# Iron in mammals: pathophysiological mechanisms of overload and deficiency in relation to disease

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## Abstract

The uptake of iron into the body is tightly regulated in humans and in other mammals. Mutations in key proteins that transport, sense, metabolize, and facilitate the utilization of iron cause perturbations in iron homeostasis that result in iron deficiency or overload diseases. This review focuses on what is currently known about these diseases and the normal function of the proteins that are mutated in the disease-state. The proteins causing hereditary hemochromatosis and anemia are discussed in detail.

## 1 Overview of iron transport and homeostasis

Iron enters the body principally through enterocyte cells in the duodenum of the intestine (Fig. 1). The iron absorbed by these cells may be in two forms, heme and non-heme. The mechanism by which heme iron enters the body is not established. For non-heme iron, duodenal cytochrome b (DcytB) or another ferrireductase, on the apical membrane of the enterocyte facing the intestinal lumen, first reduces $Fe^{3+}$ from food to the more soluble $Fe^{2+}$ (McKie et al. 2001). The divalent metal ion transporter, DMT1, then transports $Fe^{2+}$ across the apical surface of the intestinal cell (Fleming et al. 1997; Gunshin et al. 1997). Once inside, either iron remains within the cell, stored in ferritin and unabsorbed by the body, until it is lost when, after several days, the cell dies (Kaplan 2002); or iron crosses to the basolateral side where ferroportin1 then transports $Fe^{2+}$ out of the cell (Abboud and Haile 2000; Donovan et al. 2000; McKie et al. 2000). After iron exits the enterocyte, a multicopper ferroxidase on the cell surface, hephaestin (Vulpe et al. 1999), or its soluble homolog in the circulation, ceruloplasmin (Cp) (Mukhopadhyay et al. 1998; Harris et al. 1999), re-oxidizes iron to the $Fe^{3+}$ form. The serum protein transferrin (Tf) binds iron and transports it to cells throughout the body.

In most tissues, iron enters cells by receptor-mediated endocytosis. Iron bound to transferrin ($Fe_2$-Tf) binds to transferrin receptor 1 (TfR1) on the surface of cells. Endocytosis delivers the $Fe_2$-Tf-TfR1 complex to the early endosome where the acidified environment promotes the release of iron, which is reduced to $Fe^{2+}$ by an undetermined mechanism. The TfR1-Tf complex then recycles to the cell surface

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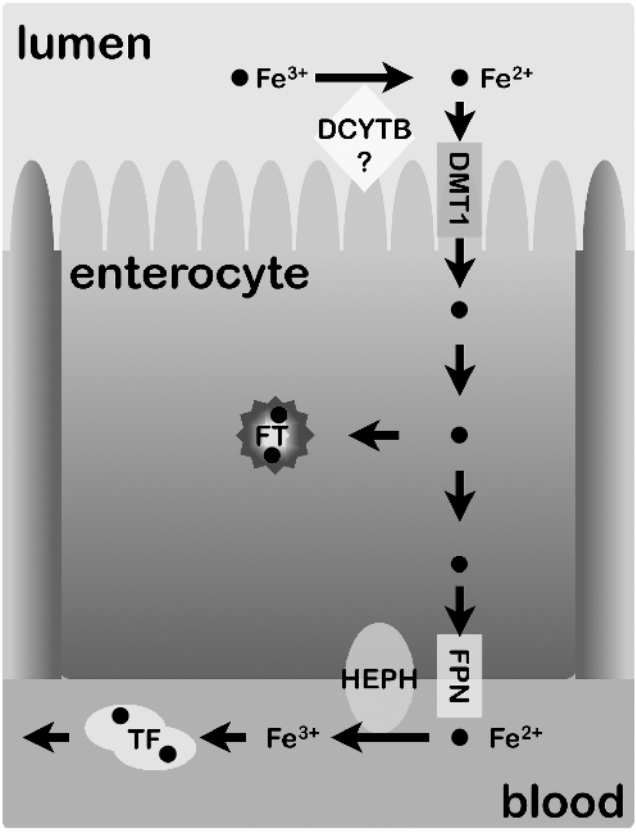


**Fig. 1.** Absorption of non-heme iron across the enterocyte. On the apical surface of enterocytes facing the lumen of the intestine, non-heme iron from the diet is reduced to $Fe^{2+}$ by DcytB or another ferrireductase and transported into the cell by divalent metal-ion transporter 1 (DMT1). Iron may be stored within the cell bound to ferritin (Ft) or transported across the basolateral surface of the cell by ferroportin (Fpn) into the blood, where iron is oxidized to $Fe^{3+}$ by hephaestin (Heph), bound by transferrin (Tf), and circulated throughout the body.

and dissociates at the neutral pH, releasing Tf into the circulation. On the endosomal membrane, DMT1 transports iron into the cytosol (Fleming et al. 1998), where it is incorporated into newly synthesized proteins or stored in ferritin (Ft) (Kaplan 2002).

Differentiating erythrocytes in the bone marrow utilize the majority of iron in the body for heme biosynthesis. Macrophages phagocytose senescent erythrocytes, degrade their heme, and return the iron to the circulation where it is bound by Tf (Fletcher and Halliday 2002). Efficient recycling of 20-30 mg of iron per day reduces the dietary iron requirement to 1-2 mg, a fraction of the 3-5 g found in