Published in final edited form as:
Curr Opin Immunol. 2009 February ; 21(1): 63–67. doi:10.1016/j.coi.2009.01.011.

Iron in Innate Immunity: Starve the Invaders

Tomas Ganz, PhD, MD
Professor of Medicine and Pathology, David Geffen School of Medicine at UCLA, Los Angeles, CA 90095-1690, E-mail: tganz@mednet.ucla.edu

Summary

Iron is essential for nearly all living organisms. Innate immunity effectively restricts iron availability to microbial invaders. Some microbes have evolved effective countermeasures that blunt the effect of iron restriction. Recent epidemiologic studies have highlighted the potentiating effect of iron on microbial infections. Laboratory studies have focused on specific immune mechanisms that mediate iron withholding from microbes constitutively and in response to infections. Specialized inflammation-regulated proteins chelate iron, trap siderophores, and transport iron or modulate its transport to alter its tissue distribution during infections.

Introduction

Iron is an essential trace element for humans and other vertebrate hosts, as well as for their microbial invaders. Although iron is abundant in the Earth's crust, its natural forms are poorly soluble, and so its supply is often insufficient for optimal growth and function of either microbes or their hosts. This review discusses specific mechanisms of innate immunity that further restrict the availability of iron on host surfaces exposed to environmental microbes, and to an even greater extent in infected tissues. Within hours of infection in humans and other vertebrates, concentrations of iron in extracellular fluid and plasma dramatically decrease (hypoferremia). Macrophages involved in recycling iron from erythrocytes limit the release of the recycled iron, thus lowering the extracellular iron concentration. Under the influence of cytokines, macrophages infected by intracellular microbes inhibit their multiplication by moving iron from the phagosomes to cytoplasmic ferritin. As part of their host defense repertoire, neutrophils accumulating in infected tissues secrete proteins that chelate various forms of iron. Among microbes that are well adapted to their hosts, some have evolved countermeasures that allow them to obtain iron from host ferroproteins, including hemoglobin, ferritin, and transferrin, other microbes specifically interfere with iron-sequestering host mechanisms. Host genetics and nutritional/medical practices also affect tissue and extracellular iron concentrations and are thought to modulate susceptibility to infection.

Epidemiology of iron and infections

Accumulated evidence supports the concept that infections with a variety of microbes are increased in frequency and severity in humans with iron overload (due to iron supplementation, hereditary hemochromatosis, erythrocyte transfusions or unknown causes, as reviewed in [1; 2] with recent new data [3–5]). Some infections (notably malaria) may be less frequent and less severe in iron-deficient patients [6;7] and this has raised questions about iron

supplementation in regions endemic for malaria [8]. The potential mechanisms of the role of iron in susceptibility and resistance to infections have been recently reviewed [9–11]. Surprisingly, iron overload may exacerbate some virus-mediated diseases as well, either by facilitating viral replication or by promoting tissue injury or secondary infections [12].

Animal models of the interaction between iron and infections

The severity of infections in mice with the specialized human pathogen Neisseria meningiditis is strongly dose-dependent on the co-administration of human iron transferrin (holotransferrin) [13]. Neisseria have a specific iron acquisition receptor for human holotransferrin that does not recognize the murine version of the protein. Mice made transgenic in human transferrin developed prolonged bacteremia with *N. meningiditis* and but their wild-type counterparts rapidly cleared the infection [14]. In a mouse model of *M. tuberculosis* infection, iron supplementation resulted in about 10-fold increase in bacterial CFU compared to unsupplemented mice[15]. These models make it plausible that the hypoferremia associated with infections could significantly decrease the rate of microbial proliferation.

Specific mechanisms of iron sequestration in innate immunity

Multiple mechanisms of innate immunity restrict the iron supply to microbial invaders (Table I). Some of these mechanisms function constitutively to protect vulnerable exposed tissues but most are inducible by exposure to pathogen-associated molecules, either directly or in response to specific cytokines.

Lactoferrin

Lactoferrin is an 80kD glycoprotein structurally very similar to transferrin (reviewed in [16]). Like transferrin, it binds two ferric ions very tightly but differs from transferrin in not releasing the iron at acid pH prevalent in infected or hypoxic areas. Lactoferrin is found at high concentration in neutrophils and mucosal secretions. It has been reported to be antimicrobial through multiple mechanisms (reviewed in [17]) including its ability to chelate iron[18]. Surprisingly, mice with ablation of the lactoferrin gene had a very mild phenotype manifested by a two-fold increase in spontaneous staphylococcal infections but no difference in resistance to *S. aureus* and *P. aeruginosa* in various models of infection. These observations suggest that the function of lactoferrin is largely redundant or that lactoferrin more narrowly targets as yet unidentified specific pathogens.

Siderocalin (also called: lipocalin-2, neutrophil gelatinase-associated lipocalin or NGAL, or in mice: 24p3)

Siderocalin is a 24 kD protein that binds enterobactin of E. coli (also called enterochelin) and other catechol-related siderophores, small secreted organic iron chelators used by microbes to acquire iron from their environment (reviewed in [19]). Siderocalin is selectively bacteriostatic to bacteria that are dependent on siderophores scavenged by siderocalin. The synthesis of siderocalin is massively induced during sepsis and mice deficient in siderocalin are more susceptible to bacteremia and death from E. coli sepsis [20]. As indicated by increased mycobacterial invasion of epithelial cells in siderocalin-deficient mice, siderocalin may also be protective in the airways [21]. Recent studies have identified bacterial evasion mechanisms [19;22] that covalently modify enterobactin to weaken its interaction with siderocalin.

Natural resistance-associated macrophage protein-1 (Nramp1, also called Slc11a1)

Nramp1 is an 90–100kD integral membrane protein of macrophage and neutrophil phagosomes that functions as a divalent metal-proton symporter (reviewed in [23]). The role of the Nramp1 gene in innate immunity was originally identified because a mutation in Nramp1 occurring in common mouse strains conferred susceptibility to infection with intracellular microbes that localize in macrophages, including *Mycobacteria, Salmonella typhimurium and Leishmania donovanii*. Although controversy about the specific mechanism still persists, it now appears that Nramp1 acts by depleting Fe^{2+}, Co^{2+} and Mn^{2+} from the phagosome, and thereby starving the phagosomal microbes of these essential nutrients. Moreover, a recent study suggests that Nramp1 also acts by an as yet unknown mechanism to decrease cellular iron content [24]. Both of these mechanisms should inhibit microbial proliferation within macrophages. Nramp1 expression in macrophages is transcriptionally induced by interferon-γ and lipolysaccharide through a mechanism involving the Interferon Regulatory Factor 8 [25], thus linking macrophage activation to a specific iron-dependent microbistatic mechanism.

Transferrin receptor-1 (TfR1)

Cell membrane TfR1 binds iron-transferrin (Tf-Fe) from plasma. After endocytosis, the TfR1-Tf-Fe complex releases its iron in acidified vacuoles, and TfR1-Tf returns to plasma membrane and returns (apo)Tf into plasma. TfR1 is essential for iron utilization by erythrocyte precursors but it is also present on many other cell types, including macrophages. Several studies have shown that TfR1 is reduced in activated macrophages and that interferon-γ potently suppresses TfR1 expression [26–29], and reduces iron incorporation by macrophages. Reduced availability of iron limits the multiplication of *Legionella pneumophila*, an intracellular bacterium that resides in macrophages. The mechanism of TfR1 suppression is not fully understood but may be in part mediated by the effects of inflammation-induced nitric oxide-nitrosonium on IRP2 [30].

Hepcidin and ferroportin

Hepcidin is a 2.7 kD peptide hormone that controls extracellular iron concentrations by regulating dietary iron absorption and the release of iron from stores in macrophages and hepatocytes. The receptor for hepcidin is the cellular iron exporter ferroportin, a 70kD integral membrane protein expressed in all iron-transporting tissues including duodenal epithelium, macrophages that recycle iron from senescent erythrocytes and iron-storing hepatocytes. When hepcidin binds to ferroportin, ferroportin is internalized and degraded, and the export of cellular iron to plasma is diminished (reviewed in [31;32]). The continued utilization of iron then depletes the relatively small pool of plasma and extracellular iron. In mice, the injection of 50 μg of hepcidin produces rapid and profound hypoferremia that lasts for 48 hours. During inflammation, the synthesis of hepcidin is transcriptionally induced by inflammatory stimuli and specifically by IL-6 [33] acting through the transcription factor STAT3 [34–36]. After an inflammatory stimulus such as IL-6 or lipopolysaccharide, the development of hypoferremia in human volunteers coincided with the rise in hepcidin[37;38]. The same response is seen in patients with malaria [39]. Thus, extracellular microbes face low iron concentrations during inflammation.

For intracellular microbes in phagosomes of macrophages, iron concentrations would be determined by the balance between mechanisms that move iron into and out of phagosomes. On one hand, hepcidin-mediated degradation of ferroportin and the resulting retention of iron in macrophage cytoplasmic ferritin could provide additional iron for intracellular pathogens, as suggested by the effects of hepcidin in macrophage-like cell lines and cultured macrophages,

with or without ferroportin overexpression [40;41]. In some cells, ferroportin is found on phagosomal membranes [42] thus providing a pathway for moving hepcidin from ferritin into phagosomes. Ferroportin was not detected in inclusion bodies of Chlamydia, and it is not clear how the accumulated cellular iron reaches the bacteria. Mechanisms that favor iron movement out of phagosomes include the presence of inflammation-stimulated Nramp1 as well as Nramp2 in phagosomal membranes [23]. Additional mechanisms that may modulate the iron content of phagosomes include the autocrine production of hepcidin by macrophages [43] and the feedback effects of intracellular iron concentrations on ferroportin expression [44;45]. The ability of intracellular microbes to manipulate the composition of phagosomes, to alter the expression of iron transporters and to degrade ferritin [46] further complicates any attempts at modeling the net effect of inflammation on the subcellular iron distribution in macrophages.

What is the effect of the hepcidin-ferroportin interaction on innate immunity in vivo? Genetic deficiency of hepcidin is the fundamental cause of hereditary hemochromatosis, with additional cases due to ferroportin mutations causing resistance to hepcidin. Hepcidin deficiency may result from mutations in hepcidin regulators (hemochromatosis protein HFE, transferrin receptor 2 and hemojuvelin) or in the hepcidin gene itself. Hereditary hemochromatoses are known to be associated with a predisposition to a variety of infections [2], most characteristically with Yersinia and Vibrio spp. However, the specific associations are subject to reporting bias which may result in underreporting of common infections compared to exotic ones. More detailed studies are needed to establish whether the predisposition is due to baseline high iron saturation of plasma transferrin, or to the reduced ability of the patients with hemochromatosis or other forms of iron overload to develop inflammatory hypoferremia.

Conclusions

The evidence is strong that iron restriction is an important component of innate immunity, and a potential target for therapeutic intervention. The specific mechanisms are multiple and complex and are met with microbial countermeasures. The net effect of iron restriction on microbes *in vivo* is a timely subject for further study.

Reference List

1•. Boelaert JR, Vandecasteele SJ, Appelberg R, Gordeuk VR. The effect of the host's iron status on tuberculosis. J Infect Dis 2007;195:1745–1753. [PubMed: 17492589]A comprehensive and balanced analysis of evidence for the role of iron in the pathogenesis of tuberculosis

2. Khan FA, Fisher MA, Khakoo RA. Association of hemochromatosis with infectious diseases: expanding spectrum. Int J Infect Dis 2007;11:482–487. [PubMed: 17600748]

3. Garcia-Vidal C, Upton A, Kirby KA, Marr KA. Epidemiology of invasive mold infections in allogeneic stem cell transplant recipients: biological risk factors for infection according to time after transplantation. Clin Infect Dis 2008;47:1041–1050. [PubMed: 18781877]Cumulative erythrocyte transfusion history is associated with invasive mold infections in allogeneic hematopoietic stem cell transplant recipients

4. McDermid JM, Jaye A, Schim van der Loeff MF, Todd J, Bates C, Austin S, Jeffries D, Awasana AA, Whittlex AA, Prentice A. Elevated iron status strongly predicts mortality in West African adults with HIV infection. J Acquir Immune Defic Syndr 2007;46:498–507. [PubMed: 18077841]

5•. Rawat R, Humphrey J, Ntozini R, Mutasa K, Iliff P, Stoltzfus R. Elevated iron stores are associated with HIV disease severity and mortality among postpartum women in Zimbabwe. Public Health Nutr 2008:1–9. [PubMed: 19000344]4 and 5. Markers of iron overload are associated with increased all-cause mortality in HIV infection but the specific mechanism responsible for increased deaths has not been pinpointed

6. Kabyemela ER, Fried M, Kurtis JD, Mutabingwa TK, Duffy PE. Decreased susceptibility to Plasmodium falciparum infection in pregnant women with iron deficiency. J Infect Dis 2008;198:163–

166. [PubMed: 18500927]Iron deficiency may protect against malaria through an as yet unknown mechanism

7•. Koka S, Foller M, Lamprecht G, Boini KM, Lang C, Huber SM, Lang F. Iron deficiency influences the course of malaria in Plasmodium berghei infected mice. Biochem Biophys Res Commun 2007;357:608–614. [PubMed: 17445762]In a mouse model of malaria, iron deficiency increased mouse survival and decreased parasitemia, in part through increased clearance of infected iron-deficient erythrocytes compared to infected normal erythrocytes

8••. Prentice AM. Iron Metabolism, Malaria, and Other Infections: What Is All the Fuss About? J Nutr 2008;138:2537–2541. [PubMed: 19022986]This knowledgeable review advises caution in using indiscriminate iron supplementation in areas with endemic malaria. Directing iron supplementation only to iron-deficient children, or combining therapy for malaria with iron supplementation may be safer strategies

9. Denic S, Agarwal MM. Nutritional iron deficiency: an evolutionary perspective. Nutrition 2007;23:603–614. [PubMed: 17583479]The work questions whether iron deficiency in *regions* with a high burden of infections is a disease or a protective evolutionary adaptation. Although the article contains some errors, the question it raises may have important implications for the treatment of iron deficiency

10. Doherty CP. Host-pathogen interactions: the role of iron. J Nutr 2007;137:1341–1344. [PubMed: 17449603]

11. Schaible UE, Kaufmann SH. Iron and microbial infection. Nat Rev Microbiol 2004;2:946–953. [PubMed: 15550940]

12•. Drakesmith H, Prentice A. Viral infection and iron metabolism. Nat Rev Microbiol 2008;6:541–552. [PubMed: 18552864]This article reviews the evidence for the facilitating role of iron in the pathogenesis of viral infections

13. Holbein BE. Enhancement of Neisseria meningitidis infection in mice by addition of iron bound to transferrin. Infect Immun 1981;34:120–125. [PubMed: 6795121]

14. Zarantonelli ML, Szatanik M, Giorgini D, Hong E, Huerre M, Guillou F, Alonso JM, Taha MK. Transgenic mice expressing human transferrin as a model for meningococcal infection. Infect Immun 2007;75:5609–5614. [PubMed: 17893132]

15. Schaible UE, Collins HL, Priem F, Kaufmann SH. Correction of the iron overload defect in beta-2-microglobulin knockout mice by lactoferrin abolishes their increased susceptibility to tuberculosis. J Exp Med 2002;196:1507–1513. [PubMed: 12461085]

16. Baker EN, Baker HM. Molecular structure, binding properties and dynamics of lactoferrin. Cell Mol Life Sci 2005;62:2531–2539. [PubMed: 16261257]

17. Jenssen H, Hancock RE. Antimicrobial properties of lactoferrin. Biochimie. 2008

18. Gallin JI, Zarember K. Lessons about the pathogenesis and management of aspergillosis from studies in chronic granulomatous disease. Trans Am Clin Climatol Assoc 2007;118:175–185. [PubMed: 18528501]

19. Abergel RJ, Clifton MC, Pizarro JC, Warner JA, Shuh DK, Strong RK, Raymond KN. The siderocalin/enterobactin interaction: a link between mammalian immunity and bacterial iron transport. J Am Chem Soc 2008;130:11524–11534. [PubMed: 18680288]The work provides structural analysis of the interaction of siderophores with siderocalin

20. Flo TH, Smith KD, Sato S, Rodriguez DJ, Holmes MA, Strong RK, Akira S, Aderem A. Lipocalin 2 mediates an innate immune response to bacterial infection by sequestrating iron. Nature 2004;432:917–921. [PubMed: 15531878]

21•. Saiga H, Nishimura J, Kuwata H, Okuyama M, Matsumoto S, Sato S, Matsumoto M, Akira S, Yoshikai Y, Honda K, Yamamoto M, Takeda K. Lipocalin 2-Dependent Inhibition of Mycobacterial Growth in Alveolar Epithelium. J Immunol 2008;181:8521–8527. [PubMed: 19050270]This article analyzes the increased susceptibility of siderocalin-deficient mice to *M. tuberculosis*, and identifies a role for siderocalin of epithelial cells in resistance to these bacteria

22•. Fischbach MA, Lin H, Zhou L, Yu Y, Abergel RJ, Liu DR, Raymond KN, Wanner BL, Strong RK, Walsh CT, Aderem A, Smith KD. The pathogen-associated iroA gene cluster mediates bacterial evasion of lipocalin 2. Proc Natl Acad Sci USA 2006;103:16502–16507. [PubMed: 17060628]

Some bacteria evade siderocalin by covalently modifying their siderophores to decrease its affinity for this host defense protein

23•. Cellier MF, Courville P, Campion C. Nramp1 phagocyte intracellular metal withdrawal defense. Microbes Infect 2007;9:1662–1670. [PubMed: 18024118]An up-to-date review of the activity and probable role of Nramp1 in phagocytes

24•. Fritsche G, Nairz M, Theurl I, Mair S, Bellmann-Weiler R, Barton HC, Weiss G. Modulation of macrophage iron transport by Nramp1 (Slc11a1). Immunobiology 2007;212:751–757. [PubMed: 18086376]A stimulating article that analyzed the impact of wild-type and mutated Nramp1 on iron distribution in RAW264.7 mouse macrophage-like cell lines. Functional Nramp1 reduced iron availability in macrophages by a complex mechanism

25•. ter-Koltunoff M, Goren S, Nousbeck J, Feng CG, Sher A, Ozato K, Azriel A, Levi BZ. Innate immunity to intraphagosomal pathogens is mediated by interferon regulatory factor 8 (IRF-8) that stimulates the expression of macrophage-specific Nramp1 through antagonizing repression by c-Myc. J Biol Chem 2008;283:2724–2733. [PubMed: 18045875]The article analyzes the mechanism of Nramp1 induction by interferon-γ

26. Byrd TF, Horwitz MA. Interferon gamma-activated human monocytes downregulate transferrin receptors and inhibit the intracellular multiplication of Legionella pneumophila by limiting the availability of iron. J Clin Invest 1989;83:1457–1465. [PubMed: 2496141]

27. Byrd TF, Horwitz MA. Regulation of transferrin receptor expression and ferritin content in human mononuclear phagocytes. Coordinate upregulation by iron transferrin and downregulation by interferon gamma. J Clin Invest 1993;91:969–976. [PubMed: 8450071]

28. Byrd TF, Horwitz MA. Lactoferrin inhibits or promotes Legionella pneumophila intracellular multiplication in nonactivated and interferon gamma-activated human monocytes depending upon its degree of iron saturation. Iron-lactoferrin and nonphysiologic iron chelates reverse monocyte activation against Legionella pneumophila. J Clin Invest 1991;88:1103–1112. [PubMed: 1918366]

29. Byrd TF, Horwitz MA. Chloroquine inhibits the intracellular multiplication of Legionella pneumophila by limiting the availability of iron. A potential new mechanism for the therapeutic effect of chloroquine against intracellular pathogens. J Clin Invest 1991;88:351–357. [PubMed: 2056129]

30. Kim S, Ponka P. Effects of interferon-gamma and lipopolysaccharide on macrophage iron metabolism are mediated by nitric oxide-induced degradation of iron regulatory protein 2. J Biol Chem 2000;275:6220–6226. [PubMed: 10692416]

31. Ganz T. Molecular control of iron transport. J Am Soc Nephrol 2007;18:394–400. [PubMed: 17229910]

32•. Ganz T, Nemeth E. Regulation of iron acquisition and iron distribution in mammals. Biochim Biophys Acta 2006;1763:690–699. [PubMed: 16790283]31–32. Recent reviews of hepcidin, ferroportin and their role in systemic iron homeostasis

33. Nemeth E, Rivera S, Gabayan V, Keller C, Taudorf S, Pedersen BK, Ganz T. IL-6 mediates hypoferremia of inflammation by inducing the synthesis of the iron regulatory hormone hepcidin. J Clin Invest 2004;113:1271–1276. [PubMed: 15124018]

34. Wrighting DM, Andrews NC. Interleukin-6 induces hepcidin expression through STAT3. Blood 2006;108:3204–3209. [PubMed: 16835372]

35. Pietrangelo A, Dierssen U, Valli L, Garuti C, Rump A, Corradini E, Ernst M, Klein C, Trautwein C. STAT3 is required for IL-6-gp130-dependent activation of hepcidin in vivo. Gastroenterology 2007;132:294–300. [PubMed: 17241879]

36••. Verga Falzacappa MV, Vujic SM, Kessler R, Stolte J, Hentze MW, Muckenthaler MU. STAT3 mediates hepatic hepcidin expression and its inflammatory stimulation. Blood 2007;109:353–358. [PubMed: 16946298]34.–36. Three complementary articles describe the molecular mechanism of transcriptional induction of hepcidin by IL-6

37. Kemna E, Pickkers P, Nemeth E, van der HH, Swinkels D. Time-course analysis of hepcidin, serum iron, and plasma cytokine levels in humans injected with LPS. Blood 2005;106:1864–1866. [PubMed: 15886319]

38. Nemeth E, Rivera S, Gabayan V, Keller C, Taudorf S, Pedersen BK, Ganz T. IL-6 mediates hypoferremia of inflammation by inducing the synthesis of the iron regulatory hormone hepcidin. J Clin Invest 2004;113:1271–1276. [PubMed: 15124018]

39••. de Mast Q, Nadjm B, Reyburn H, Kemna EH, Amos B, Laarakkers CM, Silalye S, Verhoef H, Sauerwein RW, Swinkels DW, van dV. Assessment of Urinary Concentrations of Hepcidin Provides Novel Insight into Disturbances in Iron Homeostasis during Malarial Infection. J Infect Dis. 200839. Hepcidin is increased in malaria, causes iron restriction, and this probably contributes to the anemia associated with this disease

40. Chlosta S, Fishman DS, Harrington L, Johnson EE, Knutson MD, Wessling-Resnick M, Cherayil BJ. The iron efflux protein ferroportin regulates the intracellular growth of Salmonella enterica. Infect Immun 2006;74:3065–3067. [PubMed: 16622252]

41••. Paradkar PN, De DI, Durchfort N, Zohn I, Kaplan J, Ward DM. Iron depletion limits intracellular bacterial growth in macrophages. Blood 2008;112:866–874. [PubMed: 18369153]40–41. Two articles indicate that ferroportin overexpression suppresses and accordingly, hepcidin treatment increases the growth of intracellular microbes. These findings are somewhat counterintuitive and point to a possible dichotomy between the effect of hepcidin on extracellular vs. intracellular bacteria. The results should be interpreted cautiously as they rely on overexpressing cell lines or isolated macrophages, systems that alter the physiologic regulation of hepcidin and ferroportin synthesis

42•. Van Zandt KE, Sow FB, Florence WC, Zwilling BS, Satoskar AR, Schlesinger LS, Lafuse WP. The iron export protein ferroportin 1 is differentially expressed in mouse macrophage populations and is present in the mycobacterial-containing phagosome. J Leukoc Biol 2008;84:689–700. [PubMed: 18586980]The response of ferroportin to stimulation by cytokines or mycobacteria differs between macrophages isolated from different sites. If confirmed, the observed expression of ferroportin on phagosomal membranes would further complicate any predictions about iron fluxes in and out of phagosomes

43•. Theurl I, Theurl M, Seifert M, Mair S, Nairz M, Rumpold H, Zoller H, Bellmann-Weiler R, Niederegger H, Talasz H, Weiss G. Autocrine formation of hepcidin induces iron retention in human monocytes. Blood 2008;111:2392–2399. [PubMed: 18073346]The production of hepcidin by monocytes and macrophages may locally regulate iron export from macrophages and lead to local (as opposed to systemic) iron sequestration

44. Delaby C, Pilard N, Goncalves AS, Beaumont C, Canonne-Hergaux F. Presence of the iron exporter ferroportin at the plasma membrane of macrophages is enhanced by iron loading and down-regulated by hepcidin. Blood 2005;106:3979–3984. [PubMed: 16081696]

45••. Delaby C, Pilard N, Puy H, Canonne-Hergaux F. Sequential regulation of ferroportin expression after erythrophagocytosis in murine macrophages: early mRNA induction by haem, followed by iron-dependent protein expression. Biochem J 2008;411:123–131. [PubMed: 18072938]A careful analysis of macrophage response to the heme and iron load presented by phagocytosis of erythrocytes. The cellular regulation of ferroportin is an area that needs more investigation

46. Larson JA, Howie HL, So M. Neisseria meningitidis accelerates ferritin degradation in host epithelial cells to yield an essential iron source. Mol Microbiol 2004;53:807–820. [PubMed: 15255894]

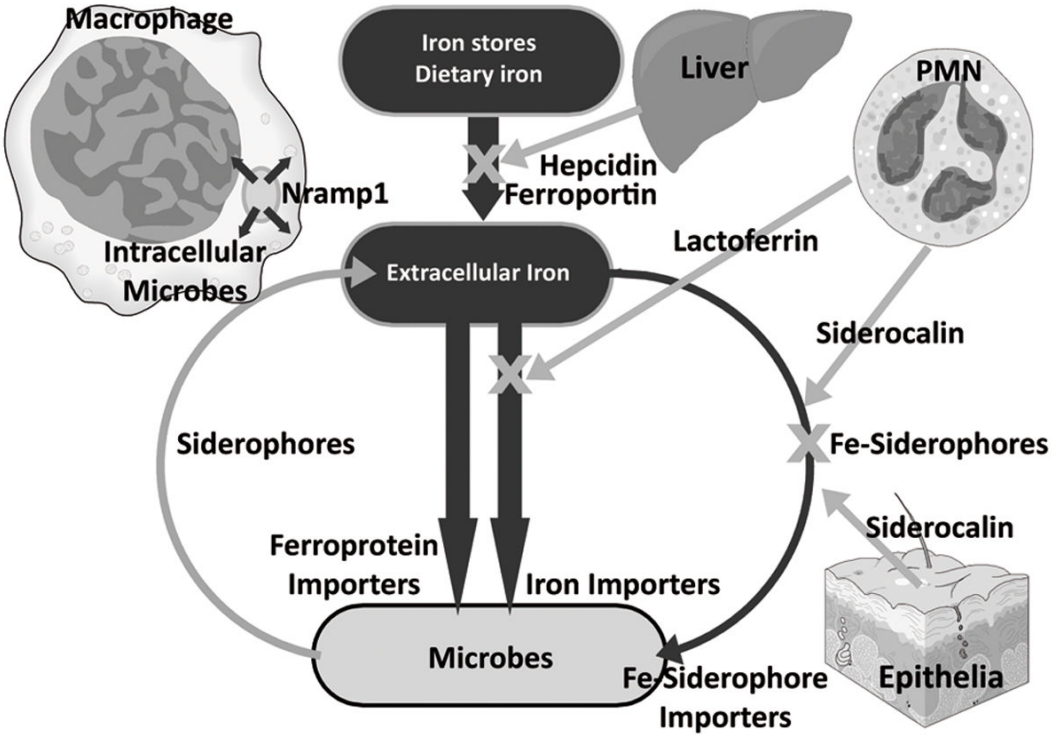

Figure 1.
Key host defense mechanisms restricting iron supply to microbes. Iron flows are shown in black.

Table I

Representative host mechanisms that sequester iron during infections

Mechanism	Protein	Tissues	Response to infection	Effect on iron
High affinity binding of Fe	lactoferrin	Neutrophils, mucosal epithelia	Local degranulation or secretion	Decreased availability to most pathogens
High affinity binding of siderophores	lipocalin-2	Neutrophils, epithelia, hepatocytes	Degranulation or secretion	Decreased availability to microbes using affected siderophores
Fe transport	Nramp1 (Slc11a1)	Macrophages, neutrophils	Activation in phagosomal membranes	Iron export from phagocytic vacuoles
Fe transport	ferroportin (Slc40a1)	Macrophages Enterocytes	Increased hepcidin degrades ferroportin	Decreased extracellular and plasma iron
Fe transport	transferrin receptor 1 (TfR1)	Many	Interferon-γ suppresses TfR1 expression in macrophages	Iron depletion of activated macrophages