Host-Pathogen Interactions: The Role of Iron

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Abstract

Iron is essential for both host and pathogen, and complex systems of acquisition and utilization have evolved in competition. Our increasing knowledge of the basic mechanisms of homeostasis and their adaptation during deficiency, overload, and infection indicate that iron is a key regulator of host pathogen interactions. This review concentrated on the clinical and public health aspects of the interaction between the iron acquisition mechanisms of select pathogens of public health importance with host iron homeostasis. Knowledge of these interactions is essential in assessing likely morbidity responses to supplementation. J. Nutr. 137: 1341–1344, 2007.

The redox potential of the Fe$^{2+}$/Fe$^{3+}$ switch is utilized in key biological systems of both eukaryotes and prokaryotes. This utility, however, is balanced with a ready capacity to participate in Fenton-type reactions with hydrogen or lipid peroxides that lead to the production of highly toxic free radicals. Cells invest in complex systems to control iron reactivity, availability, and flux to prevent free radical damage to proteins, ribonucleic acids, and cell membranes. Iron is essential and iron deficiency significantly impairs cell proliferation and immune function. Iron overload is equally detrimental, however, and because no iron excretory pathways exist, cellular homeostatic mechanisms must balance needs vs. overload and redox utility vs. toxicity.

This review summarizes the evidence for iron as a key regulator of host-pathogen interactions by describing the iron acquisition mechanisms of invading pathogens and their interactions with host regulation and illustrating how disturbances of iron homeostasis have been implicated in infectious disease pathogenesis. Clinical implications of iron-pathogen interactions are also discussed.

The host

Approximately 70% of body iron is incorporated into hemoglobin and erythropoiesis represents the single largest physiological requirement for iron. This pool of iron is rapidly turned over and iron recycling from senescent red blood cells through reticulo-endothelial (RE) macrophages provides for 90% of erythropoietic need. Dietary iron fulfills ~10%. With such large amounts of a potentially toxic element being mobilized and utilized on a daily basis, there is a need for complex, coordinated systems of transport, storage, and control, and this is reflected in the genomic investment of both eukaryotes and prokaryotes. There have been enormous advances in our understanding of iron homeostasis as the basic science behind these mechanisms has been demonstrated (1,2). Iron absorption and release from RE macrophages must be linked to erythroidlastic demand and the enterocyte and macrophage are central to iron homeostasis in the absence of an excretory pathway. The regulation of gut absorption is the primary homeostatic mechanism for total body iron content, but the transport of iron between sites of utilization and storage represents a major internal homeostatic mechanism.

Pathogens

In clinical situations where disturbances of host iron homeostasis are implicated in infectious disease pathogenesis, examining bacterial and protozoal iron acquisition mechanisms allows better understanding of when interference with, or disruption of, iron homeostasis might not benefit the host. Acquiring iron is a fundamental step in the development of a pathogen, and the complexity and redundancy of both host and pathogen mechanisms to acquire iron and control flux and availability illustrate the longstanding and ongoing battle for iron.

Iron redox enzyme systems are essential for respiration, DNA synthesis, and free radical-scavenging mechanisms in bacteria, but in the presence of inflammation, the host response is to withdraw iron. The iron-binding proteins of human blood limit the amount of free iron to the order of 10$^{-24}$. Bacteria, however, have developed mechanisms to acquire iron from transferrin, ferritin, and heme by 2 principal methods: either the synthesis of high iron affinity compounds such as siderophores, which take iron from iron-binding proteins, or by a method of direct capture of iron from these binding proteins and heme at the bacterial cell membrane. Bacteria of the enteric genus produce enterochelin,
which has the highest affinity of any siderophore. Heme and hemoproteins can also be used directly as a source of iron by Shigella, Escherichia, Yersinia, Neisseria, and Hemophilus species. The oxidation-reduction potential and pH of the local environment govern the binding of iron to transferrin (3). As pH falls, transferrin binding decreases and the availability of transferrin-bound iron increases. Tissue hypoxia often results in infection and invading bacteria can induce changes in the pH and oxidation-reduction potential of tissues as a natural result of bacterial metabolism, thereby increasing iron availability (4).

Many enteric bacteria have displayed increased virulence in situations of increased iron availability in vitro (5). In vivo evidence comes from situations of iron overload, hemolysis, and iron supplementation. Prophylactic intramuscular iron dextran given to Polynesian infants caused an increase in gram-negative neonatal sepsis that declined when supplementation stopped (6). In situations of iron overload, e.g. hemochromatosis, complicating bacteremias with Yersinia and Vibrio species were described (7). The transfusion of blood stored for periods >3 wk, thus prone to hemolysis and excess free iron, has been complicated by Yersinia bacteremias (8). The high-pathogenicity island present in pathogenic Yersinia and encoding the siderophores, yersiniabactin, has recently been identified in various Escherichia coli pathotypes responsible for bacteremia and urosepsis (9). In situations of iron overload or hemolysis, the mechanisms for the control of iron flux can be overwhelmed and bacteremia may result.

Intracellular pathogens

Intracellular pathogens, e.g. Mycobacterium tuberculosis, Salmonella, and Listeria species, evolved to evade the mammalian immune system by residing within macrophages in phagosomes. The competition between host and pathogen to control the intraphagosomal environment is crucial and a component of host immune control involves iron withdrawal. Mycobacteria acquire iron from transferrin, ferritin, and lactoferrin in the lung parenchyma by producing salicylic and citric acids and siderophores called mycobactins (10). Intraphagosomal pH and iron concentration is crucial to mycobacterial pathogenicity and both host and mycobacteria have developed competing mechanisms to adjust. NRAMP1 is a pH-dependent transporter of metal cations, including Fe2+, and is expressed exclusively in the lysosomes and late endosomes of monocytes and macrophages (11). It is recruited to phagosomal membranes where it acts to control the intraphagosomal environment, possibly in direct competition with the mycobacterial homolog MNTH (12). Iron restriction represents an important host mechanism of intracellular pathogen killing and NRAMP1 variants in humans have been associated with susceptibility or resistance to intracellular pathogens (13).

IFN-γ is crucial in the control of intracellular infections. It activates macrophages to promote the maturation and acidification of phagosomes, to decrease the expression of transferrin receptor on the phagosome membrane, and decrease the access of the bacterium to transferrin-bound iron (14). Iron has a direct inhibitory effect on the actions of IFN-γ and iron loading of macrophages results in inhibition of IFN-γ-mediated pathways and stimulates intraphagosomal mycobacterial growth (15). In conditions of iron overload, e.g. β-thalassemia patients, an increased susceptibility to salmonella and other intracellular pathogens has been described (16). Chronic inflammation and infection, however, are associated with marked effects on host iron metabolism, and determining whether these are cause or effect of disease is difficult. An autopsy series of African adults in the 1920s demonstrated an 11.4-fold increased risk of death from tuberculosis in patients with increased splenic iron (17). In HIV patients, higher bone marrow iron was associated with increased likelihood of tuberculosis (18). Information on host iron status prior to infection is difficult to find and both iron loading and iron deficiency (19) have been proposed as risk factors for human tuberculosis. Dietary iron overload is common in certain African populations and in Zimbabwean adults was associated with a 3.5-fold ([CI] 1.4–8.9) increased risk of tuberculosis (20). The haptoglobin 2-2 polymorphism is associated with increased macrophagal iron and was also associated with increased risk of death in adult Zimbabwean tuberculosis patients (21). In vitro work points to the importance of iron in the host-mycobacterium tuberculosis interaction; however, there is a paucity of in vivo data on how disturbances of host iron status affect susceptibility and disease severity. The data that do exist suggest that iron overload is associated with increased progression of disease. A more comprehensive review of the interactions between iron status and HIV and tuberculosis infection has been recently published (22).

Plasmodium falciparum

Inflammation, hemolysis, and the resultant flux of hemoglobin through macrophages during acute malaria result in increased oxidant stress (23) and availability of iron combined with a state of iron delocalization in RE macrophages (24). It is unclear how long this phenomenon persists after an episode of acute malaria; however, sequestration of iron in the bone marrow of children with chronic malaria was noted to coexist with iron-deficient erythropoiesis (25). The anemia associated with chronic asymptomatic malaria may be due to an inflammatory-mediated effect on iron redistribution to storage compartments and a resultant deficit in erythropoiesis production and/or bone marrow responsiveness (26). Many of the monocytes/macrophages of malaria-infected persons contain hemozoin. The hemozoin loading of monocytes and macrophages is an important factor in malaria-associated immunosuppression (27). Severity of disease correlates with percentage of hemozoin-laden macrophages and phagocytosis, reactive oxygen species, and NO generation are affected (28,29) (30). Twenty-one percent of inpatient child deaths from malaria in Kenya were associated with bacteremia (31) and over 40% of bacteremias complicating severe malaria were enteric in origin (32). Malaria-associated disturbances in host iron metabolism, increased oxidant stress-related damage to gut epithelium with subsequent translocation of bacteria, and immunosuppression secondary to macrophagal iron loading may contribute to these associations.

Iron deficiency anemia is common in areas of malaria transmission and has been associated with protection from malaria (33), although conventional biochemical indicators of iron status do not distinguish between true iron deficiency and iron delocalization secondary to malaria. Routine supplementation of all young children in areas of endemic iron deficiency is encouraged. However, a recent study of iron and folic acid supplementation to children <3 y in an area of intense malaria transmission demonstrated an increase in malaria and nonmalaria-related serious adverse events (34). This was a large, well-resourced, and adequately powered trial designed to assess the effect of zinc, iron, and folic acid supplementation, or all 3, on mortality. A subgroup analysis, however, demonstrated that patients that were iron deficient at the start of the trial benefited significantly from iron and folic acid supplementation.

HIV

HIV is associated with disturbances in host iron metabolism. In advanced disease, anemia can coincide with increased ferritin
and bone marrow iron content and the anemia is commonly unresponsive to iron supplementation. Increased bone marrow iron is associated with shortened survival and increased opportunistic infections (35). Whether disturbances in host iron metabolism increase susceptibility or severity of disease or whether the effect on iron metabolism is a result of disease is unclear.

In vitro studies have suggested that viral replication is inhibited after iron chelation (36). Iron overload is detrimental to host cell viability, increases p24 antigen measurements and reverse transcriptase activity whereas desferroxamine decreases p24 antigen levels, and improves cell viability (37). In a cross-sectional study of pregnant women in Zimbabwe receiving iron supplementation, ferritin was found to be an independent predictor of HIV viral load (38). However, in a cross-sectional study of pregnant women in Malawi, iron status was not related to markers of HIV disease severity. In iron-overloaded thalassemia major patients infected with HIV, the rate of progression of HIV disease was significantly associated with lower doses of desferroxamine and higher serum ferritin concentrations (39). Haptoglobin 2-2 was associated with increased iron stores, increased viral replication, and shortened survival in Belgian adults with HIV (40). It independently predicted higher viral load in pregnant Zimbabwean women (38) and was associated with lower CD4 counts in HIV-positive Ghanaians (41). In sub-Saharan Africa, endemic iron deficiency coexists in populations with high prevalence of HIV and iron plays an important role in the interaction between host and virus. To date, however, it is not clear whether disturbances in host iron metabolism cause or result from HIV progression.

In conclusion, iron is a key regulator of the host-pathogen interaction. Host homeostasis adapts during deficiency, overload, and infection to balance requirement against toxicity and availability to potential pathogens. Knowledge of these interactions is necessary to predict morbidity response to a disturbance in host iron homeostasis.

The decision to supplement either an individual or a population should include an assessment of likely morbidity response. This response may depend on the magnitude of deficiency, the dose of supplement, the presence of other nutritional deficiencies and interactions with other micronutrients, the level of immunity-compromise, the immediate pathogen environment, the intensity of transmission of malaria, and genetic variability in iron flux and oxidant stress control mechanisms. Both between and within populations, the infectious morbidity response to supplementation can vary as a result. In an environment of intense malaria transmission and high mortality in children $<5$ y, this variability translates into a measurable, detrimental effect at the population level.

Iron-deficient infants and young children do benefit from iron supplementation with improvement in cognition and possibly growth. In areas of intense malaria transmission and endemic iron deficiency, whole population iron supplementation is dangerous. The challenge now is to develop targeting strategies to supplement those children who benefit. This will not be easy, because routine biochemical assessment of iron deficiency is beyond the capacity of health providers in these areas. Therapeutic iron supplementation of iron-deficient severely anemic children living in areas of intense malaria transmission should continue, because they represent the severe end of the clinical spectrum of iron deficiency and the benefit of supplementation likely outweighs any potential risks.

Iron-deficient children benefit from supplementation. However, the decision to supplement in the presence of infection must be weighed carefully. Unless the host immune response is impaired by severe iron deficiency, there is rarely an urgency to supplement iron and it is likely to contribute little to host iron status due to the block on absorption associated with inflammation. In the presence of intracellular infections such as tuberculosis or chronic inflammatory or immunosuppressive diseases (e.g. HIV), the decision to supplement iron must be considered on an individual basis, because the potential exists to benefit a pathogen rather than the host. Currently, there is little evidence to assess morbidity response in these groups and this should be a priority research area.

**Literature Cited**


