iron have accumulated. Excessive iron appears to be directly toxic to tissues. Mechanisms of liver injury include (1) lipid peroxidation via iron-catalyzed free radical reactions, (2) stimulation of collagen formation by activation of hepatic stellate cells, and (3) interaction of reactive oxygen species and iron itself with DNA, leading to lethal cell injury and predisposition to HCC. The actions of iron are reversible in cells that are not fatally injured, and removal of excess iron with therapy promotes recovery of tissue function.

The main regulator of iron absorption is the protein hepcidin, encoded by the *HAMP* gene and secreted by the liver (Fig. 18-24). Hepcidin is named for its originally elucidated properties as a *hep*atocellular protein with bacbactericidal activities. Transcription of hepcidin is increased by inflammatory cytokines and iron, and decreased by iron deficiency, hypoxia, and ineffective erythropoiesis. Hepcidin binds to the cellular iron efflux channel ferroportin, causing its internalization and proteolysis, thereby inhibiting the release of iron from intestinal cells and macrophages. *Therefore, hepcidin lowers plasma iron levels. Conversely, a deficiency in hepcidin causes iron overload.*

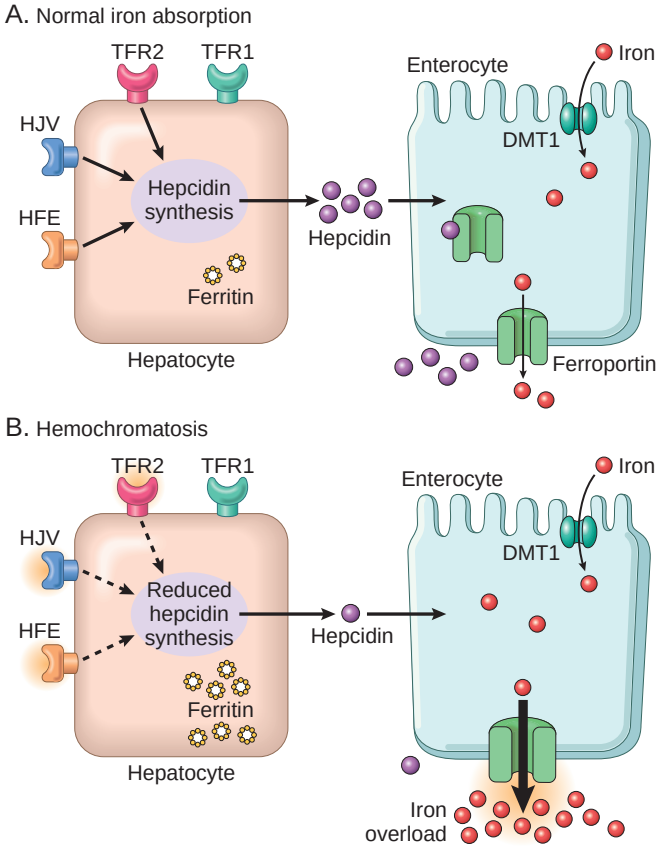

Figure 18-24 A: In normal state HFE, HJV, and TFR2 regulate hepcidin synthesis by hepatocytes maintaining normal circulating hepcidin levels. Hepcidin binds to ferroportin on enterocytes leading to internalization of the complex and ferroportin degradation.This in turn reduces efflux of iron from enterocytes Through these regulatory interactions normal iron absorption is maintained. **B:** In hereditary hemochromatosis HFE or HJV or TFR2 gene mutations reduce hepcidin synthesis thus diminishing circulating hepcidin. The resulting decreased hepcidin-ferroportin interaction allows for increased ferroportin activity, increased iron efflux from enterocytes, giving rise to systemic iron overload in hereditary hemochromatosis. HFE, HFE protein; HJV, hemojuvelin, TFR1, transferrin receptor 1; TFR2: transferrin receptor 2; DMT1: divalent metal transporter 1.

Other proteins involved in iron metabolism, do so by regulating hepcidin levels. These include (1) hemojuvelin (HJV), which is expressed in the liver, heart, and skeletal muscle, (2) transferrin receptor 2 (TFR2), which is highly expressed in hepatocytes, where it mediates the uptake of transferrin-bound iron, and (3) HFE, the product of the hemochromatosis gene. *Decreased hepcidin synthesis caused by mutations in hepcidin, HJV, TFR2, and HFE has a central role in the pathogenesis of hemochromatosis.*

The adult form of hemochromatosis is almost always caused by mutations of HFE; mutation of *TFR2* is far less common. The *HFE* gene is located on the short arm of chromosome 6 at 6p21.3, close to the *HLA* gene locus; it encodes an HLA class I-like molecule that governs intestinal absorption of dietary iron by regulating hepcidin synthesis. *The most common HFE mutation is a cysteine-to-tyrosine substitution at amino acid 282 (called C282Y).* This mutation, which causes inactivation of the protein, is present in 70% to 100% of the patients diagnosed with hereditary hemochromatosis. *The other common mutation is H63D (histidine at position 63 to aspartate).* The H63D homozygous state and C282Y/H63D compound heterozygous mutations often cause only mild iron accumulation.

The C282Y mutation of the HFE gene is largely confined to white populations of European origin, while the H63D has a worldwide distribution. The frequency of C282Y homozygosity is 0.45% (1 of every 220 persons), and the heterozygous frequency is 11%, making hereditary hemochromatosis one of the most common genetic disorders in humans. However, the penetrance of this disorder is low in patients with the homozygous C282Y mutation, so the genetic change does not lead to clinical disease in all individuals.

Adult hemochromatosis is generally a milder disease than the juvenile form. Mutations of HAMP and HJV cause severe juvenile hemochromatosis.

MORPHOLOGY

Severe hemochromatosis (hereditary or secondary) is characterized principally by (1) **deposition of hemosiderin** in the following organs (in decreasing order of severity) the liver, pancreas, myocardium, pituitary gland, adrenal gland, thyroid and parathyroid glands, joints, and skin; (2) cirrhosis; and (3) pancreatic fibrosis. In the **liver,** iron becomes evident first as golden-yellow hemosiderin granules in the cytoplasm of periportal hepatocytes that stain with Prussian blue (Fig. 18-25). With increasing iron load, there is progressive involvement of the rest of the lobule, along with bile duct epithelium and Kupffer cell pigmentation. Iron is a direct hepatotoxin and inflammation is characteristically absent. In early stages of accumulation, the liver is typically slightly larger than normal, dense, and chocolate brown. Fibrous septa develop slowly, leading ultimately to a small, shrunken liver with a micronodular pattern of cirrhosis. The liver parenchyma in later stages is often dark brown to nearly black due to overwhelming iron accumulation.

Biochemical determination of hepatic tissue iron concentration has been the gold standard for quantitating hepatic iron