

# Update on Hepcidin Regulation in Different Disorders

**Pierre Brissot, MD**

Hepcidin is a small peptide of only 25 amino acids, yet it is of major pathophysiologic importance since it is the key hormone regulating iron metabolism. Encoded by the *HAMP* gene located on chromosome 19 and primarily produced by hepatocytes, its main function is to decrease plasma iron concentration through action at two targets. On one hand, hepcidin decreases duodenal iron absorption; on the other hand, it decreases iron release from the spleen macrophages into the plasma.

Physiologically, hepcidin levels are modulated by a feedback mechanism: when body iron load increases, hepcidin synthesis is increased, leading to decreased plasma iron, and vice versa. At the cellular level, hepcidin regulates iron by binding with ferroportin, the only protein currently known to be a cellular iron exporter. When plasma hepcidin concentration is elevated, the rate of hepcidin-ferroportin binding and subsequent ferroportin internalization and degradation lead to a decreased release of iron into the plasma. Hepcidin transcription implicates numerous proteins through several molecular cascades. Major involved proteins are transferrin receptor 1, transferrin receptor 2, the bone morphogenic (BMP) 6-haemojuvelin-BMP receptor complex, and matriptase-2 (TMPRSS6).

Pathophysiologically, hepcidin dysregulation is involved in two main groups of disorders. The first group includes diseases directly related to iron dysregulation. Most forms of genetic iron overload (eg, haemochromatoses types 1, 2, and 3) are characterized by inappropriately low hepcidin levels accounting for parenchymal (hepatocytes, pancreatic cells, and cardiac cells) iron excess. Conversely, chronic hepcidinaemia can lead to chronic anaemias. In the anaemia of chronic disease, an acquired condition, hepcidin overproduction is related to the stimulation of hepcidin through a special pathway involving interleukin (IL) 6 and signal transducer and activator of transcription (STAT) 3. Iron-refractory iron deficiency anaemia (IRIDA) is a recently identified genetic entity related to matriptase-2 mutations. The second group of disorders is not directly caused by hepcidin dysregulation but implicate variations of hepcidin production. Examples include alcoholism and hepatitis C virus infection in which hypohepcidinaemia could contribute to the moderate iron excess sometimes observed in these

conditions. Another disorder is the polymetabolic syndrome in which hyperhepcidinaemia could account for the slight iron overload, mainly of macrophagic location, observed in this common syndrome.

Hepcidin discovery has been a major breakthrough in the field of iron metabolism. Not only has it proven essential in dissecting the physiology of iron metabolism, but also to identifying a series of genetic and acquired iron-related disorders and paving the road for innovative therapeutic approaches.

## **Suggested Readings**

Andrews NC. Forging a field: the golden age of iron biology. *Blood*. 2008;112:219-230.

Andriopoulos B, Corradini E, Xia Y, et al. BMP6 is a key endogenous regulator of hepcidin expression and iron metabolism. *Nat Genet*. 2009;41:482-487.

Brissot P, Troadec MB, Bardou-Jacquet E, et al. Current approach to hemochromatosis. *Blood Rev*. 2008;22:195-210.

Finberg KE, Heeney MM, Campagna DR, et al. Mutations in TMPRSS6 cause iron-refractory iron deficiency anemia (IRIDA). *Nat Genet*. 2008;40:569-571.

Lee PL, Beutler E. Regulation of hepcidin and iron-overload disease. *Annu Rev Pathol*. 2009;4:489-515.

Meynard D, Kautz L, Darnaud V, Canonne-Hergaux F, Coppin H, Roth MP. Lack of the bone morphogenetic protein BMP6 induces massive iron overload. *Nat Genet*. 2009;41:478-481.

Piperno A, Mariani R, Trombini P, Girelli D. Hepcidin modulation in human diseases: from research to clinic. *World J Gastroenterol*. 2009;15:538-551.