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Iron and intestinal immunity

Bobby J. Cherayil*, Shiri Ellenbogen, and Nandakumar N. Shanmugam

Mucosal Immunology Laboratory, MassGeneral Hospital for Children, Building 114, 16th Street, Charlestown, MA 02129

Abstract

Purpose of review—Recent advances in the study of iron metabolism have led to a better understanding of the molecular basis for the interactions between iron and the inflammatory response. We will review this new information in the context of the gastrointestinal tract.

Recent findings—The effects of iron on microbial enteropathogens are well known. Recent work has demonstrated that iron also has potentially important effects on the intestinal microbiota. On the host side, hepcidin, a key regulator of mammalian iron metabolism, has emerged as an important mediator of the cross-talk between iron homeostasis and inflammation. Hepcidin-dependent changes in iron flux can influence the expression of inflammatory cytokines, and conversely, inflammatory cytokines can induce hepcidin expression and alter iron homeostasis. Hepcidin levels have been found to be elevated in some studies of inflammatory bowel disease, while manipulating hepcidin expression in animal models of this condition has beneficial effects on both inflammation and dysregulated iron metabolism.

Summary—The information on iron metabolism that has become available in recent years has shed new light on the pathogenesis of inflammatory diseases of the gastrointestinal tract, and is also starting to suggest new approaches to treating such diseases.

Keywords

Iron; hepcidin; inflammation; microbiota

INTRODUCTION

The availability of iron, an essential micronutrient for almost all organisms, can influence host-microbial interactions, either by altering microbial growth and virulence or by influencing the host immune system [1–3]. This idea is reflected in observations demonstrating that the course of infectious disease can be affected by iron deficiency or overload. Conversely, there is increasing awareness of the fact that states of immune activation can modulate iron metabolism and lead to the development of an iron-restricted anemia [2,4]. Understanding the bidirectional cross-talk between iron homeostasis and the immune response is relevant to a number of conditions that are of interest to gastroenterologists, including enteropathogenic infections and inflammatory bowel disease (IBD) [1,3,5]. This task has been made easier by recent advances that have clarified how iron metabolism is regulated at the molecular level [6]. Using this information as a starting point, we will review the mechanisms that mediate the effects of iron on intestinal immune function, as well as the effects of abnormal gut immunity on iron homeostasis.

*Correspondence: Bobby J. Cherayil, Room 3600, Building 114, 16th Street, Charlestown, MA 02129. Phone: 617-726-4170, Fax: 617-726-4172, cherayil@helix.mgh.harvard.edu.

OVERVIEW OF MAMMALIAN IRON METABOLISM

Like much in life, balance is very important when it comes to iron. Since iron is an essential micronutrient on the one hand but also has the ability to form toxic oxidative radicals on the other, both iron deficiency and iron excess can be harmful. For that reason, iron concentrations in the body are carefully regulated, both systemically and within individual cells. Two distinct but interacting sets of regulatory mechanisms maintain iron homeostasis at the systemic and cellular levels [7,8] (Figures 1 and 2).

Regulation of systemic iron homeostasis

The majority of the iron required for normal metabolism is recycled from aged erythrocytes that are phagocytosed by macrophages of the reticuloendothelial system. This amounts to about 22 mg of iron per day, with an additional 2 mg/day being absorbed from the diet by enterocytes in the duodenum. In simplified terms, the flux of iron through duodenal enterocytes and macrophages involves a similar set of proteins (Figure 1). Nramp2 is responsible for transporting iron from the diet across the apical membrane of the enterocytes, and also for transport from the lumen of the phagosome into the cytosol in macrophages. Transfer of iron into the circulation across the basolateral membrane of enterocytes and the plasma membrane of macrophages involves the transporter ferroportin (FPN). Serum iron circulates in combination with the protein transferrin (Tf), and can be endocytosed into cells by binding to the type 1 transferrin receptor (TfR1). Iron is released from transferrin in endosomal compartments and is transported into the cytosol by Nramp2.

The liver plays an important role in regulating serum iron levels. Hepatocytes are responsible for integrating information on systemic iron status and secreting an appropriate amount of the key regulator of iron homeostasis, the peptide hormone hepcidin. When serum iron levels are high, iron-transferrin complexes bind to TfR1 on hepatocytes, thereby displacing the TfR1-associated protein HFE. HFE then binds to the hepatocyte-specific type 2 transferrin receptor (TfR2), and this interaction transduces signals that act together with signals activated by bone morphogenetic proteins (BMPs) such as BMP6 to up-regulate transcription of the hepcidin gene. The secreted hepcidin binds to FPN on enterocytes and macrophages and induces its internalization and lysosomal degradation, thus reducing entry of iron into the circulation and restoring homeostasis. Conversely, when serum iron concentrations fall, hepcidin expression is inhibited, thereby increasing FPN expression and allowing more iron to enter the circulation. Thus, the iron-regulated synthesis of hepcidin and the hepcidin-dependent down-modulation of FPN constitute an important feedback loop that maintains serum iron concentrations within a narrow range. It is important to mention that cytokines such as IL-6 also up-regulate hepcidin expression, a phenomenon that contributes to alterations in iron metabolism during infections and inflammatory states [2].

Regulation of cellular iron homeostasis

Although intracellular iron is influenced by serum levels of the metal, a separate regulatory system exists to ensure that the labile iron pool (LIP) or “free” iron inside cells is maintained within narrow limits [7,8]. The LIP is a transitory, cytosolic pool of iron complexed with small organic molecules that is susceptible to chelation. It is an important source of the iron required for crucial biologic processes, but it can also catalyze the generation of potentially toxic oxidative radicals. These 2 properties require that it be controlled in a stringent fashion.

LIP homeostasis is maintained by a negative feedback loop in which free intracellular iron modulates the expression of the proteins that bring iron into the cytosol (TfR1, Nramp2), export it from the cell (FPN) or store it in an inactive form (ferritin) (Figure 2). The mRNAs

encoding each of these proteins contain a conserved stem-loop motif known as an iron-responsive element (IRE) in either the 5' (FPN, ferritin heavy and light chains) or the 3' (TfR1 and Nramp2) untranslated region. When intracellular free iron levels fall, iron-regulatory proteins (IRPs 1 and 2) bind to the IREs. The IRE-IRP interaction increases expression of TfR1 and Nramp2 by stabilization of their transcripts, and decreases expression of FPN and ferritin by inhibiting translation of their mRNAs. The net effect of these changes is to increase import of iron and decrease its export and storage, thus restoring the LIP to its basal state. Conversely, if intracellular free iron concentrations rise, the IRE-IRP interaction is inhibited as a result of conformational changes in IRP1 and proteasomal degradation of IRP2. Consequently, the expression of TfR1 and Nramp2 decreases and that of FPN and ferritin increases. The resultant decrease in iron import and increase in export and storage reduce the size of the LIP, thus maintaining homeostasis.

EFFECTS OF IRON ON INTESTINAL COMMENSALS AND PATHOGENS

Iron can have direct effects on the survival and growth of most microorganisms, the exceptions being *Lactobacillus* and *Borrelia*, which require very little, if any, of this element [1, 9–11]. Not surprisingly, dietary iron content has been shown in a number of studies to influence the composition of the intestinal microbiota, both in animals and in humans [12–16]. The results of these experiments have not revealed clear patterns of intestinal microflora alterations that correlate with iron deficient and iron supplemented diets. However, a recent analysis indicated that prolonged consumption of iron-fortified biscuits by African children led to an increase in the proportion of fecal enterobacteria and a decrease in lactobacilli [16]. Given the importance of the microbiota in shaping the development and function of the intestinal immune system [17–19], iron-dependent changes in the microflora could have an impact on the immune responsiveness of the gut. This is an issue that deserves further investigation.

Studies in tissue culture and animal models suggest that iron can promote the replication and virulence of several microbial pathogens, including those that infect via the gastrointestinal tract [1,3]. Experiments from our laboratory showed some time ago that changes in expression of FPN could affect the intracellular growth of *Salmonella typhimurium* in epithelial cells and macrophages, with increased levels of FPN inhibiting *Salmonella* replication and decreased expression of the protein favoring growth of the pathogen [20]. The underlying mechanism was linked to FPN-mediated efflux of iron and consequent changes in the amount of the element available to the intracellular bacteria. Similar observations were made by other investigators with several other organisms that reside in macrophages, supporting the general notion that cellular iron concentration is an important factor determining the outcome of infection with intracellular pathogens [21,22]. Since changes in macrophage FPN expression can accompany multiple disease states, including primary disorders of iron metabolism, anemia and inflammation [2,6–8], these conditions could all influence the course of infection with organisms such as *Salmonella* as a result of alterations in intracellular iron levels.

Iron has been shown recently to play an important role in the interactions between *Salmonella* and the intestinal commensal flora [23,24]. An early component of the intestinal inflammatory response to *Salmonella* is the secretion of the protein lipocalin 2 (Lcn2) by epithelial cells into the lumen. Lcn2 binds and sequesters siderophores that are produced by most bacteria as part of their strategy for acquiring iron from the microenvironment. *Salmonella* expresses a structurally modified siderophore that is not susceptible to binding by Lcn2, thus gaining a competitive advantage over the microbiota and facilitating its colonization of the gut.

Because of the effects of iron on pathogen growth and virulence, there has been concern that dietary iron supplementation may increase the risk of infectious disease in human populations. However, the epidemiologic data on this issue has been reassuring. While some studies suggest that iron supplementation may increase the incidence of malaria and tuberculosis in hyper-endemic locales, the results of a large meta-analysis indicated that the occurrence of most types of infection was not altered by supplemental iron, and that the risk of gastrointestinal infection (as manifested by diarrhea) was only slightly elevated [25]. Thus, it would appear that the potential dangers of iron supplementation are not sufficient to outweigh the beneficial effects of correcting iron deficiency on growth and cognitive development. Moreover, the possible risk of infection associated with providing extra iron is likely to affect iron replete rather than iron deficient individuals, an issue that has not been addressed satisfactorily by most studies.

EFFECTS OF IRON ON INTESTINAL INFLAMMATORY RESPONSES

Iron concentrations in the lumen of the gut can have a significant impact on intestinal inflammatory responses. Several studies in rodent models of non-infectious colitis have shown consistently that increasing the amount of iron in the diet exacerbates intestinal inflammation [26]. A study in humans also suggests that oral, but not parenteral, iron supplementation can increase clinical disease activity in patients with IBD [27]. At the other end of the spectrum, a diet deficient in iron may suppress intestinal inflammation, as shown recently in a mouse model of Crohn's disease. In this study, placing the animals on an iron-free diet (together with parenteral iron supplementation) completely prevented the development of intestinal inflammation [14]. The effects of luminal iron on intestinal inflammation could be mediated by local iron-catalyzed generation of oxidative radicals, but other mechanisms may also be involved, including modulation of the activity of signaling pathways and transcription factors, and alteration of the commensal flora [3,12–16]. Based in part on these observations, current guidelines recommend the use of parenteral rather than oral iron supplements for the treatment of iron deficiency in IBD [5].

Work from our laboratory has shown that disturbances of systemic iron metabolism can also alter inflammatory responses in the gastrointestinal tract. *Hfe* knock-out mice, which develop abnormalities of iron homeostasis similar to human type I hemochromatosis, including low hepcidin expression, increased FPN on macrophages and enterocytes, and progressive iron overload, have reduced severity of *Salmonella* enterocolitis [28]. The attenuated intestinal inflammation was associated with impaired pro-inflammatory cytokine expression by macrophages from the mutant animals, a result of low intracellular iron in these cells [28,29]. How exactly low intracellular iron inhibits the macrophage inflammatory response is not clear, but our initial observations suggest that an abnormality of signaling downstream of Toll-like receptor 4 prevents normal translation of certain cytokine mRNAs [29–31]. Extending these findings to non-infectious forms of intestinal inflammation, we used inhibitors of the BMP signaling pathway to lower hepcidin levels in mice with wild-type *Hfe*, and showed that they significantly reduced the severity of intestinal inflammation in multiple models of IBD [29,32]. This approach could be clinically beneficial since, as will be discussed in greater detail in the next section, chronic inflammatory states such as IBD are often associated with elevated hepcidin expression [2].

EFFECTS OF INTESTINAL INFLAMMATION ON IRON METABOLISM

It has been recognized clinically for some time that patients with inflammatory disorders often develop an iron-restricted anemia known as anemia of chronic disease or anemia of inflammation [4,33]. While multiple factors undoubtedly contribute to the pathogenesis of this condition, recent discoveries in the iron metabolism field have highlighted the role

played by hepcidin [2,6]. Experiments in animals and humans have shown that several pro-inflammatory mediators can up-regulate transcription of the hepcidin gene, with most of the effects being mediated directly or indirectly by IL-6. Increased circulating levels of hepcidin down-regulate FPN on enterocytes and macrophages, with consequent inhibition of iron release into the serum, compromised erythropoiesis secondary to reduced iron availability, and anemia. The anemia is often refractory to oral iron supplements since the low levels of FPN on the duodenal epithelium impair absorption of iron from the diet.

Inflammation of the intestine is associated with increased hepcidin expression in the liver. We have demonstrated this in mouse models of *Salmonella* enterocolitis and IBD, with IL-6 probably being involved in the hepcidin up-regulation [29,32]. Other investigators have found that hepcidin is elevated in mice with the spontaneous Crohn's-like ileitis associated with unregulated TNF α expression [34]. There are relatively few studies of hepcidin levels in human IBD, and the results have not been consistent. An analysis of a small group of pediatric Crohn's patients found that urinary hepcidin levels were significantly elevated in active disease and correlated with markers of inflammation [35]. On the other hand, a larger study of adults with IBD, both active and inactive, found that serum hepcidin concentrations were lower in patients than in controls, although there was a correlation with serum IL-6 [36]. In yet another adult IBD cohort, serum hepcidin levels were found to be no different from controls, although in this particular study, it was the inactive pro-form of the peptide that was measured [37]. Finally, in a very recent analysis of 100 adults with active and inactive IBD, serum hepcidin levels were significantly higher and serum pro-hepcidin significantly lower in patients compared to controls [38]. Serum hepcidin correlated with markers of disease activity and inflammation, and was lower in individuals with iron deficiency anemia.

The issue of how the expression of hepcidin changes during IBD is an important one, both in terms of understanding its contribution to the associated anemia and when considering possible therapies. As demonstrated in our animal experiments, blocking expression of hepcidin in situations where levels of the peptide are elevated may help to ameliorate the intestinal inflammation as well as the dysregulated iron metabolism that gives rise to the anemia [29,32]. Hepcidin expression in an individual patient is likely to be determined by the combined effects of a number of factors – the cytokine milieu, iron status, anemia, etc. – that act either positively or negatively on the gene. Further studies of IBD will be required to identify the clinical characteristics that distinguish those individuals who will benefit from interventions that inhibit hepcidin expression.

CONCLUSION

It is apparent from the foregoing that iron can influence the intestinal immune system in multiple ways. Iron-dependent alterations in host responses and the growth of intestinal commensals and pathogens play roles in these effects. It is also clear that inflammation in the gastrointestinal tract can impact iron homeostasis. Thanks to rapid advances in the biomedical sciences, we now have at our disposal a database of knowledge on the inflammatory response and on iron metabolism. This information provides a framework for understanding and treating diseases characterized by disturbances of these 2 important aspects of physiology, which were once viewed as being quite distinct but are now known to be intimately linked.

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KEY POINTS

- Intestinal luminal iron influences commensal and pathogenic microbial growth and can promote inflammation in the gastrointestinal tract.
- Disturbances of systemic iron metabolism can alter inflammatory responses, including in the gut, via changes in circulating hepcidin levels.
- Inflammatory states, including conditions such as IBD, are associated with increased expression of hepcidin and consequent abnormalities of iron metabolism that lead to an iron-restricted anemia.
- Inhibiting elevated hepcidin expression may have therapeutic benefits in IBD by helping to suppress inflammation and correct dysregulated iron metabolism.

Figure 1.

Mechanisms that regulate systemic iron homeostasis. Hepcidin is secreted by hepatocytes in response to signals that reflect iron status and inflammation. Iron overload and inflammatory cytokines such as IL-6 up-regulate hepcidin, while iron deficiency, anemia and hypoxia inhibit it. Hepcidin binds to the iron exporter ferroportin (FPN) on macrophages and duodenal enterocytes, leading to its internalization and degradation.

Figure 2.

Mechanisms that regulate cellular iron homeostasis. Iron-responsive elements (IREs) are present in the 5' or 3' untranslated regions of mRNAs encoding ferroportin (FPN) and ferritin or the type 1 transferrin receptor (TfR1) and Nramp2, respectively. They are bound by iron-regulatory proteins (IRPs) under low iron conditions, leading to either inhibition of translation or stabilization of the transcript. When cellular iron levels are high, these effects are reversed as a result of decreased IRE-IRP binding.