Chronic Inflammation and Iron Metabolism

Erin A. Osterholm, MD, and Michael K. Georgieff, MD

Iron is an essential component of almost all biological systems. It is required for energy production, oxygen transport and use, cellular proliferation, and destruction of pathogens. The biological properties of iron stem from the variability of its ferrous/ferric iron redox potential. Protein ligands adapt these redox potentials to meet various biologic requirements. Iron-containing proteins are essential to many biochemical functions, including oxygen transport by the hemoproteins hemoglobin and myoglobin. Other hemoproteins include the activators of molecular oxygen—cytochrome oxidases, peroxidases, catalases, and cytochrome P450s—as well as the cytochromes that transfer electrons from substrate oxidation to cytochrome c oxidase. Iron sulfur proteins are another class of iron-containing proteins that mediate one electron redox processes as integral components of the respiratory chain in mitochondria. They also are involved in the control of gene expression, DNA damage recognition and repair, oxygen and nitrogen sensing, and the control of cellular iron acquisition and storage.

The vital importance of maintaining iron supply is most obvious in children. Children, unlike adults, have high iron requirements because of significant cellular metabolic demands caused by the high growth rates of their developing tissues and the rapid expansion of their red cell mass. The human brain at birth is the most highly metabolic organ, consuming ~50% of the body's energy needs.[1] Highly metabolic organs need a plentiful supply of substrates, including iron, that support energy metabolism. This metabolic need is reflected in the different physiologic iron absorption requirements (per kilogram) at varying stages of development to maintain normal hemoglobin concentrations as the red cell volume expands with growth and for normal iron delivery to tissues. Per the Food and Nutrition Board of the Institutes of Medicine, the recommended dietary allowance for enteral iron starts at 0.27 mg/day in the birth to 6-month age group, increases to 11 mg/day in 7- to 12-month-old infants, and then is 7 mg/day in the 1- to 3-year age group. Women of child-bearing age require 18 mg/day, and this value increases to 27 mg/day during pregnancy.[2] Failure to maintain iron sufficiency during fetal life and in early childhood causes long-term alterations to developing organs, most importantly the brain.[3] Thus, ensuring adequate iron delivery to children during rapid growth phases is essential.

Although maintaining iron delivery to children is vital to support their growth and neurodevelopment, there exists a conundrum in that there are potential negative consequences of iron supplementation in certain contexts such as infectious states. Iron supports the growth and differentiation of other rapidly growing cells, including infectious agents. Bacteria are able to form biofilms and grow more rapidly when iron is abundant.[4,5] Bacteria have evolved mechanisms to acquire iron in low iron environments that include the secretion and reuptake of iron-binding organic molecules termed siderophores. Pathogens have developed the ability to acquire iron from host iron-binding proteins like hemoglobin, lactoferrin, and transferring.[4]

The body has evolved a finely tuned mechanism to limit iron availability during infection. In the short term, this is advantageous and promotes basic survival by protecting from overwhelming infection. In the long term, anemia of inflammation, also known as the anemia of chronic disease, can place the child's growth and future development at risk by limiting iron availability. Given the potential for long-lasting effects, we will discuss the important interrelationships between chronic disease and iron metabolism. Although there remain few pediatric specific examples in the literature, the mechanisms gleaned from the adult literature strongly suggest some of the same iron regulation events that take place with acute inflammation and iron metabolism apply to chronic disease in children. Therefore, we will: (1) provide background to explain the importance of the supply and demand and regulatory proteins involved in iron metabolism; (2) review how these regulation principles apply to anemia of inflammation; and (3) propose how these principles apply to anemia of chronic disease and provide clinically relevant examples.

Regulation of Total Body and Cellular Iron

Given that the cells of various body organs are being renewed constantly, there are constant iron requirements that must be met, most significantly during periods of rapid cell growth and maturation. There are certain time periods in which iron requirements are particularly high, including the fetal period, infancy and early childhood, and adolescence (especially for females). Almost two-thirds of iron in the body is found in the erythroid components

AGP	Alpha-1-acid glycoprotein
CRP	C-reactive protein
HFE	Human hemochromatosis protein
IL-6	Interleukin-6
TfR1	Transferrin receptor 1

From the Division of Neonatology, Department of Pediatrics, University of Minnesota Children's Hospital, Minneapolis, MN

The authors declare no conflicts of interest.

http://dx.doi.org/10.1016/j.jpeds.2015.01.017

(circulating red blood cells). Therefore, alterations in erythropoiesis have a dominant effect on regulation of iron through absorption, storage, and transport. The requirement for iron for vital biologic functions like erythropoiesis necessitates that an uninterrupted iron supply be available for cellular turnover. This demand, however, is balanced with the importance of preventing the potential toxic effects that would result from the presence of free iron. Thus, total body and cellular iron acquisition and iron storage are regulated processes.

Dietary iron enters the body through absorptive intestinal mucosal cells, thereby regulating net total body iron accumulation. Iron also enters the plasma from macrophages that recycle iron from senescent erythrocytes. Iron is delivered to the plasma and extracellular fluid by ferroportin, a transmembrane protein encoded by the *SCL40A1* gene (solute carrier family 40 member) that is expressed on the surfaces of duodenal intestinal endothelial cells and reticuloendothelial macrophages.[6,7] Ferroportin binds ferrous iron, but iron transfer to apotransferrin requires an oxidation step via a multicopper oxidase because apotransferrin has a high binding affinity for ferric iron. Ferric iron that enters plasma from macrophages or the intestine is bound to plasma transferrin and is delivered to cells through the interaction of diferric transferrin and cell-surface transferrin receptor.[8] Important homeostatic mechanisms prevent excessive iron absorption in the small intestine and regulate the rate of iron release from macrophages involved in recycling. This is important because the body has no way to excrete iron in a regulated manner. Cellular iron not used by other ferroproteins accumulates in ferritin. Ferritin has a large, but ultimately limited capacity, for iron and in fact, capacity may be exceeded in times of iron excess. Toxic free iron in tissues can cause significant organ damage as is seen in severe forms of hemochromatosis. These toxic effects of free iron are caused by iron's ability to catalyze formation of reactive oxygen species, stimulating inflammatory responses, and allowing activity of pathogens.[9]

Systemic iron homeostasis is regulated by keeping plasma transferrin-bound iron within a narrow range.[10] Iron bound to transferrin remains soluble but is prevented from generating free radicals. Transferrin is the major carrier and vehicle for iron delivery to individual cell types (eg, erythrocytes, neurons, cardiomyocytes), which have the ability to further regulate iron import and storage. The circulating transferrin pool contains only ~3 mg of iron at any one time, but 10 times that much iron, most destined for developing red blood cells, moves through the transport system every day in an adult.[11,12]

Systemic iron homeostasis is maintained by the regulation of the rate of ferroportin- mediated iron delivery from the intestinal epithelial cell and the macrophages to circulating transferrin. The expression of ferroportin on cell membranes is regulated by hepcidin. Hepcidin binds to ferroportin, causing the complex to be internalized into clathrin-coated pits, phosphorylated, ubiquinated, and degraded. It functions via a negative feedback loop so that during times of iron sufficiency, hepcidin expression is increased, leading to reduced ferroportin and therefore, reduced iron absorption. Hepcidin acts as the central regulator to control iron absorption, iron recycling, and the size of the iron stores. Most hepcidin is synthesized in hepatocytes as an 84 amino acid propeptide that is processed in the Golgi apparatus into an active 25 amino acid peptide before secretion into the circulation. Circulating hepcidin is bound to a α2-macroglobulin. Renal excretion is the major pathway of hepcidin clearance.[13-17]

Iron stores, erythropoietic activity, hypoxia, and inflammation are the most important factors that regulate hepcidin gene expression and serum protein concentration. These factors act through 3 interrelated pathways controlled by circulating iron concentration, hepatocellular iron stores, and inflammatory cytokines. Hepatocytes and developing erythrocytes express transferrin receptor 1 (TfR1) and a second isoform, transferrin receptor 2, both of which are affected by human hemochromatosis protein (HFE). Mono- or diferric transferrin binds to both TfR1 and transferrin receptor 2. It displaces HFE from TfR1. HFE is then able to interact with transferrin receptor 2 to produce a complex that induces hepcidin transcription by bone morphogenic protein-6/sons of mothers against decapentaplegic signaling.[13,18-21]

The Pathophysiology of Anemia of Inflammation

Hepcidin contributes to innate immunity and is a major component of the anemia of inflammation. The anemia of inflammation develops in multiple clinical scenarios, including infection, inflammatory disorders, trauma, and malignancies. The mechanism by which hepcidin functions likely evolved as a way to control the amount of bioavailable iron in the plasma for bacteria during acute infection. This nonspecific mechanism for restricting bioavailable iron to all cells, however, limits erythropoiesis as well. Thus, the anemia of inflammation is characterized by decreased serum iron concentration (hypoferremia), iron sequestration in macrophages, increased serum ferritin concentration, and a blunted response to erythropoietin. Red cell survival can be decreased as well. Anemia of inflammation is often a mild normocytic, normochromic anemia, although it can be severe with microcytic and hypochromic red cells if the inflammation-induced restriction of iron availability is long-standing. Although the effect of limiting iron availability on erythropoiesis via this mechanism is well described, it is likely that any organ with a high cellular iron requirement (eg, the developing brain, heart) also would be compromised by the persistent hypoferremia.[22]

Hypoferremia in patients with anemia of inflammation occurs despite sufficient macrophage iron stores, indicating a block in macrophage iron recycling and return of iron to the serum. Increasing evidence suggests that the primary mediator of this block is hepcidin. Hepcidin is a component