Targeting Iron Homeostasis in Acute Kidney Injury

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Summary: Iron is an essential metal involved in several major cellular processes required to maintain life. Because of iron's ability to cause oxidative damage, its transport, metabolism, and storage is strictly controlled in the body, especially in the small intestine, liver, and kidney. Iron plays a major role in acute kidney injury and has been a target for therapeutic intervention. However, the therapies that have been effective in animal models of acute kidney injury have not been successful in human beings. Targeting iron trafficking via ferritin, ferroportin, or hepcidin may offer new insights. This review focuses on the biology of iron, particularly in the kidney, and its implications in acute kidney injury.
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Iron is an essential element that is necessary for life. The primary function of iron in the body is the transportation of oxygen. Iron is bound to the heme group in hemoglobin, which allows red bloods cells to supply oxygen to the tissues. Hemoglobin also facilitates the transfer of carbon dioxide from the tissues to the lungs for removal from the body. Myoglobin is another heme protein that uses iron to store and transport oxygen in muscle cells. More than 70% of the body's iron is contained within hemoglobin and myoglobin. Another 12% can be found in iron storage proteins such as ferritin and transferrin. The remaining 15% of the body's iron is in heme-containing proteins (such as cytochromes, respiratory burst enzymes, catalase, nitric oxide synthase, myeloperoxidase, and others) that are ubiquitous and imperative to the maintenance of proper functioning of cells and tissues.

Heme is a highly conjugated heterocyclic organic ring with ferrous iron in the center, which is a necessary component of several proteins in the body involved in respiration and energy metabolism. Cytochromes, such as cytochrome c, contain a heme group and are responsible for the production of adenosine triphosphate in the electron transport chain. Other heme-containing enzymes such as cytochrome P450s are monooxygenases that catalyze the metabolism of a wide variety of endogenous and exogenous compounds for either synthesis or detoxification. Although peroxidases such as catalase are protective and catalyze the reduction of hydrogen peroxide to water, cyclooxygenases convert fatty acids into vasoactive prostaglandins. In addition, iron is an essential component of several enzymes involved in the synthesis of collagen and neurotransmitters. Iron also is necessary for proper immune function.

Although iron is essential for life, it is extremely labile in certain forms and, as a result, can be highly reactive and toxic. Iron can be found in two different redox states: the ferrous state (Fe^{2+}) and the ferric state (Fe^{3+}). The fact that iron can bind six different ligands simultaneously accounts for the high reactivity levels of this metal and its ability to undergo Fenton chemistry. When the body insufficiently reduces oxygen to water, a superoxide radical is formed, but it is subsequently converted to hydrogen peroxide by superoxide dismutases. During the Haber-Weiss reaction, the ferrous form of iron can catalyze a reaction with the seemingly innocuous superoxide and hydrogen peroxide to form the toxic hydroxyl radical. Consequently, the superoxide radical can remove iron from iron-sulfur clusters in proteins, which can lead to certain diseases.[1] On the other hand, the deleterious effects of the hydroxyl radical are well established. Several researchers have studied the ability of the hydroxyl radical to cause oxidative DNA damage, ultimately leading to disease.[2] Because of the potential reactivity of iron, its movement throughout the body is strictly controlled. Table 1 shows some of the major proteins involved in regulating iron homeostasis.

IRON TRAFFICKING IN SPECIFIC ORGANS

The body obtains iron from the diet. Some iron-rich foods include meats, dark green leafy vegetables, beans, dried fruits, and other iron-fortified foods such

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Table 1. Some Key Proteins Involved in Iron Homeostasis

Protein	Function
DMT1	The divalent metal transporter 1 imports Fe^{2+} into the cell
Ferritin	Iron storage protein with heavy (H)- and light (L)-chain subtypes
	H-ferritin has ferroxidase activity that allows for the safe incorporation of iron into ferritin for storage
Ferroportin	An iron transporter that exports iron from the cell
Hepcidin	A peptide synthesized in the liver that controls iron absorption by regulating ferroportin expression
Hephaestin	A ferroxidase localized mostly in the small intestine that is responsible for converting Fe^{2+} to Fe^{3+}
NGAL	Neutrophil gelatinase- associated lipocalin (also known as lipocalin-2) sequesters iron to inhibit bacterial growth
	It is also a biomarker for acute kidney injury
Transferrin	A glycoprotein that can bind up to two atoms of iron in biological fluids. Binding is reversible and the iron pool in transferrin has a high turnover rate

as cereal. Dietary iron is absorbed in the intestine and metabolized and stored in other tissues, including the liver and the kidneys. Iron is eliminated from the body through blood loss, urinary excretion, and by discarding mucosal and skin cells. The small intestine, particularly the duodenum, is the organ responsible for dietary iron absorption (Fig. 1). The acidic environment of the stomach increases the solubility of the iron acquired from the diet, usually as Fe^{3+}, to aid with passage through the digestive tract. In the intestinal lumen, ascorbic acid and ferric reductases such as duodenal cytochrome b, a plasma membrane protein located in the brush-border membrane of enterocytes, reduces ferric iron to the ferrous form (Fe^{2+}).[3] Iron can enter enterocytes at the apical surface using the proton gradient powered divalent metal transporter-1 (DMT1).[4] It is thought that iron uses transcytosis or a chaperone to travel from the apical membrane to the basolateral membrane, but the exact mechanism has not yet been elucidated.[5] The efflux of iron from the basolateral side of the enterocyte is facilitated by ferroportin (FPN)[6]; interestingly, there also is evidence to suggest that FPN may modulate the activity of DMT1 at the apical membrane.[7] Although it is unclear

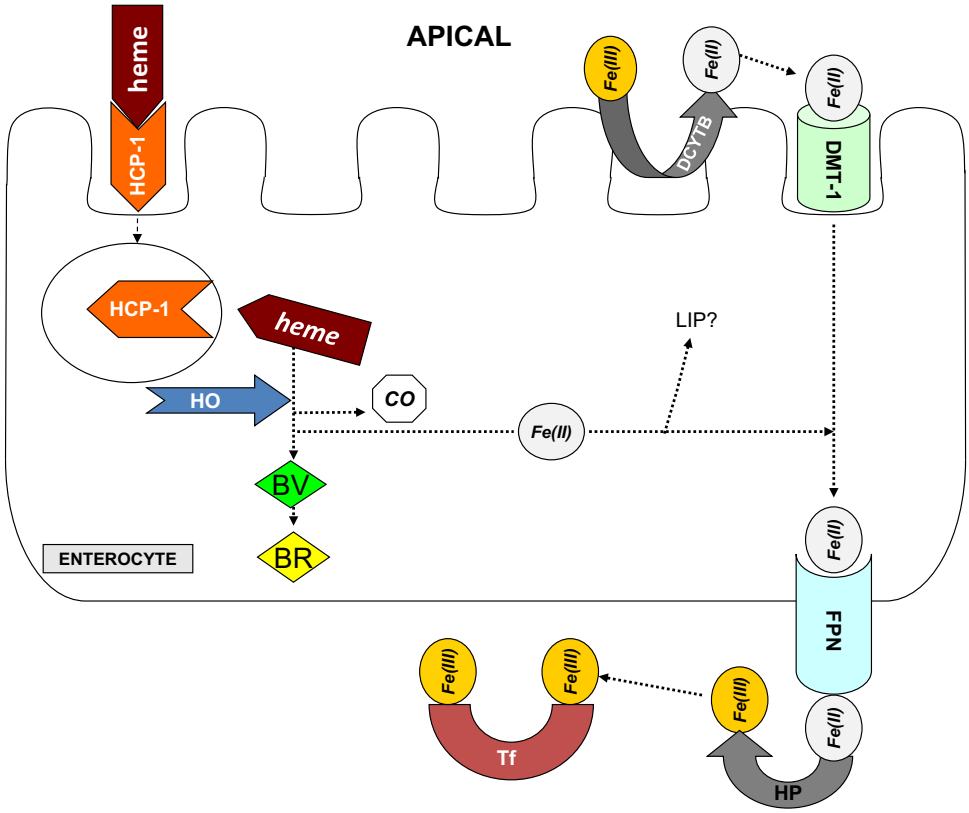

Figure 1. Intestinal iron absorption. This figure shows iron absorption in an enterocyte. BR, bilirubin; BV, biliverdin; CO, carbon monoxide; DCYTB, duodenal cytochrome b; HCP-1, heme carrier protein-1; HP, hephaestin; Tf, transferrin. Reprinted with permission from Zarjou et al.[100]