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Hepcidin: A Lifesaver

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Abstract

The role of iron homeostasis mechanism is summarized in this article. Iron plays an important role in managing bodily functions such as growth and development, makes hemoglobin, and some hormones. Hepcidin acts differently in different conditions such as if the body needs more oxygen, the hepcidin levels go down allowing iron to enter the plasma and if the amount of the iron present is more than needed, hepcidin levels increase. Hepcidin, enough amount present in the body, having the ability to protect the body against infectious and genetic diseases could function exactly opposite of saving life in case of insufficient amount of a lifesaver hormone, “hepcidin”. Few examples of the diseases caused by low hepcidin are tuberculosis, and hemochromatosis.

What is Hepcidin?

A cysteine-rich peptide containing 25 amino acids and four disulfide bridges, hepcidin (hepatic bactericidal protein), is produced in the liver as the final mediator in a complex pathway to regulate iron levels in the human body[7]. The available amount of iron for essential bodily functions, like making hemoglobin, and erythrocytes, is regulated by hepcidin, as well as limiting the available amount of iron in the body to avoid iron overload in the cells[4].

How the Hepcidin act?

Iron homeostasis is regulated by hepcidin. Hepcidin levels increase due to the increased levels of iron storage, infection, and inflammation. Low tissue oxygen or increased erythropoietic demand reduce hepcidin concentration. When the iron levels are decreased, or more iron is required to carry out the cellular processes, the hepcidin levels go down as it would help iron to enter the plasma[5]. A feedback loop present between the iron and the hepcidin works as a bridge, to trigger an appropriate physiological concentration of iron in case of lower iron levels in the plasma[5].

Molecular Mechanism of Hepcidin: Activators

HJV is a BMP (Bone Morphogenetic Protein which regulates hepcidin expression) co-receptor, proved a link between the bone morphogenetic protein (BMP) signaling pathway and iron metabolism in Figure 1[2].

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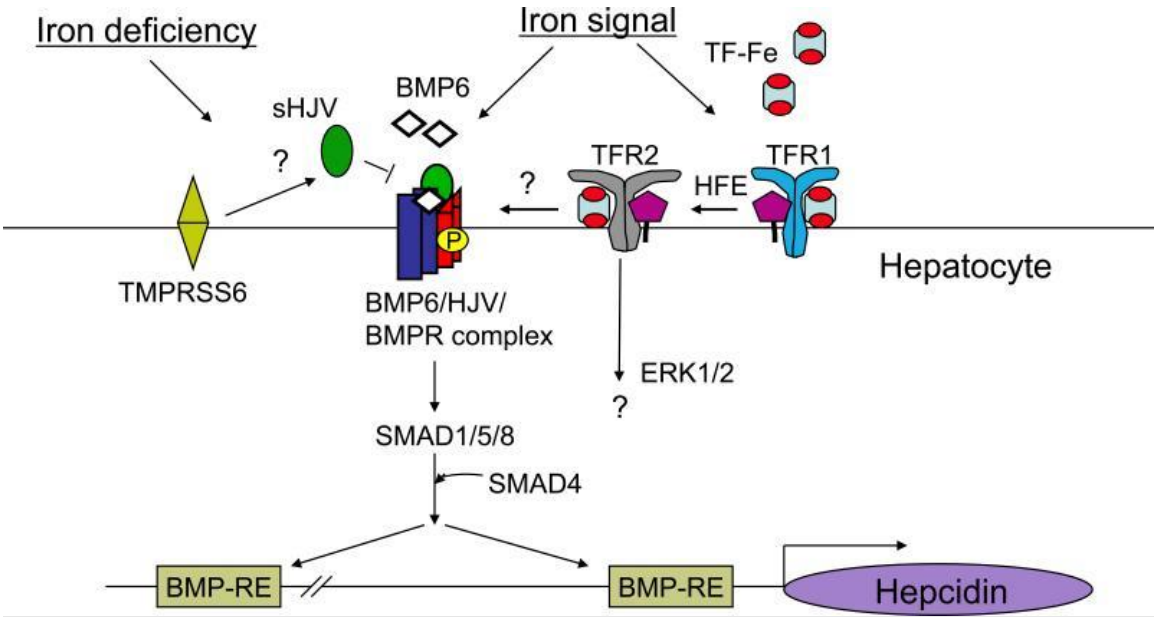

Figure 1: A diagram showing the role of bone morphogenetic protein (BMP) signaling pathway, HJV, HFE, and TFR2 to sense iron and regulate hepcidin in the liver. When responding to iron, to activate the SMAD1/5/8 pathway, BMP6 binds to the HJV. Activated SMAD1 directly binds to the BMP and REs to induce hepcidin transcription. To bind HFE to TFR1, TF-Fe causes HFE displacement to create a complex with TFR2 and TF-Fe to induce hepcidin expression. TMPRSS6, the serine protease, works to suppress hepcidin expression if iron deficiency is detected in the body[2].

Bone morphogenetic protein (BMP) is part of the transforming growth factor β (TGF - β) which binds to the cell-surface type I and type II serine-threonine kinase receptors. After the formation of the complex, the process of phosphorylating continues from type I receptors phosphorylating type II receptors to SMAD1, SMAD5, and SMAD8 proteins. If there are low levels of BMP ligands, the HJV would bind to BMP ligands and receptors to enhance intracellular SMAD signals. BMP-SMAD signals are responsible for increasing hepcidin expression at the transcriptional level[2]. The importance of the BMP-HJV-SMAD signaling pathway in maintaining hepcidin expression, and iron homeostasis *in vivo*, is supported by different lines of evidence. A test result proved that targeting disruption of the SMAD4 in the mouse liver could lead to low hepcidin levels and iron overload[2].

Molecular mechanism: Iron

Iron activates BMP6-HJV-SMAD signaling pathway to stimulate hepcidin expression[5]. In the hepatocyte culture, a BMP-SMAD signaling would decide if the holotransferrin will increase the hepcidin expression or not, as the holotransferrin is blocked by the BMP-SMAD signaling pathway inhibitors[2]. The BMP inhibitors work the same in zebra fish, blocking the increase of hepcidin expression, proving that iron activates the BMP6-SMAD signaling pathway in the liver, and depends on the BMP-SMAD signaling to increase hepcidin expression. However, the researchers are still trying to understand the mechanism in depth that senses iron levels to increase BMP6-HJV-SMAD signaling[2]. Increase in the iron levels make the holotransferrin bind to TFR1 in the liver, displacing HFE, that results in increased hepcidin levels through on interaction with TFR2 and transferrin as shown in Figure 1. All the information provided above concludes that whether HFE and TFR2 induce hepcidin expression by interacting with the BMP6-HJV-SMAD or separate, but the signaling pathway is not fully understood[2].

What if the human body fails to produce enough Hepcidin?

Infectious Disease (Mycobacterium Tuberculosis):

Researchers have concluded that a single nucleotide change in a gene, that is responsible for the hepcidin production, could make a human body prone to extrapulmonary tuberculosis as a body with this condition

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tend to produce significantly less amount of hepcidin if exposed to infection, Mycobacterium tuberculosis, a powerhouse of TB[6]. The less the Hepcidin, the less the ability of macrophages to destroy Tuberculosis.

Not being stopped by security upon entering the body, would allow the bacteria to slowly spread and destroy the lungs and other parts of the body travelling through the circulation, eventually leading a human being to death[6].

Genetic Disease (Hemochromatosis):

A genetic disease, hemochromatosis (HH), is caused when the body fails to produce enough hepcidin, resulting in absorbing more iron than needed. This condition can be treated by removing the surplus metal, up to 29 liters per year in extreme cases. A few years back, this was the only way to save a precious human life, regardless of how uneasy or painful it would be for every patient. But now, the science has shown its life-saving magic, and the scientists have been successful to produce minihepcidin (a molecule that works the same as the hepcidin), effectively reversing iron overload, infections, and bacteria that loves to stay at a place where there is iron present[1].

Hepcidin being a lifesaver for the Human Body?

As the hepcidin takes the responsibility to fight off the killer bacteria, responsible of causing bacterial pneumonia, makes it a lifesaver for the patients with no hope left. In the cases of pneumonia quickly growing resistant to antibiotics, hepcidin comes up as ray of a new life for vulnerable patients. A researcher, Kathryn Michels said, a new drug is being made to carry out the same function as hepcidin and would be effective to control iron overload in conditions like hemochromatosis and treat infections such as pneumonia[3].

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