Ferroportin mutation in autosomal dominant hemochromatosis: loss of function, gain in understanding

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Normal iron homeostasis requires close matching of dietary iron absorption with body iron needs (1). Hereditary hemochromatosis (HH), a common abnormality of iron metabolism, is characterized by excess absorption of dietary iron despite elevated stores, and secondary damage to the liver, pancreas, and other organs (2). Classic HH is caused by mutation of the *HFE* gene and is inherited as an autosomal recessive trait. However, a substantial percentage of individuals with hemochromatosis, especially in non–Northern European populations, have no mutations in *HFE* (3). Many such cases differ from classic HH in the relative distribution of iron between the plasma, hepatocytes, and reticuloendothelial (RE) cells (4).

Pietrangelo et al. recently reported a pedigree with atypical hemochromatosis inherited as an autosomal dominant trait (5). In this issue of the *JCI*, Montosi et al. report the surprising finding that the gene mutated in these patients (*SLC11A3*) encodes the iron export protein ferroportin1 (also known as IREG1, or MTP1) (6). They conclude that the identified mutation (A77D) probably results in loss of ferroportin1 function, suggesting that the affected individuals are haploinsufficient for this gene product. In a nearly simultaneous report, Njajou et al. (7) describe a similar pedigree with autosomal dominant hemochromatosis and a different missense mutation (N144H) in the same gene. Njajou et al., however, conclude that the iron overload phenotype was likely due to gain rather than loss of ferroportin function (i.e., an activating mutation). Why the opposite conclusions?

As shown in Figure 1, ferroportin1 plays key roles in two different aspects of iron homeostasis, absorption of dietary iron by duodenal enterocytes and release of iron from body stores by RE cells (8–10). One might expect a gain-of-function mutation in ferroportin1 to lead to iron loading by increasing iron absorption. Increased ferroportin1 expression in duodenal enterocytes of patients with classic HH may contribute to their iron loading (11). However, we suggest that the primary cause of iron overload in patients with both described ferroportin1 mutations is decreased ferroportin1 function in RE cells, rather than increased function in enterocytes. While excess dietary iron absorption in classic HH leads to hepatocellular loading prior to RE cell loading (2), patients with the A77D ferroportin1 mutation demonstrate early and predominant loading of iron in RE cells. This situation is analogous to that seen with defects in the gene encoding ceruloplasmin (*Cp*). The ferroxidase activity of ceruloplasmin converts ferrous iron
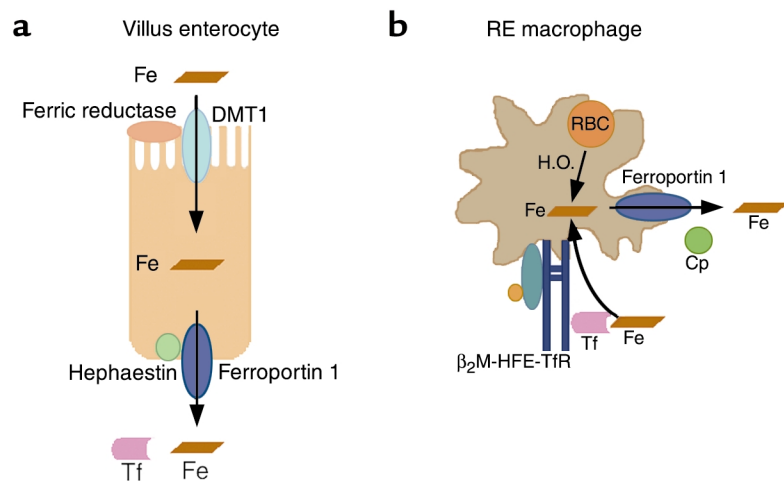

Figure 1
Ferroportin1 in absorption of dietary iron (**a**) and release of iron stores (**b**). (**a**) Dietary nonheme iron at the luminal surface of the villus enterocyte is reduced by ferric reductase and taken up by DMT1. The iron may be retained, or transported across the basolateral surface by ferroportin1 (blue oval), oxidized by hephaestin, and bound to transferrin (Tf) for plasma transport. (**b**) Transferrin-bound iron (Tf-Fe) is taken up by the RE cell by a complex containing β_2-microglobulin (β_2M), the transferrin receptor (TfR), and the HFE protein (teal oval), which is defective in the classic, autosomal recessive form of hemochromatosis. Heme iron taken up by phagocytosis of senescent erythrocytes (RBC) is released by heme oxygenase (H.O.). The iron may be stored as ferritin, or exported via ferroportin1, after which it is oxidized by ceruloplasmin (Cp), and bound to transferrin for plasma transport. Hephaestin and ceruloplasmin, both indicated by green circles, are structurally similar and perform analogous functions, but their patterns of expression are distinct. Two recent papers, including one in this issue of the *JCI*, have implicated ferroportin in an atypical, autosomal dominant form of hemochromatosis (6, 7).

to the ferric state, which is necessary for iron binding to the plasma transport protein transferrin. Patients with aceruloplasminemia (12) and *Cp* knockout mice (13) have impaired release of iron from RE cells but unimpaired release of iron from enterocytes, as the enterocyte ferroxidase activity is provided by the ceruloplasmin homologue hephaestin (14). Similarities between patients with aceruloplasminemia and the A77D mutation in ferroportin1 include increased RE cell iron, subsequent hepatocellular iron loading, relatively low transferrin saturations (despite high ferritin levels), and mild anemia. Patients with the N114H mutation likewise show hepatocellular iron loading with relatively low transferrin saturations and high ferritin levels. (RE iron status and hemoglobin concentrations of these patients were not discussed.)

Haploinsufficiency for ferroportin would (at least initially) favor low serum iron by decreasing dietary iron absorption and by impairing iron release from macrophages. This could explain the low transferrin saturations, the anemia early in life, and the sensitivity to phlebotomy observed in many of these patients. The hepatocellular iron loading might be explained by the secondary effects of the "erythropoietic regulator" stimulating intestinal iron absorption, or possibly by ferroportin1 haploinsufficiency in hepatocytes. Ferroportin1 is also highly expressed in placenta, where it is thought to mediate maternal-fetal iron transport (15). No mention is made in either report of neonatal anemia in these patients, suggesting that haploinsufficiency does not limit this process. However, mutations of both *ferroportin1* alleles in zebrafish lead to early embryonic lethality because of failure of iron transport from the yolk sac (9).

Several questions remain, including whether both the ferroportin missense mutations indeed lead to loss of function, the frequencies of the two mutant alleles, and how haploinsufficiency for ferroportin1 interacts with mutations in *HFE*. The effect of such interactions is of interest, as it appears that manifestation of the HH phenotype is greatly influenced by genetic modifiers (16, 17). Identifying the specific gene mutations contributing to iron overload should allow genotype-phenotype correlation, leading, in turn, to more accurate genetic counseling regarding prognoses and associated illnesses. Whether a gain- or loss-of-function mutation, each one identified brings us closer to a complete understanding of the many proteins that interact to regulate iron homeostasis.

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