Another link in the chain

The discovery of HFE, the gene most commonly mutated in hereditary hemochromatosis, led to the optimistic view that the molecular chain of events regulating iron homeostasis would soon be defined.1 The chain is still incomplete 7 years later. In this issue, 2 papers provide a new link. The ability to detect HFE mutations revealed that the clinical phenotype of patients homozygous for the common C282Y mutation of HFE ranges from simply an elevated transferrin saturation to organ damage due to iron overload. This observation, along with the finding in mice of strain-specific differences in liver iron metabolism, has suggested that other genes may modify the hemochromatosis phenotype.2 Genetic screens of patients with iron overload, but lacking HFE mutations, have revealed mutations in a number of other genes involved in iron metabolism including a second transferrin receptor (TfR2), the iron responsive element of H ferritin, and a hepatocyte peptide, hepcidin.2,3 A gene associated with juvenile hemochromatosis, hemojuvelin (HFE2), has been recently reported.4 All are viable candidate modifier genes.

The discovery that knock-out mice for the transcription factor USF2 exhibited iron overload led to the identification of a second downstream gene, HAMP, inadvertently silenced by the Usf2 mutation.2 HAMP proved to be the gene encoding hepcidin. Lack of hepcidin expression was shown to be responsible for the iron overload. Hepcidin, a 25–31-amino acid peptide member of the defensin family of antimicrobial peptides, is mainly expressed in the liver. Hepcidin mRNA is up-regulated by liver iron accumulation and by inflammatory stimuli. Hepcidin appears to inhibit iron export from enterocytes and macrophages. Hepcidin is not appropriately up-regulated when hepatocytes become iron loaded in HFE-associated hemochromatosis, and up-regulation of hepcidin by inflammation is likely the cause of the hypoferremia associated with the anemia of chronic disease.5 This suggests that mutated HAMP genes might modify the phenotype of HFE-associated hemochromatosis, a suggestion supported by the findings of Merryweather-Clarke et al.6

In this issue, Jacolot and colleagues (page 2835) analyzed the influence of HAMP mutations in patients with HFE-associated hemochromatosis. Nicolas and colleagues (page 2841) have used a mouse model of hemochromatosis in which Hfe has been disrupted and one allele of Hamp has been silenced by the Usf2 knock out. These articles represent a nexus of basic and clinical research and establish that HAMP modifies the hemochromatosis phenotype.

Jacolot et al found that heterozygosity for HAMP mutations was associated with marked penetrance of the hemochromatosis phenotype in C282Y homozygotes. Compound heterozygosity for a HAMP mutation and the C282Y HFE mutation was also associated with an iron overload phenotype. In the accompanying paper by Nicolas et al, similar findings were observed in mice. Hepcidin mRNA levels were decreased in Hfe−/− mice but were even lower when the Hfe−/− genotype was combined with heterozygosity for disruption of the Usf2 locus. Liver iron content was highest in Hfe−/− Usf2+/− mice. Together, these results clearly demonstrate the influence of hepcidin deficiency on the hemochromatosis phenotype but do not establish hepcidin as the sole modifier.

Simplistically, any regulated pathway consists of at least 3 components: a sensor, a signal, and a receptor. Hpecidin is an excellent candidate for a humoral signal molecule. It is sensitive to minor perturbations in iron metabolism and has a short plasma half-life. Iron absorption is influenced by at least 4 factors: erythropoiesis, body iron stores, hypoxia, and inflammation. Hepcidin transcript levels...
are affected by each of these factors consistent with hepcidin’s role as the absorptive signal. In contrast, no clear candidate has emerged as the sensor but the pathway regulating hepcidin expression appears to involve both HFE and HFE2. The search for a hepcidin receptor is a current focus of research in several laboratories. The molecular events regulating iron homeostasis have not yet been completely defined, but hepcidin is clearly an important link in the regulatory chain.

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