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HFE, iron homeostasis and genetic hemochromatosis

In the last few years there have been major advances in our understanding of the molecular control of cellular iron metabolism and of molecular genetics of disorders characterized by abnormal iron absorption.

A first fundamental step has been the recognition that the synthesis of transferrin receptor (TfR) and ferritin is regulated by cytoplasmic mRNA-binding proteins, now identified as the iron regulatory proteins (IRPs).[1] IRP1 and IRP2 control the expression of genes involved in iron metabolism whose transcripts contain RNA-stem-loop structures known as iron-responsive elements (IREs). Based on this knowledge, clinical investigators have recently clarified the molecular pathogenesis of the hereditary hyperferritinemia/cataract syndrome (HHCS).[2] This is a new genetic disorder inherited as an autosomal dominant trait and characterized by elevated serum ferritin not related to iron overload and congenital nuclear cataract. Several point mutations in the IRE of ferritin light-chain mRNA have been found in the families so far described.[3,4] These mutations have been shown to prevent IRP binding variably, thus leading to excessive L-ferritin synthesis. HHCS stands as a noteworthy example of a human genetic disorder that arises from RNA mutations within a protein binding site, and in which the energetics of the binding interaction determine the severity of the disease.[5] This exemplifies a new paradigm in which polymorphisms or mutations in mRNA cis-acting elements may be responsible for phenotypic variability in normal and disease states.[6]

Another major step has been the cloning of HFE, the gene of HLA-related genetic hemochromatosis.[7] HFE is an atypical HLA-class I-like gene, mapping approximately 4 megabases telomeric to HLA-A. Since the first report it was considered as a strong candidate gene for hemochromatosis, as most patients were found to be homozygous for a missense mutation changing cysteine at position 282 to tyrosine (C282Y) while other patients were found to carry a second mutation that changes histidine at position 63 to aspartic acid (H63D).[8] It is now well established that most patients with HLA-related genetic hemochromatosis are homozygous for the C282Y mutation while others are compound heterozygotes for C282Y and H63D. Homozygosity for C282Y is found in more than 90% of North Europeans clinically diagnosed with idiopathic hemochromatosis. However, recent studies have shown a lower frequency (64%) for C282Y homozygosity in severely iron-loaded Italian patients.[9] The fact that significant iron loading can occur in individuals with no evidence of HFE mutations or abnormalities in erythropoiesis suggests that genes other than HFE are involved in iron loading.[10] Indeed, juvenile genetic hemochromatosis,[11] the so-called African iron overload,[12,13] and other conditions[14] are examples of genetic syndromes of iron overload due to genes other than HFE. In addition, although HFE-related genetic hemochromatosis is genetically homogeneous, its phenotypic expression is variable, depending on both environmental and genetic factors.[15]

Clearly, iron homeostasis is regulated by several genes that we are just starting to know. The first one, HFE, is far from being fully characterized. Several studies clearly indicate that HFE is involved in the regulation of iron homeostasis[16] and that its mutations are very likely responsible for the human disease.[17,18] However, both the role of HFE in the normal iron metabolism and the mechanisms by which C282Y and H63D disrupt the normal functioning of HFE have yet to be clearly defined. In this issue of Haematologica, a Finnish and an Italian group report on the expression of normal and mutant HFE in different tissues.[19,20] Their works represent steps forward to a deeper insight into the molecular pathogenesis of genetic hemochromatosis.

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