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Carine Fillebeen, PhD
Research Associate
Lady Davis Institute

Edouard Charlebois
PhD Candidate, Department of Medicine
McGill University

Kostas Pantopoulos, PhD
Senior Investigator, Lady Davis Institute
Professor, Department of Medicine, McGill University

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Hepcidin-mediated hypoferremic response to acute inflammation requires a threshold of Bmp6/Hjv/Smad signaling

Carine Fillebeen, Nicole Wilkinson, Edouard Charlebois, Angeliki Katsarou, John Wagner and Kostas Pantopoulos

Iron balance is maintained by hepcidin, a liver-derived peptide hormone that inhibits iron entry into the bloodstream. Iron-dependent induction of hepcidin is critical for preventing excessive dietary iron absorption and depends upon signaling via bone morphogenetic protein 6 (BMP6) and hemojuvelin (HJV), a BMP coreceptor. Disruption of this pathway leads to hepcidin deficiency that causes hereditary hemochromatosis, a disease of systemic iron overload. During infection, hepcidin is induced by the inflammatory cytokine interleukin 6 (IL-6); this promotes hypoferremia to prevent iron utilization by invading bacteria. If inflammation remains unresolved, persistent hypoferremia due to aberrant overexpression of hepcidin limits iron's availability for erythropoiesis and contributes to the "anemia of inflammation". This is a common side effect of chronic inflammatory disorders, such as rheumatoid arthritis, inflammatory bowel disease, chronic kidney disease and some cancers, and its effective treatment remains an unmet medical need. Using an HJV knock-out mouse model, this paper reveals a critical role of BMP6/HJV in the inflammatory response of hepcidin, in crosstalk with IL-6. Consequently, pharmacological targeting of BMP6/HJV may prevent over-production of hepcidin and thereby offer new options for treating anemia of inflammation.

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