Novel genes, proteins, and inherited disorders of iron overload: iron metabolism is less boring than thought

Until a few years ago, only three proteins of iron metabolism were known: transferrin, transferrin receptor and ferritin. From a clinical point of view, a step forward was the observation that both ferritin and transferrin receptor have soluble forms. The level of serum ferritin parallels the concentration of storage iron within the body, regardless of the cell type in which it is stored, so that determining serum ferritin levels represents a very convenient means of assessing iron balance in clinical practice.[1] The soluble transferrin receptor assay is much less employed in clinical settings, despite the fact that its determination is a convenient way of assessing erythroid activity.[2-4]

Of central importance to our understanding of iron metabolism was the later discovery that cellular iron homeostasis in mammalian cells is maintained by the co-ordinated regulation of transferrin receptor and ferritin synthesis that occurs at the translational level and is mediated by cytoplasmic mRNA-binding proteins, known as iron regulatory proteins (IRPs).[5] These proteins are capable of sensing cellular iron status and of interacting with mRNA stem-loop structures known as iron-responsive elements (IREs). Mutations that cause disease through increased efficiency of mRNA translation have been discovered, allowing recognition of hereditary hyperferritinemia/cataract syndrome and defining translational pathophysiology as a novel mechanism of human disease.[6]

Following the identification of HFE as the gene of HLA-related genetic hemocromatosis, homozygosity for the HFE C282Y mutation has been found in more than 90% of North European[7] and more than 80% of American patients of European origin clinically diagnosed as having genetic hemochromatosis.[8] However, markedly lower frequencies (50-64%) for C282Y homozygosity have been found in severely iron-loaded patients belonging to populations of Southern Europe.[9,10] Additional HFE mutations have been reported, the most frequent one being the A193T mutation leading to the S65C missense substitution,[11,12] while no conclusive evidence of abnormal gene expression in heterozygotes has been found.[13] The precise function of the HFE protein in physiologically inhibiting iron absorption[14] is not fully clear. The HLA-related hemochromatosis is defined as hemochromatosis HFE (OMIM 235200).

The availability of molecular tools for studying HFE mutations has allowed investigators to identify novel forms of non-HFE related genetic hemochromatosis (GH). Fifteen years ago we described juvenile GH as a distinct nosological entity.[15] Patients present with hypogonadotropic hypogonadism, and, unless proper treatment is started, die early because of cardiac dysfunction. In a collaborative study, the juvenile locus was later mapped to chromosome 1q.[16] Juvenile genetic hemochromatosis is defined as hemochromatosis type 2, or HFE2 (OMIM 602390). This gene must play a crucial role in iron metabolism, perhaps acting as the erythroid regulator of iron absorption hypothesized by Clement Finch decades ago.

In a few Italian families with non-HFE related hereditary hemochromatosis Camaschella *et al.* later found that affected individuals were homozygous for point mutations in the gene coding transferrin receptor 2 (TfR2), suggesting that this may represent the molecular basis for this familial iron overload syndrome.[17-19] TfR2 is a member of the *transferrin-like receptors* family with unknown function, but characterized by a restricted pattern of expression in the liver.[20] The TfR2 mutations responsible for hemochromatosis type 3, or HFE3 (OMIM 604250) appear to be private mutations.

In nearly simultaneous reports, a Dutch[21] and an Italian[22] group recently described pedigrees with atypical hemochromatosis inherited as an autosomal dominant trait. The two groups found different missense mutations in the gene encoding the iron export protein ferroportin1 (also known as IREG1, or MTP1).[23-25] This dominant type of genetic iron overload is defined as hemochromatosis type 4, or HFE4 (OMIM 606069). Ferroportin1 plays key roles in two different aspects of iron metabolism, absorption of dietary iron by duodenal enterocytes and release of iron from body stores by reticuloendothelial cells.

Nicolas *et al.*[26] recently reported severe tissue iron overload in upstream stimulatory factor 2 (USF2) knockout mice. Studies on genes that may account for the abnormalities of iron homeostasis in USF2(-/-) mice allowed the authors to identify hepcidin as the gene responsible for iron overload in these animals. This observation prompted Majore *et al.* to look for mutations in the hepcidin gene in Italian patients with non-HFE related GH. Their findings, reported in this issue,[27] are negative, but this does not exclude that hepcidin may be involved in the pathogenesis of inherited iron overload in humans, and that HFEn will be discovered in the near future.

Although the most common GH at present is the HFE-related disorder in population of Northern European extract, physicians working in other regions of the world are facing a less boring reality. Heterogeneity is challenging in both biology and clinical medicine, but it is also stimulating, inducing investigators to pursue new ideas and allowing science to progress.

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