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Targeting the Hepcidin Binding Site of Ferroportin

Hepcidin is a peptide hormone secreted in response to iron loading and inflammation. Hepcidin regulates iron homeostasis by binding to the iron exporter ferroportin, inducing its internalization and degradation. Internalization of ferroportin results from the activation of the protein kinase Jak2 and phosphorylation of ferroportin. Hepcidin-activated Jak2 also phosphorylates the transcription factor Stat3, resulting in a transcriptional response.

Treatment of ferroportin expressing macrophages with hepcidin results in changes in a wide variety of genes. Changes in transcript levels for many of the affected genes is a direct effect of hepcidin and is dependent on the presence of Stat3. Hepcidin-mediated transcriptional changes modulate endotoxin induced transcription in both cultured macrophages and in vivo, suppressing IL-6 and TNFa. Hepcidin-mediated transcription in mice suppresses toxicity and morbidity due to single doses of endotoxin, poly(I:C) or turpentine.

These results suggest a new function for hepcidin in modulating acute inflammatory responses.