Modifiers of Iron Overload in Hereditary Hemochromatosis: novel genetic and immunological players

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Summary:
This project integrates the general objective of the IBMC research group: Basic & Clinical Research on Iron Biology”, which is to address the complex relationships between iron homeostasis and the immune system. Hereditary Hemochromatosis (HH) constitutes an ideal clinical model to study the interactions between lymphocytes and iron homeostasis. It is an MHC class I linked disorder of iron overload with a great heterogeneity in clinical expression, varying from a simple biochemical abnormality to a severe clinical picture of liver cirrhosis or hepatocarcinoma. Our group first demonstrated that the concomitant inheritance of a defective number of peripheral blood CD8+ T lymphocytes significantly influences the clinical severity of iron overload and that the genetic transmission of CD8+ T cell numbers is associated with particular MHC haplotypes (1,2). The next approach to this question is to position a candidate major locus implicated in the genetic transmission of CD8+ T lymphocytes, and/or the modulation of iron homeostasis, by Deep Sequencing of the chromosomal region between HFE and HLA-DR (in collaboration with the Genecore facility at EMBL, Heidelberg) in well characterized HH patients and controls.

Besides the genomic approach to look for potential modifiers of iron overload in HH, a candidate gene approach is also needed, and novel players are to be considered. Of relevance to this question is the recent finding of iron overload in mice defective in CCL2 (MCP1 in humans), a lymphocyte derived cytokine involved in the recruitment of monocytes to sites of inflammation. In a collaborative study with Martina Muckenthaler at EMBL, Heidelberg, we will explore the role of MCP1 as a putative modifier of iron overload in patients with HH, in combination with a deeper characterization of the CCL2 -/- animal model.

References