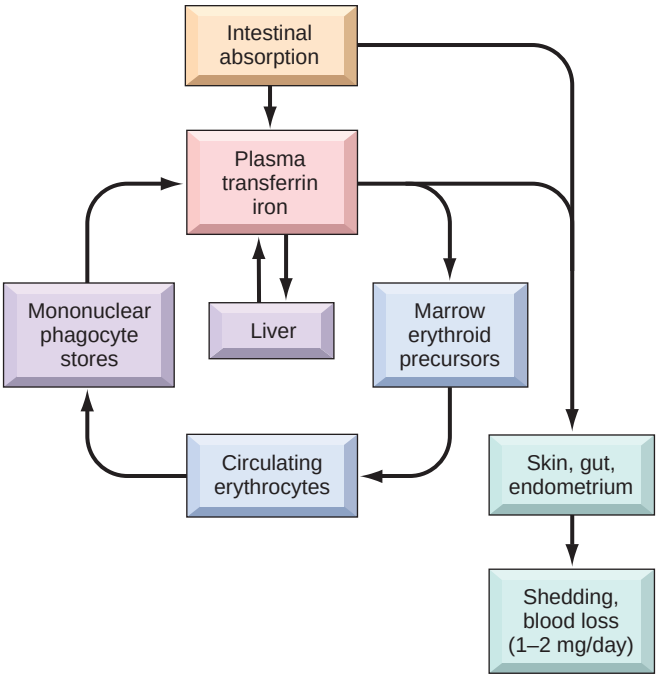

Figure 14-21 Iron metabolism. Iron absorbed from the gut is bound to plasma transferrin and transported to the marrow, where it is delivered to developing red cells and incorporated into hemoglobin. Mature red cells are released into the circulation and, after 120 days, are ingested by macrophages, primarily in the spleen, liver, and bone marrow. Here iron is extracted from hemoglobin and recycled to plasma transferrin. At equilibrium, iron absorbed from the gut is balanced by losses in shed keratinocytes, enterocytes, and (in women) endometrium.

Free iron is highly toxic (Chapter 18), and it is therefore important that storage iron be sequestered. This is achieved by binding of iron in the storage pool to either ferritin or hemosiderin. *Ferritin* is a ubiquitous protein-iron complex that is found at highest levels in the liver, spleen, bone marrow, and skeletal muscles. In the liver, most ferritin is stored within the parenchymal cells; in other tissues, such as the spleen and the bone marrow, it is found mainly in macrophages. Hepatocyte iron is derived from plasma transferrin, whereas storage iron in macrophages is derived from the breakdown of red cells. Intracellular ferritin is located in the cytosol and in lysosomes, in which partially degraded protein shells of ferritin aggregate into *hemosiderin* granules. Iron in hemosiderin is chemically reactive and turns blue-black when exposed to potassium ferrocyanide, which is the basis for the *Prussian blue stain*. With normal iron stores, only trace amounts of hemosiderin are found in the body, principally in macrophages in the bone marrow, spleen, and liver, most being stored as ferritin. In iron-overloaded cells, most iron is stored in hemosiderin.

Because plasma ferritin is derived largely from the storage pool of body iron, its levels correlate well with body iron stores. In iron deficiency, serum ferritin is below 12 μg/L, whereas in iron overload values approaching 5000 μg/L may be seen. Of physiologic importance, the storage iron pool can be readily mobilized if iron requirements increase, as may occur after loss of blood.

Iron is both essential for cellular metabolism and highly toxic in excess, and total body iron stores must therefore be regulated meticulously. Iron balance is maintained by regulating the absorption of dietary iron in the proximal duodenum. There is no regulated pathway for iron excretion, which is limited to the 1 to 2 mg lost each day through the shedding of mucosal and skin epithelial cells. In contrast, as body iron stores increase, absorption falls, and vice versa.

The pathways responsible for the absorption of iron are now understood in reasonable detail (Fig. 14-22), and differ partially for nonheme and heme iron. Luminal nonheme iron is mostly in the Fe^{3+} (ferric) state and must first be reduced to Fe^{2+} (ferrous) iron by ferrireductases, such as b cytochromes and STEAP3. Fe^{2+} iron is then transported across the apical membrane by divalent metal transporter 1 (DMT1). The absorption of nonheme iron is variable and often inefficient, being inhibited by substances in the diet that bind and stabilize Fe^{3+} iron and enhanced by substances that stabilize Fe^{2+} iron (described later). Frequently, less than 5% of dietary nonheme iron is absorbed. In contrast, about 25% of the heme iron derived from hemoglobin, myoglobin, and other animal proteins is absorbed. Heme iron is moved across the apical membrane into the cytoplasm through transporters that are incompletely characterized. Here, it is metabolized to release Fe^{2+} iron, which enters a common pool with nonheme Fe^{2+} iron.

Iron that enters the duodenal cells can follow one of two pathways: transport to the blood or storage as mucosal iron. This distribution is influenced by body iron stores. Fe^{2+} iron destined for the circulation is transported from the cytoplasm across the basolateral enterocyte membrane by ferroportin. This process is coupled to the oxidation of Fe^{2+} iron to Fe^{3+} iron, which is carried out by the iron oxidases hephaestin and ceruloplasmin. Newly absorbed Fe^{3+} iron binds rapidly to the plasma protein transferrin, which delivers iron to red cell progenitors in the marrow (Fig. 14-21). Both DMT1 and ferroportin are widely distributed in the body and are involved in iron transport in other tissues as well. For example, DMT1 also mediates the uptake of "functional" iron (derived from endocytosed transferrin) across lysosomal membranes into the cytosol of red cell precursors in the bone marrow, and ferroportin plays an important role in the release of storage iron from macrophages.

Iron absorption is regulated by *hepcidin*, a small circulating peptide that is synthesized and released from the liver in response to increases in intrahepatic iron levels. Hepcidin inhibits iron transfer from the enterocyte to plasma by binding to ferroportin and causing it to be endocytosed and degraded. As a result, as hepcidin levels rise, iron becomes trapped within duodenal cells in the form of mucosal ferritin and is lost as these cells are sloughed. Thus, when the body is replete with iron, high hepcidin levels inhibit its absorption into the blood. Conversely, with low body stores of iron, hepcidin synthesis falls and this in turn facilitates iron absorption. By inhibiting ferroportin, hepcidin not only reduces iron uptake from enterocytes but also suppresses iron release from macrophages, which are an important source of the iron that is used by erythroid precursors to make hemoglobin. This, as we shall see, is important in the pathogenesis of anemia of chronic diseases.

Alterations in hepcidin have a central role in diseases involving disturbances of iron metabolism. This is illustrated by the following examples.