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About

Over the last decade there has been an accumulation of evidence that the 25 amino acid anti-microbial peptide hepcidin is the much sought after regulator of body iron metabolism.1,2 This hepatic hormone was originally discovered by three laboratories working independently.3,4,5 With its identification has come a greater understanding of the molecular pathogenesis of a variety of disorders of iron metabolism, including hereditary hemochromatosis. 2

It has now become widely accepted to be induced by multiple stimuli including high body iron, infection and inflammation, whilst there is evidence that this peptide is suppressed by iron deficiency anaemia, hypoxia and erythropoietin.1,2 The exact molecular signalling pathways involved in its regulation is still currently under study, however what is clear is that hepcidin mediates its effects by binding and causing the internalisation of the iron efflux protein ferroportin.6 In the context of inflammation and infection hepcidin is crucial to mediating the anaemia of chronic disease, which simplistically is the result of hepcidin mediating a loss of cellular iron efflux at the level of macrophages resulting in an imbalance in the circulating iron pool in relation to the bodies demand for iron.2

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Furthermore, research performed in our laboratory has implicated hepcidin in the process of cancer.7 In particular we have demonstrated that in colorectal carcinogenesis there is a modulation in cellular iron transport proteins, namely increased expression of proteins involved in cellular iron acquisition (transferrin receptor-1 and DMT-1) and a loss of expression and function in the cellular iron efflux proteins hephaestin and ferroportin respectively.8 We speculate that this latter loss of ferroportin function is mediated by increased hepcidin expression. These events ultimately culminate in the accumulation of cellular iron which we believe is crucial to driving oncogenic signalling and thus a more aggressive behaviour.9

To date the study of hepcidin has been hampered by the lack of a commercially available ELISA assay. Whether ever such an assay will become available is unclear because any such assay must be able to distinguish between variants of hepcidin; namely the precursor prohepcidin and also the degradation products hepcidin 20 and 22.10 On the basis that levels of prohepcidin have largely failed to correlate with body iron levels would suggest that any such ELISA must be purely specific for the bioactive hepcidin 25 and must not cross react with any of the other variants. Hitherto the scientific community has turned its attention to mass spectrometry to measure hepcidin in biological fluids.7,11-15 However, several of these assays have failed to use an internal calibrant of hepcidin and in some instances where this has been used the internal calibrant is not hepcidin 25 but a variant, which makes quantitation difficult and subject to error.

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