GENETIC BASIS

A homozygous G to A mutation in the *HFE* gene resulting in a cysteine to tyrosine substitution at position 282 (C282Y) is the most common mutation. It is identified in 85–90% of patients with hereditary hemochromatosis in populations of northern European descent but is found in only 60% of cases from Mediterranean populations (e.g., southern Italy). A second, relatively common *HFE* mutation (H63D) results in a substitution of histidine to aspartic acid at codon 63. Homozygosity for H63D is not associated with clinically significant iron overload. Some compound heterozygotes (e.g., one copy each of C282Y and H63D) have mild to moderately increased body-iron stores but develop clinical disease only in association with cofactors such as heavy alcohol intake or hepatic steatosis. Thus, *HFE*-associated hemochromatosis is inherited as an autosomal recessive trait; heterozygotes have no, or minimal, increase in iron stores. However, this slight increase in hepatic iron can act as a cofactor that may modify the expression of other diseases such as porphyria cutanea tarda (PCT) or nonalcoholic steatohepatitis.

Mutations in other genes involved in iron metabolism are responsible for non-*HFE*-associated hemochromatosis, including juvenile hemochromatosis, which affects persons in the second and third decades of life (Table 428-1). Mutations in the genes encoding hepcidin, transferrin receptor 2 (TfR2), and hemojuvelin (Fig. 428-1) result in clinicopathologic features that are indistinguishable from HFE-associated hemochromatosis. However, mutations in ferroportin, responsible for the efflux of iron from enterocytes and most other cell types, result in iron loading of reticuloendothelial cells and macrophages as well as parenchymal cells.

PATHOPHYSIOLOGY

Normally, the body-iron content of 3–4 g is maintained such that intestinal mucosal absorption of iron is equal to iron loss. This amount is approximately 1 mg/d in men and 1.5 mg/d in menstruating women. In hemochromatosis, mucosal absorption is greater than body requirements and amounts to 4 mg/d or more. The progressive accumulation of iron increases plasma iron and saturation of transferrin and results in a progressive increase of plasma ferritin (Fig. 428-2). A liver-derived peptide, hepcidin, represses basolateral iron transport in the intestine and iron release from macrophages and other cells by binding to ferroportin. Hepcidin, in turn, responds to signals in the liver mediated by HFE, TfR2, and hemojuvelin (Fig. 428-1). Thus, hepcidin is a crucial molecule in iron metabolism, linking body stores with intestinal iron absorption.

The *HFE* gene encodes a 343-amino-acid protein that is structurally related to MHC class I proteins (HFE). The basic defect in *HFE*-associated hemochromatosis is a lack of cell surface expression of HFE (due to the C282Y mutation). The normal (wild-type) HFE protein forms a complex with β_2-microglobulin and transferrin receptor 1 (TfR1). The C282Y mutation completely abrogates this interaction. As a result, the mutant HFE protein remains trapped intracellularly, reducing TfR1-mediated iron uptake by the intestinal crypt cell. This impaired TfR1-mediated iron uptake leads to upregulation of the divalent metal transporter (DMT1) on the brush border of the villus cells, causing inappropriately increased intestinal iron absorption (Fig. 428-1). In advanced disease, the body may contain 20 g or more of iron that is deposited mainly in parenchymal cells of the liver, pancreas, and heart. Iron may be increased 50- to 100-fold in the liver and pancreas

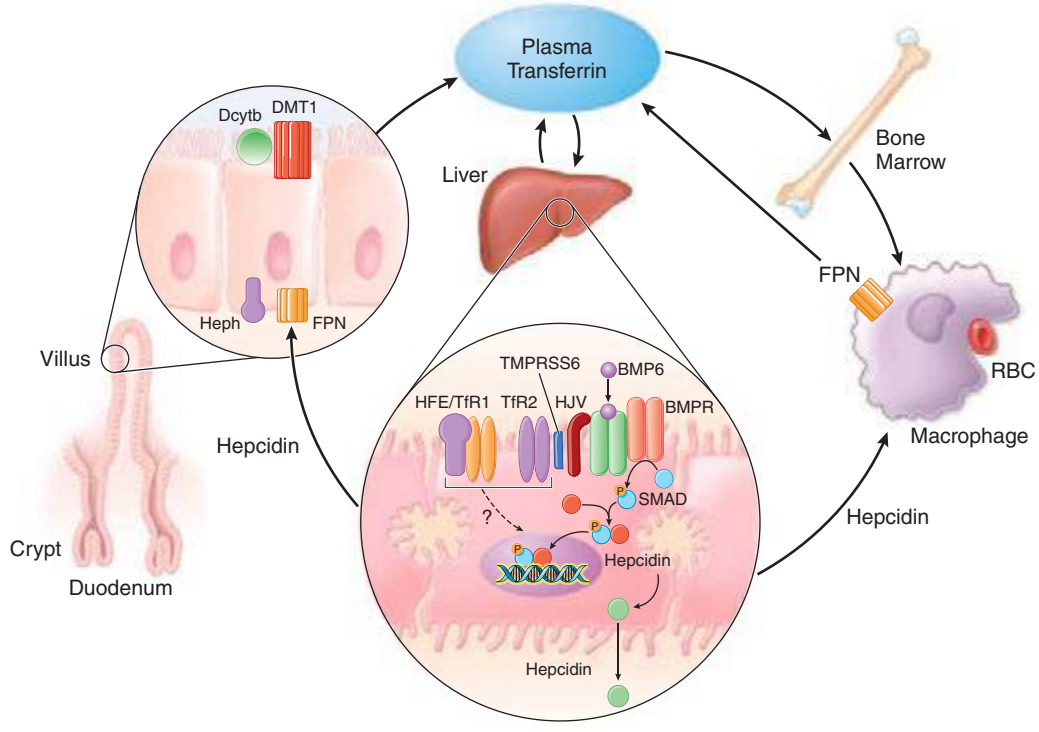

FIGURE 428-1 Pathways of normal iron homeostasis. Dietary inorganic iron traverses the brush border membrane of duodenal enterocytes via the divalent metal-ion transporter 1 (DMT1) after reduction of ferric (Fe^{3+}) iron to the ferrous (Fe^{2+}) state by duodenal cytochrome B (DcytB). Iron then moves from the enterocyte to the circulation via a process requiring the basolateral iron exporter ferroportin (FPN) and the iron oxidase hephaestin (Heph). In the circulation, iron binds to plasma transferrin and is thereby distributed to sites of iron utilization and storage. Much of the diferric transferrin supplies iron to immature erythrocyte cells in the bone marrow for hemoglobin synthesis. At the end of their life, senescent red blood cells (RBCs) are phagocytosed by macrophages, and iron is returned to the circulation after export through ferroportin. The liver-derived peptide hepcidin represses basolateral iron transport in the gut as well as iron released from macrophages and other cells and serves as a central regulator of body-iron traffic. Hepcidin responds to changes in body-iron requirements by signals mediated by diferric transferrin through two mechanisms. One involves HFE and TfR2, whereas the other involves hemojuvelin (HJV) and the bone morphogenetic protein (BMP)/SMAD pathway. TMPRSS6 is a protease that modulates HJV activity. Heme is metabolized by heme oxygenase within the enterocytes, and the released iron then follows the same pathway. Mutations in the genes encoding HFE, TfR2, hemojuvelin, and hepcidin all lead to decreased hepcidin release and increased iron absorption, resulting in hemochromatosis (Table 428-1).