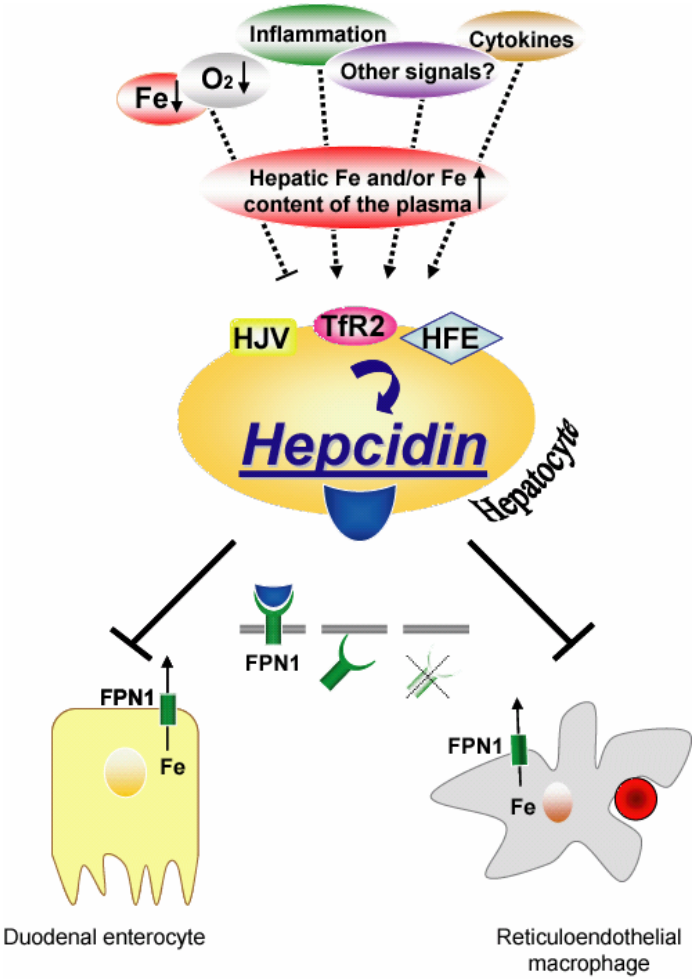
Hepcidin modulation and regulation during inflammation

The iron-regulatory hormone and hepatic acute phase protein hepcidin is strongly implicated in the anaemia of inflammation (AI), a common clinical disorder that affects patients with acute and chronic infections, trauma, inflammatory disorders and malignancies. The disease is characterized by hypoferremia, low serum iron-binding capacity and normal to elevated ferritin levels. Several cytokines that participate in the pathogenesis of AI (e.g. IL-1, TNF-α and IL-6) also modulate iron metabolism. Importantly, hypoferremia is induced within few hours after injection of hepcidin into mice. Hepcidin binds to the iron export protein ferroportin and triggers its degradation to decrease iron egress from duodenal enterocytes, macrophages and hepatocytes, thus contributing to the hypoferremia that hallmarks AI. Hepcidin may hence be considered to be a principal iron regulatory hormone, a key mediator of AI, and a bridge between innate immunity and iron metabolism.

In addition to proinflammatory cytokines, HFE, TfR2 and hemojuvelin (HJ), three genes mutated in the hereditary hemochromatosis (HH), control appropriate hepcidin expression. Recent work demonstrates that HJ is a bone morphogenetic protein (BMP) 2 coreceptor that mediates BMP signalling. BMP positively regulates hepcidin expression, a response that is enhanced by HJ expression. Further work supports a role for the TGF-β pathway and SMAD4 in the transcriptional activation of hepcidin in response to iron overload or IL-6. Hepcidin expression is further controlled by the CCAAT/enhancer-binding protein (C/EBP).

Little information is presently available about promoter elements and transcription factors that control hepcidin expression. To address this issue, I established a cell-based assay system to investigate the cis-acting elements and trans-acting factors for hepcidin expression under steady state conditions and in response to inflammatory stimuli. I am particularly interested in the identification of signalling pathways that mediate expression of hepcidin dependent on the HH proteins to further our understanding of molecular mechanisms involved in HH.



Iron, hypoxia, inflammation and infection as well as cytokines either affect hepcidin expression directly or via changes in the hepatic iron content or the iron available in the serum. Studies of different HH subtypes suggest that HFE, HJV and TfR2 are involved to maintain appropriate systemic hepcidin levels. Hepcidin then inhibits iron export (e.g. from intestinal enterocytes or monocytes) by affecting the stability of the iron exporter ferroportin (Fpn).