] "Iron deficiency anemia is an illness in which the blood does not contain adequate iron. Adolescents and women before menopause are more likely to develop this type of anemia. This condition is caused by internal bleeding from the gastrointestinal tract, donating too much blood, or loss of blood from heavy times. Anemia is caused by a lack of iron, which can be caused by "several factors." The factors can contribute to iron deficiency anemia are poor iron absorption, deficiency in certain vitamins (folic acid and vitamin B12), pregnancy or childhood growth spurts, heavy menstrual cycles, gastrointestinal (intestinal) bleeding,

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dietary factors (iron-poor or restricted diet), kidney bleeds, infection with parasitic hookworms, problems with RBC and the bone marrow, prescription medications (aspirin ibuprofen or naproxen).[2] Symptoms involved: fatigue, laziness, faintness, attacks of short of breath, headaches, irregular heartbeats (palpitations), changed the taste, sore mouth, and ringing in the ears anemia during pregnancy raises the danger of complications for mother and her baby, such as decreased birth weight, and postnatal depression. Low iron reserves can also cause anemia in the newborn baby in baby.[3] Both iron deficiency and overabundance are harmful conditions. Body iron concentrations are tightly controlled by the hepatic hormone hepcidin, which regulates dietary iron absorption and the release of stored iron. Hepcidin's dysfunction is linked to all iron-related illnesses. An unbelievable amount of progress has been made in our understanding of iron homeostasis and hepcidin regulation during the past two decades. The BMP/SMAD pathway is primarily responsible for regulating hepcidin expression at the transcriptional level. The primary ligand and key upstream positive regulator of hepcidin reacting to iron levels is BMP-6, which is generated in non-parenchymal cells of the liver.[4]

Markers for Diagnosis of Iron Deficiency

The most basic test might be the complete blood count (CBC) test which helps in providing a wealth of information, including RBC count, hemoglobin, and red blood cell indices (MCV and MCH).[5]

The amount of leukocytes and platelets is also essential. When it comes to diagnosing anemia, all of this information is useful. Reactive thrombocytosis is frequently associated with iron-deficient anemia. Serum iron, transferrin, transferrin saturation percentage, and the soluble transferrin receptor (sTfR) are all parameters related to iron metabolism.[5]

Blood Smear Test

This reveals the amount of hemoglobin (hypochromia), as well as variations in form (poikilocytosis) and size (anisocytosis), all of which aid in the diagnosis. The diverse proteins involved in transporting and storing iron have clinical importance.[5]

Ferritin

The most significant iron storing protein. The liver, spleen, and bone marrow have high quantities of this protein. It has between 15 and 20% of the body's iron content. The cells secrete a little quantity of ferritin, which then enters the bloodstream—the amount of this protein and the amount of iron stored relationship directly. The storage iron pools are well-indicated by serum ferritin.[5] However, because ferritin is an acute-phase reactant, it is commonly necessary to perform a C-reactive protein (CRP) test to rule out the presence of any infections or inflammatory processes. As a result, ferritin is a particularly helpful tool for assessing iron metabolism. A latent iron inadequacy is indicated by values less than 12 ng/mL. A ferritin value of more than 400 ng/mL indicates an iron overload.[5]

Transferrin, Transferrin Saturation

Transferrin is an iron-saturated protein generated in the liver. It contains between 15 and 45% iron. More of this protein would be generated if there is a functional iron deficiency; high levels are reported in iron deficiency and during pregnancy.

Soluble transferrin receptor (sTfR): The erythroid precursors contain around 75% of the transferrin receptors. When there is a functional iron deficit, the number of transferrin receptors increases, the soluble form is referred to as (sTfR). This is the unique biological marker that linked erythropoiesis to an iron deficit. As a result, it works in tandem with ferritin. Because the acute-phase reactants have no effect on the sTfR, it detects an iron deficit in the presence of infection, inflammation, or tumors.[5]

Bone Morphogenetic Protein

Bone morphogenetic proteins (BMPs are signaling molecules that belong to the transforming growth factor-beta (TGF-) superfamily. A crucial role in iron homeostasis has recently been revealed for particular BMPs and their responsibilities in embryonic development, germ-line specification, and cellular differentiation. Hepatic iron reserves are linked to hepatocellular expression of the iron-regulatory hormone hepcidin by BMP6.[6]

The main regulator of systemic iron homeostasis is hepcidin, a peptide hormone produced in the liver. By restricting intestinal iron absorption, iron recycling by macrophages, and iron mobilization from hepatic reserves, hepcidin regulates plasma iron concentration and tissue distribution of iron. Hepcidin works by attaching to ferroportin, the only known cellular iron exporter, and causing its breakdown.[7]

Structure and Function of BMPs

In the 1990s, the crystal structures of human BMP2 were revealed. More than 20 homodimeric or heterodimeric morphogenetic proteins have been identified in humans and other animals, and they play an important role in the development and function of a wide range of cell types in various tissues.[8]

Because "these are the original bone components trapping endogenous BMPs, early investigations used demineralized bone matrix and collagen sponges as the major scaffolds. Collagen (type I, insoluble, and heavily crosslinked), chitosan, and hyaluronic acid are natural polymers that allow cells to adhere, disseminate, and differentiate, making them key BMP delivery mechanisms".[8]

BMP Signaling Pathway

BMP causes ectopic bone formation, when a ligand binds to its receptor, a complex forms in which the Type II BMP receptor phosphorylates and activates the type I BMP receptor, as shown in Figure 1.

The signal is subsequently propagated via the Type I BMP receptor phosphorylating a family of signal transducers known as the Smad proteins. "Smad1 can interact with either Smad4 or Smad6 after being phosphorylated by the BMP type I receptor.

The Smad1-Smad6 complex is inert, but the Smad1-Smad4 complex causes BMP-sensitive genes to be expressed. The ratio of Smad4 can modulate the strength of the signal transduced by BMP to Smad6 in the cell.

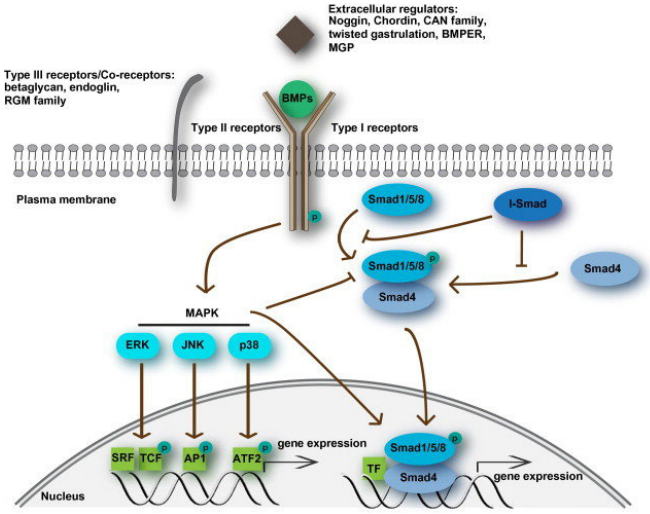

Figure 1: BMP Signaling Pathway

BMPs work by activating a transmembrane heteromeric receptor complex made up of type I and type II serine/threonine kinase polypeptides, also known as the BMP receptor (BMPR) type IA and IB and BMPR Type II, respectively.[9] active receptor kinases. In the nucleus, the phosphorylated Smads form the transcription factors Smad 1, 5, and 8 are phosphorylated by the heterodimeric complex with Smad 4 and stimulate target gene expression in collaboration with coactivators.[9]

The figure above illustrated that BMP dimer could bind to its type II receptor, type I receptors which are recruited, forming a heterotetramer with two receptors of each kind. Because the receptors are close together, the type II receptor can phosphorylate the type I receptor.

The Smad cascade, one of two recognized downstream routes, is activated by type I receptor stimulation of certain Smad proteins, whereas the other process comprises two mitogen-activated protein kinase (MAPK) cascades.

Table 1: BMP6 and iron deficiency: a review of recent research

Title	*Authors*	*Objectives*	*Markers*	*Results*
Heterozygous Mutations in BMP6 Pro-peptide Lead to Inappropriate Hepcidin Synthesis and Moderate Iron Overload in Humans(2016).[11]	Raed Daher *et al*.	Investigate BMP6 function in patients who have unexplained iron overload	Serum ferritin, liver iron level, serum level of hepcidin	Three heterozygous missense mutations in BMP6 were discovered that resulted in a loss of SMAD protein signaling and a decrease in hepcidin synthesis.
Down-regulation of Bmp/Smad signaling by Tmprss6 is required for the maintenance of systemic iron homeostasis(2016).[19]	Karin E. Finberg *et al.*	Investigate the key pathway promoting hepcidin transcription in hepatocytes by examining the relationship between Tmprss6 and the bone morphogenetic protein	, complete blood count, serum iron level, and serum non-heme level for different organ	The research suggested that down-regulation of Bmp/Smad signaling by Tmprss6 is required to regulate hepcidin expression and maintain systemic iron homeostasis.
Identification of new BMP6 pro-peptide mutations in patients with iron overload (2017).[20]	Chiara Piubelli *et al.*	Identification of new BMP6 pro-peptide mutations in patients with iron overload	Serum ferritin, liver iron level, BMP6 mutation, hipicidin measurement.	The findings appear to independently corroborate BMP6 as a novel gene to be added to the list of mutant genes involved in determining the phenotype of iron overloading in humans.
Evaluation of a bone morphogenetic protein six variant as a cause of iron loading (2018).[21]	Cameron J *et al.*	This study aimed to characterize the molecular function of the identified BMP6 variant.	Serum ferritin, transferrin saturation (TS), alanine aminotransferase (ALT), aspartate aminotransferase (AST), and gamma-glutamyl transferase	The data from this study suggest no functional relationship between the p.Q118dup BMP6 pro-peptide variant and iron overload.
Bone morphogenetic protein 6 (BMP-6) modulates lung function, pulmonary iron levels, and cigarette smoke-induced inflammation (2018)[22]	F. M. Verhamme *et al.*	If BMP-6 is important for normal lung function?	Serum iron, lung histology, lung function, pulmonary inflammation	The findings imply that BMP-6 is crucial for proper lung function and that BMP-6 downregulation, as seen in individuals with chronic obstructive pulmonary disease (COPD), contributes to pulmonary inflammation following cigarette smoking exposure.
Expression of serum BMP6 and hepcidin in cancer-related anemia (2020).[23]	Zhen Cheng *et al.*	Study the function of human bone morphogenetic protein-6 (BMP6) and hepcidin in cancer-related anemia.	Levels of Hemoglobin (Hb), serum C-reactive protein (CRP), BMP6, hepcidin, and ferritin (SF)	Anemia is linked to high c reactive protein (CRP) and hepcidin overexpression in patients with elevated CRP. BMP6 and hepcidin. In persons with high CRP, anemia is connected to hepcidin overexpression, whereas BMP6 overexpression is linked to anemia.

Regulating gene transcription is the end result in any instance.[10]

Bone Morphogenetic Protein 6

The major endogenous regulator of hepcidin production is bone morphogenetic protein 6 (BMP6), which belongs to the transforming growth factor (TGF) family (1). BMP6 appears to be largely produced by non-parenchymal cells in the liver in response to hepatocyte iron reserves (2) and by duodenal enterocytes in responding to dietary iron. It has received a wide range of applications since it was discovered and some of recent studied are listed in Table 1.

By binding to hemojuvelin (HJV), a membrane glycophosphatidylinositol-linked BMP coreceptor required for efficient hepcidin induction and BMP receptors on the surface of hepatocytes, BMP6 begins a signaling cascade.[10]

The development of the SMAD1/5/8–SMAD4 complex, which translocates to the nucleus and activates the promoter of the hepcidin gene, is triggered by BMP6 binding (HAMP). The BMP6-SMAD regulatory pathway is potentiated by HJV.[10]

BMP6 levels rise in response to an increase in body iron levels, resulting in an increase in BMP-SMAD signaling. Hepcidin synthesis due to enhanced BMP SMAD signaling is also increased.[11]

The expression of hepcidin, a peptide hormone mostly released by hepatocytes, is tightly regulated to maintain systemic iron homeostasis by an elegant but poorly understood process. By binding and promoting the down-regulation of ferroportin, the only known iron exporter, hepcidin inhibits the efflux of iron out of intestinal epithelial cells, macrophages, and hepatocytes.[12,13]

Inappropriately high levels of hepcidin result in iron accumulation in macrophages and hepatocytes and a lack of iron export from the intestinal epithelial cells into the bloodstream, which leads to iron deficiency anemia.[14]

The canonical BMP-signaling pathway is initiated upon a BMP ligand binding to a BMP receptor (BMPR) complex on the cell surface, which activates the receptor to trigger the phosphorylation of SMAD1, SMAD5, and SMAD8 in the cytoplasm.[15] The expression of *BMP6* mRNA in the liver is upregulated by increased iron stores in the liver.[16-18]

IMPLICATIONS AND CONTRIBUTION TO KNOWLEDGE

BMP6 has many functions that make it clinically important for study. “It has been reported that BMP6 improves glycemia in Type 2 diabetes (T2D) mice and regulates glucose metabolism in hepatocytes representing an exciting prospect for future treatments of diabetes. Also, BMP 6 play an important role in the bone remolding and healing. Furthermore, BMP-6 has a role in signaling normal B cell biology and pathologic conditions like B cell malignancies and autoimmune disorders. Since the BMP6 is the key endogenous regulator of hepcidin production, a role in erythropoiesis and iron homeostasis, this review could be clinically important for many studies, particularly for those looking into the use of recombinant BMP 6 in the treatment of various body disorders linked to BMPs. also, it might provide light on the relationship of BMPs, which is a central regulator of circulating iron in anemia patients, and their role in iron-related illnesses.[19-24]

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