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ROADMAP OF THE IRON ABSORPTION PATHWAY

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Iron is important for a wide range of metabolic functions in all living organisms, including oxygen transport, DNA synthesis, and electron transport. Iron balance in the body is carefully maintained to ensure that enough iron is absorbed to compensate for body losses of iron.In healthy humans, absorptive cells in the proximal small intestine carefully manage body iron concentrations (about 60 parts per million [ppm]), altering iron absorption to match body losses of iron. There are three different mechanisms for iron absorption in the proximal small bowel. There are two different paths for ferric and ferrous iron, as well as the heme pathway.

Enterocytes have three mechanisms for absorbing dietary iron, although the most absorbed iron comes from heme. Heme is enzymatically degraded and reaches the enterocyte as a metalloporphyrin, free of globin. Heme oxygenase within the cell releases iron from heme, which then enters the body as inorganic iron. Ferric iron makes up the majority of dietary inorganic iron. The integrin-mobilferrin route allows this to enter the absorptive cell (IMP). The divalent metal transporter-1 (DMT-1/DCT-1/Nramp-2) transports some dietary iron into the absorptive cell after it is reduced in the gut lumen. Paraferritin, a big protein complex capable of ferrireduction, interacts with proteins from both pathways within the enterocyte. To protect the cell from oxidative harm, extra iron is stored as ferritin. Ferroportin and hephaestin, both of which connect with an apotransferrin receptor, let iron exit the cell and enter plasma. By transferring iron from plasma into the cell via a holotransferrin receptor, the enterocyte is aware of its body's iron requirements.

Heme enters the cell as a fully functional metalloporphyrin via a vesicular process. It is destroyed by heme oxygenase within the enterocyte, releasing iron, and then passing through the basolateral cell membrane in competition with nonheme iron to bind transferrin in the plasma.

Ferric iron enters cells by a different route than ferrous iron. Competitive inhibition tests, blocking antibodies against divalent metal transporter-1 (DMT-1) and beta3-integrin, and transfection experiments with DMT-1 DNA have all demonstrated this. Ferric iron enters cells via beta3-integrin and mobilferrin, whereas ferrous iron enters cells via DMT-1, according to this study.

The amount of iron in enterocytes varies in direct proportion to the body's need for it. Absorptive cells from iron-deficient humans and animals contain very little stainable iron, whereas those from iron-rich subjects contain much more. In the same way that iron shortage causes little stainable iron in the enterocyte, phenotypic hemochromatosis creates little stainable iron in the enterocyte if left untreated. Upregulation of a receptor, saturation of an iron-binding protein, or both are possible mechanisms for iron in the enterocyte.Endotoxin rapidly reduces iron absorption without affecting enterocyte iron content, which shows that endotoxin and cytokines affect iron absorption through a different mechanism than iron shortage, increased erythropoiesis, or hypoxia. This is the hepcidin impact, as well as the hepcidin versus erythropoietin balance.

Transferrin binds the majority of iron transported to nonintestinal cells. The conventional transferrin receptor pathway (high affinity, low capacity), in which the transferrin iron complex enters the cell within an endosome, delivers transferrin iron to nonintestinal cells. The iron from transferrin is released when the endosome is acidified, allowing it to enter the cell. The endosome transports the apotransferrin to the plasma, where it is repurposed. and the transferrin receptor-independent pathway (low affinity, high capacity).

Disorders intestinal iron absorption can result in functional iron deficiency or iron overload. Insights into mechanisms of iron absorption and transport have im-proved understanding of a range of clinical conditions that cause iron deficiency or iron overload, and have led to novel therapeutics that may transform management of iron withholding or overload states.