

Clinical Perspective

The Role of Iron Metabolism in Host Innate Immunity to Infections

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Iron metabolism disorder is an important public health problem both in the United States and developing world. Iron is essential for both the host and the pathogen. While infections are important causes of morbidity and mortality globally, the relation between iron disorder and infection has received much attention, which is also an important aspect of 'Nutritional immunity'.

Although iron is abundant in nature, the extremely low solubility (10^{-18}M) of Fe^{3+} at pH 7 means that organisms face the problem of obtaining enough iron from environment. Deficiencies in iron uptake from the host can affect the virulence of bacteria.^{2,11} Iron overload diseases have been associated with altered responses to infection. Individuals with this disorder have an increased risk of infection with pathogens such as *Yersinia enterocolitica* and *Vibrio vulnificus*.^{3,5,7} Microorganisms have developed elaborate mechanisms to seize iron, often in competition with their host. The macrophage, which is both the host's main iron recycler and the home for intracellular bacteria such as *Salmonella* is the ideal battle field for iron. On host side, a well known gene that plays an important role in control of early intra-macrophage multiplication of *S. typhimurium* and in determining disease outcome is Nramp1 (Natural resistance-associated macrophage protein 1), a divalent metal transporter. Nramp1 in macrophages may also help to inhibit intracellular growth of *Salmonella* and other microorganism, mechanism of which probably involve the removal of iron from the phagosomal compartment where these microorganisms reside. Consistently, ex vivo experiments showed that change in expression or function of cellular iron exporter ferroportin (FPN), caused by mutations in the FPN gene itself or occurring secondary to abnormalities in hepcidin levels, may influence the growth of intracellular *Salmonella* by altering the iron available for microbial acquisition.⁴ It has also been suggested that hemochromatosis may confer protection against intra-macrophage pathogens, thereby providing a survival advantage to the host during epidemics of such organisms. This idea has been used to explain the unusually high frequency of *HFE* gene variants in European populations,⁸ and has received support from recent cell culture studies.^{9,10}

In addition, iron is required for various innate host defense mechanisms, including respiratory burst, which is a vital defense mechanism against salmonellae, listeriae, and other bacteria.¹ Depleting iron exacerbates *Salmonella typhimurium* (*S. typhimurium*) infection in mice through the inhibition of reactive oxygen intermediates (ROI) production. Iron depletion of *Listeria*-infected macrophages blocks ROI production and enhances listerial growth. Alternatively, excess iron will down-regulate reactive nitrogen intermediates (RNI) and NO production, which will lead to an impaired innate host defense. Exogenous iron inhibits macrophage NO formation against *Plasmodium falciparum*.⁶ Both elevated and reduced iron availability impair host innate immune response, which addresses the importance of a normal iron balance for optimal functioning of the host immune system. Clearly, for iron-overloaded host, both a direct impairment of immune responses and improved access of the invading pathogens to iron will increase the susceptibility to infection.

Although the relation of iron disorders with infections has long been appreciated clinically, the mechanisms involved in this association have not been studied previously. Analyzing the role of iron on the control of bacterial infection will shed new light on this issue, and provide novel insights into the interactions between pathogens and their hosts.

References

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Editorial Comment

Baochong B. Chang, MD, PhD

Iron absorption and storage is strictly regulated in our body. We observe major medical problems and even death in extreme cases, in patients of iron overload or iron deficiency. The article by Lijian Wang, MD highlighted some research advances of potential mechanisms involving iron disorder, host defense and infection.

References

1. Macrophage is a key player between host and microorganisms through natural resistance-associated macrophage protein 1 (Nramp1), iron exporter ferroportin (FPN) and hepcidin.
2. Iron affects the host immunity through reactive oxygen intermediates (ROI), nitrogen intermediates (RNI), etc.
3. HFE gene mutations found in human hematochromatosis may be associated with intestinal bacteria infection. Further researches are to be done to reveal more detailed mechanisms.