Hepcidin and the Iron-Infection Axis

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Iron lies at the center of a battle for nutritional resource between higher organisms and their microbial pathogens. The iron status of the human host affects the pathogenicity of numerous infections including malaria, HIV-1, and tuberculosis. Hepcidin, an antimicrobial-like peptide hormone, has emerged as the master regulator of iron metabolism. Hepcidin controls the absorption of dietary iron and the distribution of iron among cell types in the body, and its synthesis is regulated by both iron and innate immunity. We describe how hepcidin integrates signals from diverse physiological inputs, forming a key molecular bridge between iron trafficking and response to infection.

Of the 30 or so essential micronutrients, iron has a very particular role in mediating host-pathogen interactions. It has been the focus of an ongoing evolutionary battle for nutritional resource because its valency states endow it with useful oxidoeductive properties that have been adopted by numerous enzyme and oxygen transport systems across most life forms, and because it is extremely insoluble at neutral pH. Iron is the only micronutrient known to have a regulatory hormone that responds to both nutrient status and infection: The recently discovered hepcidin (Box 1) integrates diverse signals from iron status and infectious threat and orchestrates a series of host-protective responses.

It has long been established in animal models that a host’s iron status can influence infection, and there is parallel evidence in humans. For example, a study of iron-deficient Somali refugees recorded five times the number of infections (including reactivation of preexisting malaria, brucellosis, and tuberculosis) in those receiving iron supplements relative to a placebo group (7). However, the subsequent evidence for associations between host iron status and infectious diseases in humans has been mixed, reflecting several issues: (i) The evolutionary battle is finely balanced; (ii) most studies of therapeutic iron supplementation assess hematological rather than infectious outcomes, and a physician may be satisfied if the presenting condition of anemia or iron deficiency abates; (iii) iron status is often poorly defined, and hemoglobin represents an imperfect proxy, particularly when infections are prevalent; and (iv) the effects are likely to be context-specific, depending on the patient’s preexisting iron status, exposure to potential infections and co-infections, and genetic background (2) (Fig. 1). A large iron supplementation trial of young children in Pemba Island, which was prematurely terminated as a result of an excess of serious adverse events (including deaths) in those receiving iron, illustrates these complexities (3).

Host Mechanisms for Withholding Iron from Microorganisms

Unbound iron or heme (released during constitutive or infectious hemolytic conditions), as well as providing the most critical growth-limiting nutrient to potential pathogens, can generate toxic free radicals that would cause host tissue damage if not contained. Systems have therefore evolved to ensure that iron and heme are tightly chaperoned. In humans, the dominant chaperone proteins are transferrin, lactoferrin, and ferritin for iron; haptoglobin for hemoglobin; and hemopexin for heme. These are regulated according to need and participate in receptor-mediated uptake by target cells. The fact that all are acute-phase proteins whose levels are modulated by infection (negatively in the case of transferrin, positively for the others) is an important clue concerning the centrality of iron in host defense against potential pathogens. The abundance of lactoferrin in breast milk and other epithelium-protecting secretory fluids, together with its release by neutrophils at foci of infection, is further compelling evidence.

The bacteriostatic effects of iron-binding proteins were first reported by Schade and Caroline (4), who noted that specific iron-binding proteins in egg white (ovotransferrin) and blood (transferrin) inhibited the growth of certain bacteria—an effect easily reversed by adding iron. Under normal physiological circumstances, although there is abundant iron in body fluids, these iron-binding proteins are only partially saturated and the amount of free iron in equilibrium is about 10⁻¹⁸ M, far too low to sustain bacterial growth (5). When an infectious threat is recognized by the host, these very low levels of iron are reduced still further by the “hypoferremia of infection,” a host-defense mechanism also recognized in the 1940s and now known to be largely mediated by hepcidin (see below). In several genetic conditions (e.g., hemochromatosis), transferrin saturation rises and free iron (so-called non–transferrin-bound iron, NTBI) may become available, enhancing the threat of infection (6). Iatrogenic causes of NTBI include transfusional iron overload and, less recognized, simple oral iron supplementation. Oral iron supplementation provides a nonphysiological bolus dose of highly absorbable iron that can temporarily overwhelm the regulatory and chaperone mechanisms that normally mediate the safe passage of iron from enterocytes to the target tissues.

During the relatively unhygienic conditions of our evolutionary history (conditions that remain prevalent in many regions of the world), humans were under constant and simultaneous threat from a range of potentially fatal microorganisms and, like an overstretched general fighting a war on many fronts, would have been forced to select which battles to fight first. The hypoferremia of infection is only one of numerous innate and adaptive defenses. It is targeted against iron-dependent extracellular organisms that could otherwise cause a rapidly fatal septicemia. But in choosing to divert iron toward macrophages, the host provides an opportunity for intracellular organisms. The niche selection of such pathogens may have evolved to capitalize on the rich source of the growth-critical nutrient iron in the macrophages of a host that is busy protecting itself from other pathogens.

Mechanisms for Iron Acquisition by Microorganisms

Almost all microorganisms are dependent on iron to a greater or lesser extent. This appears to be true for most human pathogens, and, in competition with the host’s evolution of iron-withholding strategies, they have evolved an array of mechanisms for scavenging iron. There are more than 500 known bacterial siderophores (small, high-affinity iron-chelating compounds), some with iron binding constants that would challenge the skills of the best synthetic chemists. Further confirmation of the centrality of iron for pathogen vigor is provided by the high level of genomic investment in iron-acquiring mechanisms and by the frequent concentration of such genes in high-pathogenicity islands. For example, highly pathogenic strains of Yersinia enterocolytica, Y. pseudotuberculosis, and Y. pestis possess a common high-pathogenicity island (apparently acquired by horizontal capture from another organism) that encodes proteins necessary for the synthesis, transport, and regulation of the siderophore yersiniabactin (7).

Genetic detective work based on the full sequence of Y. pestis suggests that acquisition of these improved iron-acquiring capabilities allowed the organism to make a niche transition from being an enteric to a systemic pathogen (8). Niche specificity is determined by the source from which bacteria obtain iron and by the efficiency with which they can do so (Fig. 2).

Hepcidin: Master Regulator of Iron Metabolism

In the 1930s, a consensus developed that iron homeostasis in humans is maintained by regulating intestinal absorption (9). About 1 mg of iron
is typically absorbed per day from the diet, with the majority destined to be incorporated into heme during erythropoiesis in the bone marrow. Senescent red blood cells are phagocytosed and degraded by macrophages, with about 25 mg of iron per day recycled back into serum via this route (fig. S1A). How is this iron cycle controlled?

Although many molecular pathways are involved, the current thinking is that the circulating peptide hormone hepcidin, produced predominantly by hepatocytes, is hierarchically the master regulator (see Box 1). The final step of transfer of iron from the lumen of the gut into serum, as well as the return of recycled iron to the circulation from macrophages, are both mediated by the multitransmembrane protein ferroportin (fig. S1B). Hepcidin’s mode of action is to bind ferroportin and induce its degradation, thus inhibiting cellular iron efflux (10). Hepcidin exerts control over systemic iron trafficking by regulating the transfer of dietary, recycled, and stored iron from intracellular compartments to extracellular fluid (see Box 1 and fig. S1B). The mature bioactive hepcidin peptide consists of 25 amino acids, eight of which are cysteines, and like the Drosophila antifungal peptide drosomycin, hepcidin has four internal disulfide bonds. Hepcidin sequences are found in fish, mammals, reptiles, and amphibians, but not in birds or invertebrates.

An abundance of genetic evidence in humans and experimental animals indicates that the ferroportin-hepcidin interaction is the dominant and nonredundant regulator of iron homeostasis in vertebrates. For example, hepcidin knockout mice rapidly become iron-loaded (11), as do humans with ferroportin variants that resist hepcidin control (12), and genetic defects that cause hepcidin overproduction lead to severe iron-deficiency anemia (13). The regulation of hepcidin expression is complex, influenced by diverse physiological inputs, and incompletely understood at a molecular level (see fig. S2). Increases in iron induce hepcidin transcription through the bone morphogenetic protein (BMP) signaling pathway, forming a feedback mechanism that prevents iron overload. Defects in genes that disrupt the BMP pathway cause abnormalities in iron balance, ranging from early-onset severe iron accumulation (e.g., BMP6 deficiency in mice) to development of iron overload in later life in individuals with HFE-linked hemochromatosis, which leads to mildly suppressed hepcidin levels. Hepcidin synthesis is greatly reduced by iron deficiency, hypoxia, and increased erythropoietic drive (including that associated with β-thalassemia), causing higher levels of iron to be absorbed from the diet. The molecular mechanisms that mediate hepcidin suppression under these conditions are still not completely clear. Hepcidin expression is upregulated during inflammation. For example, turpentine-induced inflammation is associated with elevated hepcidin in mice, and

**Box 1. The Emergence of Hepcidin**

Hepcidin was discovered by three laboratories working independently (42–44); two of these groups were looking for new antimicrobial peptides, and the third was searching for iron-regulated liver-expressed genes. In retrospect, this underscores the nature of hepcidin as being an iron hormone of innate immune ancestry. The laboratory of Tomas Ganz invented the name hepcidin, because the gene is highly expressed in the liver (hep-) and was found to possess some microbicidal activity (-cidin). Hepcidin gene expression was observed to be induced by inflammation in mice, and peptide levels were highly increased in the urine of one human donor with a systemic infection. The degree to which hepcidin can be directly antimicrobial is uncertain, but it is thought to be weak relative to specialized microbicidal peptides such as defensins. In addition, the high degree of conservation of hepcidin genes (relative to defensins) among vertebrate species that have evolved during exposure to different pathogen types is more consistent with hepcidin having a nonmicrobical role. The link of hepcidin to iron regulation, suggested by the up-regulation in iron-loaded mice, was further strengthened when mice that were engineered to lack the transcription factor Usf2 and also lacked the neighboring hepcidin-encoding gene Hamp1 were found to be iron-overloaded (11). Follow-up studies confirmed that mice lacking Hamp1 alone recapitulated this phenotype, whereas mice overexpressing hepcidin were severely (usually mortally) anemic at birth. The molecular mode of action of hepcidin was then elucidated by Nemeth et al., who found that hepcidin binds and causes the intracellular degradation of ferroportin, a well-conserved (among vertebrates) iron exporter.

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The nonredundant nature of the hepcidin-ferroportin interaction for controlling systemic iron levels and iron partitioning has since been confirmed by a large number of human and mouse studies.

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**Fig. 1.** The host-pathogen battle for iron. Exemplar organisms illustrated: hemorrhagic *E. coli* (O157:H7), herpes simplex virus, and *Plasmodium falciparum* blood-stage infection. [Image credits: people by Felicia Webb; bacteria images copyright Dennis Kunkel Microscopy Inc.]
hypoferrremia after turpentine treatment does not occur in mice lacking hepcidin (14). Experiments in which hepcidin peptide was injected into mice showed a dose-dependent suppression of serum iron of 80% within 1 hour, which was sustained for up to 2 days, although the majority of hepcidin had been cleared in 24 hours (15). This profound systemic effect is likely due to the blockade of macrophage iron recycling while bone marrow consumption of iron continues unabated. In mice that constitutively overexpress hepcidin, a decrease in hepatocyte iron is observed (16), whereas hepatic iron deposition, high serum iron, and a relative paucity in macrophage iron are associated with hepcidin deficiency (for example, in hemochromatosis).

The aggregate of the above findings is that hepcidin integrates signals from iron in serum and the liver, from bone marrow iron requirements, and from inflammation, thus acting as a useful biomarker reflecting iron status. However, hepcidin also determines iron availability and distribution. Because of the importance of iron for pathogen proliferation, and because infections agents tend to have distinct tropisms for particular cell types or anatomical niches (for example, <em>Plasmodium</em> has hepatocyte and erythrocyte life stages, whereas <em>Mycobacterium tuberculosis</em> infects macrophages), how hepcidin is controlled during infections affects iron-dependent pathogen growth and pathogenesis (Fig. 3).

### Innate Immune Signaling Regulates Hepcidin

Specific host mediators causing hepcidin up-regulation in the context of infection and inflammation have been investigated (see <fig>fig. S2</fig> for details and references). Interleukin (IL)-6, IL-22, and IL-1 interferon stimulate hepcidin transcription through STAT3 signaling, and several microbial-derived Toll-like receptor (TLR) ligands can induce hepcidin expression, likely via induction of IL-6. In particular, agonists that bind plasma membrane-expressed TLRs seem to induce hepcidin, consistent with a role for hepcidin in innate immunity against extracellular pathogens. However, mechanisms that sense internal cellular status can also regulate hepcidin. Endoplasmic reticulum (ER) stress and the accumulation of misfolded proteins, which may occur during infections, can trigger hepcidin synthesis. Through IL-6, IL-22, type I interferon, TLR ligands, and the ER stress response, molecular control of hepcidin is linked to innate responses to pathogens.

The development of innate immune responses influences the polarity and magnitude of subsequent adaptive immunity. Activation of hepcidin trancription is positively regulated by SMAD and STAT3 signaling, which together also play a role in T helper cell 17 (Th17) responses. The proliferation of T and B lymphocytes is iron-dependent, and expression of the iron acquiring transferrin receptor (CD71) is associated with their activation. The possibility exists that by controlling the availability of transferrin-chaperoned iron in serum, and through linkage with T cell differentiation programs, hepcidin may influence and be associated with particular types of adaptive immune responses.

The first demonstration of hepcidin stimulation during an in vivo infection with live pathogens was made in fish, where up-regulation of liver expression by a factor of 4500 was observed after sea bass were infected with <em>Streptococcus iniae</em> (17). Although hepatocytes are the main source of hepcidin, early reports in mammalian infection systems analyzed hepcidin production by leukocytes. Experiments in a granulomatous pouch model of <em>Escherichia coli</em> in mice revealed hepcidin up-regulation in immune cells at the site of infection (18). Later work confirmed that neutrophils and macrophages synthesized hepcidin in response to Gram-positive (group A <em>Streptococcus</em> and Gram-negative (<em>Pseudomonas aeruginosa</em>, <em>Salmonella typhimurium</em>) bacteria in a TLR4-dependent fashion, both in vitro and in skin, after subcutaneous infection (19). This work suggests that local production of hepcidin may alter iron availability to pathogens at foci of infection, without necessarily altering systemic iron balance.

Lower serum iron levels and anemia are common in malaria. Increased systemic hepcidin levels are observed during the blood stage of <em>Plasmodium</em> infection; upon antimalarial treatment, hepcidin levels and serum iron return to normal (20), but the mechanism of hepcidin up-regulation during malaria in humans is unclear. Other pathogens shown to increase liver hepcidin in mice with concomitant reduction of transferrin saturation are influenza virus A and <em>Candida albicans</em>, and both pathogens likely increase hepcidin via an inflammatory STAT3-mediated response (21). Likewise, after intraperitoneal injection of <em>P. aeruginosa</em>, liver hepcidin mRNA levels also increase (19). In general, infections or stimuli that invoke a systemic inflammatory response are likely to induce liver hepcidin expression, reduce serum iron, and increase iron accumulation in reticuloendothelial cells.

### Hepcidin and the Pathogenesis of Infections

An exception to infection stimulating hepcidin expression is chronic hepatitis C virus (HCV) infection. Hepatic iron accumulation occurs in 30 to 40% of HCV patients and is a morbidity factor for disease pathogenesis; excess iron damages the liver through generation of free radicals, and iron removal may be beneficial. Reduced levels of hepcidin occur in untreated chronic HCV patients despite ongoing inflammation, likely causing the predisposition to hepatic iron loading (22). Hepcidin induction occurs rapidly after commencement of antiviral therapy with pegylated type I interferon and ribavirin, and the degree of hypoferrremia resulting from this treatment corre-
Immunity is a complex interplay between iron regulation and antiviral responses with later viral clearance, suggesting an influence on pathogens that are involved in hemochromatosis. Elevated iron levels, such as those observed in hemochromatosis, enhance vulnerability to certain pathogens, such as *Yersinia pestis*, that are hemoplasms. This single case shows that altered iron availability, caused by altered hepcidin expression, can play a major role in the outcome of host-pathogen interactions. The impact of hepcidin on an infectious disease has been best studied in malaria. Increased erythropagocytosis and dyserythropoiesis during malaria contribute to malaria-associated anemia. However, hepcidin likely plays a significant role as well, for example, in children with post-malarial anemia and elevated hepcidin show poor incorporation of oral iron into erythrocytes.

Elevated iron levels as a result of low hepcidin in hemochromatosis enhance vulnerability to certain pathogens, such as *Vibrio* species, that are not usually able to scavenge iron from the human host. A striking example of this effect is the enhanced virulence of an attenuated *Yersinia pestis* strain, within which high-affinity iron acquisition genes had been deleted, that occurred in a researcher with undiagnosed hemochromatosis who was working with this organism (6). This single case shows that altered iron availability, caused by altered hepcidin expression, can play a major role in the outcome of host-pathogen interactions.

Macrophages facilitate a rapid throughput of iron and strongly express ferroportin, so the growth of pathogens that target and infect this cell type may be particularly influenced by hepcidin. *M. tuberculosis* infection is more severe in iron-loaded mice, and increased dietary iron uptake can be associated with a higher risk of developing tuberculosis in humans (30, 31). A role for the hepcidin-ferroportin axis in the pathogenesis of *M. tuberculosis* infection, as well as being likely on theoretical grounds, is also supported by the finding that single-nucleotide polymorphisms in NTS within macrophages is iron-dependent and is reduced by higher levels of ferroportin that export iron, an effect counteracted by hepcidin (29). Therefore, the increased levels of hepcidin that are observed in malaria [but not in hemolytic anemia, in which hepcidin is suppressed (14)] may exacerbate the virulence of NTS.

Mice overexpressing hepcidin have less liver iron and a reduced level of parasite growth in the liver; administration of hepcidin peptide has a similar inhibitory effect (25). This effect of hepcidin may offer defense against superinfection, whereby an ongoing blood-stage infection prevents the establishment of a second *Plasmodium* infection by stunting the growth of the liver stage (25). These experimentally determined interrelationships among hepcidin, iron, and parasite growth may underlie some important observations of human *Plasmodium* infection—for example, that iron deficiency protects against severe malaria in children (26) and that iron administration is linked to increased incidence of infection (3).

Nontyphoidal *Salmonella* (NTS) is a common cause of bacteremia in the developing world, and NTS is often particularly severe in individuals infected with *Plasmodium*. Hemolysis during malaria can increase susceptibility to NTS through recruitment of immature neutrophils from the bone marrow that have increased levels of hemeoxygenase-1 (HO-1), resulting in a reduced capacity for the microbial oxidative burst (27). Furthermore, the higher iron levels produced by HO-1 may favor proliferation of NTS within infected granulocytes. However, hemolysis alone does not entirely explain the enhanced virulence of NTS in the presence of *Plasmodium*, because hemolytic anemia, equivalent to that induced by malaria but induced by injection of antibodies to red blood cells, does not fully recapitulate the severe NTS dissemination seen in malaria (28). The growth of...
ferroportin associate with different levels of susceptibility to tuberculosis (32). How hepcidin and ferroportin might influence iron acquisition by *M. tuberculosis* is not yet clear; although high levels of hepcidin would increase iron storage within macrophages, the iron is mostly caged within ferritin shells, and it is not known whether *M. tuberculosis* can scavenge iron sequestered in this way. On the other hand, in conditions of high iron export, although the steady-state level of iron in macrophages may be low, the throughput of loosely chelated “labile” iron may be higher, and *M. tuberculosis* synthesizes siderophores that could access iron in this form. An additional factor is that the generation of microbial molecules (including reactive oxygen species and nitric oxide) by macrophages is iron-dependent. Up-regulation of ferroportin (and consequent loss of cellular iron) in macrophages reduces the synthesis of nitric oxide and allows intracellular growth of *M. tuberculosis* (33). This double-edged nature of iron—as a nutrient needed for pathogen growth and for host antimicrobial defenses—may be particularly important for macrophage-tropic organisms, and how this balance is regulated by hepcidin requires careful exploration.

The Future of Hepcidin

The discovery of hepcidin as the master hormonal regulator of iron metabolism has revitalized research into iron and infection. The ancestry, structure, and regulation of hepcidin reflect the underlying link between iron regulation and immunity. Because we understand that hepcidin controls both the overall level of iron and its location, the question is no longer only how much iron influences infectious diseases, but also where the iron is located. From this perspective, associations of altered iron status and infectious disease progression need to be re-investigated. For example, tuberculosis severity is enhanced by HIV-1 co-infection, which is a particular problem in sub-Saharan Africa and elsewhere. HIV-1 replication is also iron-dependent, and in vitro the hepcidin–ferroportin interaction influences viral growth (34). Furthermore, increased iron status in HIV-1–infected individuals, and higher macrophage iron in particular, correlates with poor prognosis (35, 36). However, there is currently a dearth of information on hepcidin levels and regulation during acute and chronic HIV-1 infection and how this affects susceptibility to secondary infections, co-infections, and progression to AIDS. There is a similar lack of information on hepcidin regulation during two other infections that are major causes of iron deficiency worldwide: bilharzia (schistosomiasis) and hookworm infection.

In general, understanding whether altered hepcidin regulation contributes to the development of an iron-defficient state will be important for formulating the best way to counteract iron deficiency at the individual and population level. Dietary iron supplementation in the context of high infectious disease burden has been controversial since the Pemba trial found that iron increases the incidence of malaria in infants (3). Iron supplementation may also be futile (or even detrimental) in individuals with increased hepcidin, as the blockade on ferroportin likely prevents iron absorption and transport to the bone marrow. In these nutritional contexts, diagnostic hepcidin measurement in target populations could be crucial.

A major future direction for the field is deliberate therapeutic manipulation of hepcidin activity. Advances are being made in this area through the development of small-molecule modulators of hepcidin regulation pathways, neutralizing antibodies to hepcidin, and supra-active mini-hepcidins, among others (37–39). The ability to determine hepcidin activity theoretically allows control of the level of iron absorption from the diet, as well as partitioning of iron among serum, liver, bone marrow, and the reticuloendothelial system. Such interventions would have potential clinical utility. For example, hepcidin antagonists may enhance recovery from anemia and treatment of iron deficiency in infants, in pregnancy, and in the elderly, whereas therapeutics that safely increase hepcidin activity may benefit people with iron-loading disorders (16).

Deprivation of iron from invading pathogens is in theory a useful strategy for decreasing virulence. Infectious organisms may acquire the ability to both evade immune surveillance and resist antibiotics, but they cannot escape their basic iron requirement for growth. If the properties of hepcidin can be exploited to divert iron away from pathogens that scavenge the nutrient from particular niches, the resulting inhibition of pathogen replication may allow time for immunity to develop and control infections before rapid microbial growth overwhelms the infected individual.

Another concept recently proposed is that of tolerance to microbial burden (40), such that infection is not met with catastrophic immunopathology, and higher levels of pathogens are harbored. Interestingly, intracellular iron levels affect innate immune TLR signaling in response to infection, and hepcidin antagonists can be used to attenuate inflammation (41). Thus, as well as controlling iron availability to pathogens, hepcidin regulation has the potential to allow manipulation of the host response, and hence could be exploited to augment other therapeutic and preventive interventions, including vaccination.

References and Notes

18. M. Xu et al., Retrovirology 7, 104 (2010).

Acknowledgments: Supported by the Medical Research Council UK (MC-A760-50000) and the Beit Memorial Fellowship for Medical Research. We thank R. Moxon, L. Eddowes, and A. Armitage for critical reading of the manuscript.

Supplementary Materials

www.sciencemag.org/cgi/content/full/338/6108/768/DCl Figs. S1 and S2 References (45–58)

10.1126/science.1224577