Iron Regulation

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Why does the planet Mars glow red in the night sky? The answer, of course, has to do with iron. In the early solar system, stellar energy originated from the fusion of two light nuclei that combined to make a heavier nucleus in a thermonuclear reaction. Hans Bethe was awarded the 1967 Nobel Prize in physics for describing nucleosynthesis, the mechanism by which fusion of four hydrogen nuclei makes a helium-4 nucleus, accounting for the bulk of energy that is produced by the sun. However, the nucleosynthetic process does not end with helium, because larger nuclei also can be fused in brilliant stars to make heavier elements. In a classic paper of 1957, Hoyle et al. described a wide range of nuclear processes that are important in synthesizing the chemical elements during stellar evolution (1). Of importance, the end of the nuclear burning chain is marked by the formation of elemental iron, which has a particularly stable nuclear structure. Because the synthesis by nuclear fusion of elements that are heavier than iron actually costs rather than liberates energy, by the time a star has synthesized a core of iron, it is doomed.

Because the matter of the stars ends up forming the planets, iron is abundant in the earth. Inside the early earth, intense heating converted most iron oxide into molten metallic iron, which subsequently seeped down to form a huge liquid core within the earth. Although the preponderance of the earth’s core is composed of iron and nickel, creating the earth’s magnetic field, approximately 6% of matter in the earth’s mantle is also composed of iron. In comparison with Earth, Mars never achieved high enough temperatures to melt iron oxide into the core; as a consequence, Mars has proportionately more iron oxide in the upper layers of the planet, leading to its distinctive rusted color (2).

Iron is equally abundant in human physiology. The most abundant transition metal in the body, iron is an essential nutrient that is required by every human cell. Critical to iron’s importance and biologic processes is its ability to cycle reversibly between the ferrous and ferric oxidation states. Because of its reversible redox cycling, iron is quantitatively the most important catalytic element in human enzymology with crucial and vital roles in oxidative phosphorylation, oxidative metabolism, and cellular growth and proliferation, as well as in transport and storage of oxygen, nitric oxide, and carbon monoxide. Iron functions physiologically either in the form of hemoproteins or in non–heme-containing proteins (e.g., iron-sulfur proteins).

Despite the abundance of iron in nature and in the human body, iron absorption, transport, storage, and excretion are tightly regulated. Whereas the concentration of iron in the human body normally is approximately 40 to 50 mg Fe/kg body wt, kinetic studies demonstrate that the total body labile iron pool is estimated to contain only approximately 70 mg of iron. The economy of iron reutilization is truly remarkable; in health, only 1 to 2 mg of iron is lost each day, with a concomitant 1 to 2 mg of iron absorbed from the gastrointestinal tract to maintain a steady state (Figure 1). Indeed, every aspect of iron regulation, from absorption in enterocytes in the gastrointestinal tract through transport, cellular metabolism, and reclamation of iron from degraded heme proteins, is exquisitely economized.

Why is iron so tightly regulated in human physiology? A glance at the rusted iron oxides in the mantle of Mars provides a reminder. As a transition metal with an incomplete 3d orbital shell, iron is a free radical that readily reacts with dioxygen (O2), itself a diradical. Transition metals such as iron relieve the spin restriction of dioxygen and thereby enhance rates of biomolecule oxidation. It is widely known that free ferrous iron is a potent catalyst for lipid peroxidation and DNA and protein oxidation. Sequestration of iron, primarily through binding to transferrin (Tf), Tf receptor (TIR), and ferritin and through the activity of iron-regulatory proteins, clearly is designed to prevent toxicity from the free radical chemistry that is catalyzed by unbound iron.

Frontiers in Nephrology in this issue of JASN focuses on...
recent discoveries regarding the regulation of iron absorption, transport, storage, and metabolism. Each article addresses an important area of research that recently has advanced our knowledge of iron regulation. Moreover, these advances highlight several exciting aspects of iron regulation that may affect directly kidney development and kidney response to injury. Exciting discoveries regarding the interaction of inflammation with iron transport have the potential to improve iron therapies for patients who have inflammation with kidney disease.

Zhang et al. describe how IRP and iron-responsive elements act in renal proximal tubule cells to regulate iron function in the kidney. Zhang et al. describe the glomerular filtration of Tf and subsequent proximal tubule reabsorption of Tf via the cubilin receptor and further describe the role of IRP1 and IRP2 in regulating target transcripts, including ferritin and TfR, in the kidney. A complex relationship also exists between hypoxia-sensing elements and iron-regulatory elements in the kidney. Thus, hypoxia-sensing depends on iron-dependent prolyl hydroxylases, whereas hypoxia-inducible factor–dependent pathways also may regulate Tf and TfR transcription. An improved understanding of iron regulation in the kidney may lead to therapeutic advances in acute kidney injury as well as better understanding of the development of renal cancers.

Ganz reviews the molecular control of iron transport. This review focuses on the biology of hepcidin, a 25–amino acid iron-regulatory hormone whose discovery 5 yr ago is revolutionizing our understanding of iron transport. Hepcidin binds to ferroportin, a cellular iron export channel, leading to its degradation and preventing iron efflux from iron-exporting tissues into plasma. Hepcidin synthesis is induced by iron loading and inflammation and suppressed by hypoxia and erythropoietic activity. By simultaneously regulating intestinal iron absorption and the release of iron from macrophages and hepatic stores, hepcidin can be viewed as a master regulator of systemic iron availability.

The divergent regulation of hepcidin synthesis by hypoxic and inflammatory stimuli strongly suggests that hepcidin may be very important in the “inflammatory block” on iron availability in the anemia of inflammation. Ultimately, strategies that lower hepcidin synthesis may prove to be beneficial in the treatment of anemia in patients with inflammation. Clinical progress currently is being slowed by the lack of an available, reliable, practical assay system for measuring serum hepcidin levels. This is due primarily to difficulties in developing specific antibodies against hepcidin as a result of its compact folding structure (3). However, this is likely to be a rapidly evolving field, and recently Tomosugi et al. (4) demonstrated that hepcidin accumulates in hemodialysis patients using a ProteinChip Mass Spectometry assay. This discovery may prove to be important in the pathogenesis of erythropoietin resistance in the anemia of renal disease.

Historically, Tf was the first known growth factor for the embryonic kidney (5). Although Tf is clearly an important iron carrier in the kidney, other proteins also are involved in carrying iron during kidney development and in response to kidney injury. Lipocalcins are low molecular weight carrier proteins that bind iron-containing siderophores. Schmidt-Ott et al. re-
view the biology of NGAL, a member of the lipocalcin family that is expressed by epithelial cells during growth transitions. NGAL binds to bacterial siderophores and may play a role in reducing iron availability to bacteria during sepsis. Recent data indicate that NGAL may help regular renal tubule epithelial growth during development. During acute kidney injury, serum and urinary NGAL concentrations are markedly upregulated. Indeed, urinary NGAL levels may be a biomarker for acute kidney injury that is detectable before a rise in the serum creatinine concentration (6). Furthermore, endocytic delivery of a lipocalcin-siderophore-iron complex can rescue the kidney from ischemia reperfusion injury in animal models. These discoveries are exciting, and much remains to be discovered concerning the physiologic and pathophysiologic role of NGAL during kidney development and in response to acute kidney injury.

Although the mechanisms for gastrointestinal absorption of nonheme iron have been well studied in the past decade, the first mammalian heme transporter has been described only recently (7). Tracz et al. review the physiology and pathophysiology of heme transport and metabolism, focusing on implications for kidney disease. The heme molecule possesses the biologically useful ability to bind oxygen, nitric oxide, and carbon monoxide avidly and can readily transfer electrons. Heme-containing proteins are particularly abundant in the proximal tubule, where as part of the cytochrome P450 system they play a detoxifying role. However, free heme, produced during cell injury, is highly toxic to mitochondria. Heme oxygenase, an inducible protein, metabolizes heme, a prooxidant, and leads to the generation of bilirubin, a metabolite with antioxidant properties. Induction of heme oxygenase may be cytoprotective in the setting of acute kidney injury. Strategies that lead to induction of heme oxygenase, including ischemic preconditioning, may have clinical utility in high-risk settings for acute kidney injury or in the setting of established acute kidney injury.

Most patients who have the anemia of chronic kidney disease (CKD) and receive erythropoiesis-stimulating agents end up functionally iron deficient, receiving oral or intravenous iron preparations. The majority of patients with ESRD cannot be maximally repleted with oral iron and end up receiving intravenous iron. Because the intravenous administration of iron bypasses many of the exquisitely calibrated iron-regulatory systems (Figure 1), there has been an ongoing concern that iron administration may contribute to cardiovascular and/or infectious complications in patients with CKD and ESRD. Horl reviews the available data concerning clinical aspects of iron use in the anemia of kidney disease. How should iron therapy be monitored? Unfortunately, the utility of currently available tests is limited by moderate sensitivity and specificity. This lack of readily available clinical tests with precision in determining likelihood of iron responsiveness is a vexing clinical problem. As Horl points out, the best criteria for determining iron-deficient erythropoiesis is the response to intravenous iron products. Similarly, there are no simple, readily available biochemical tests to determine when iron administration may be toxic. Research tests such as lipid peroxidation biomarkers and neutrophil phagocytosis assays likely also have limited sensitivity and specificity. Horl reviews currently available data and provides sensible clinical recommendations for iron administration and monitoring. How best to administer, measure, and monitor intravenous iron therapy in patients with CKD and ESRD is likely to remain a controversial topic until more refined assays and more definitive data from clinical trials are available.

Articles that compose this installment of Frontiers in Nephrology on iron regulation provide comprehensive, state-of-the-art reviews as well as novel exciting data. They also point out new directions for research in some of the most critical areas that confront nephrology, including kidney development, the kidney response to acute injury, and how best to administer and monitor iron therapy in the setting of CKD. The field of iron regulation is ripe for further advances in basic, translational, and clinical science that hopefully can improve outcomes for patients with kidney diseases.

Disclosures
None.

References