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Pathophysiology of iron homeostasis during inflammatory states

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Keywords

Hepcidin; ferroportin; interleukin-6

Infectious and non-infectious inflammatory conditions are often associated with significant changes in systemic iron metabolism. One of the important consequences of this altered metabolic state is a decrease in plasma iron levels that is caused by reduced intestinal absorption and increased intracellular sequestration of the metal. The decrease in circulating iron can compromise erythropoiesis and lead ultimately to the development of an anemia that is usually referred to as the anemia of inflammation (AI). AI is usually a mild to moderate normocytic, normochromic anemia characterized by low plasma iron concentrations in the presence of normal or elevated serum ferritin levels (1). It typically occurs in the setting of chronic infections and autoinflammatory states but can also accompany malignancies and chronic renal disease. Even though hypoferremia is an important factor in the development of AI, other abnormalities that are associated with inflammation, such as decreased erythropoietin production, impaired erythropoiesis and increased erythrocyte destruction are additional contributors to the pathogenesis of the anemia (1-3). It is also worth remembering that persistently low circulating iron levels may have adverse effects on biological processes other than erythropoiesis, e.g. neurocognitive development, an issue of particular importance in infants and young children (4). This article will review our current understanding of the mechanisms that lead to hypoferremia in inflammatory diseases. Most of what we know about this problem is derived from studies in adult humans or from experiments in mice. It is likely that the basic pathophysiology will be very similar in infants and children but this is an issue that deserves further investigation. We will start by summarizing the mechanisms that regulate systemic iron metabolism under normal conditions, and then go on to describe how inflammation causes abnormalities in this

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process. We will conclude with a brief description of the management of inflammation-associated hypoferremia.

NORMAL IRON HOMEOSTASIS AND ITS REGULATION

Over the last 10-15 years, there has been a tremendous increase in our understanding of how systemic iron homeostasis is regulated at the molecular level (5) (Figure 1). Most of the iron that is required for carrying out normal biological processes (about 25 mg/day) is recycled from the hemoglobin liberated during the destruction of aged red blood cells (RBCs), with only a minor fraction (about 2 mg/day) being obtained from the diet. Macrophages, chiefly in the spleen but also in other tissues, constitute the major cell type involved in iron recycling from RBCs, and duodenal enterocytes represent the main site of dietary iron absorption. Very similar sets of molecules handle iron in both types of cell. The transporter natural resistance-associated macrophage protein 2 (Nramp2, also known as Slc11a2 and DMT1) moves iron across the phagosomal membrane of macrophages as well as the apical membrane of enterocytes. Iron that reaches the cytosol by this means is then pumped out, either at the basolateral surface of the enterocyte or the plasma membrane of the macrophage, by ferroportin (FPN, also known as Slc40a1), the only known iron exporter in mammals. Iron that is in excess of that released into the plasma or utilized by the cell is stored in the cytoplasm complexed to ferritin. Plasma iron circulates bound to transferrin and can be taken up by cells via the ubiquitously expressed type 1 transferrin receptor. Because the entry of iron into the plasma from both macrophages and enterocytes is mediated by FPN, one of the major mechanisms that regulates circulating iron levels involves modulating the expression of this transporter. This function is carried out by the peptide hormone hepcidin (6). Hepcidin is secreted predominantly by the liver, and its expression is regulated, exclusively at the level of transcription, in response to changes in iron status. When plasma or tissue iron levels increase, hepcidin expression is up-regulated. Hepcidin binds to FPN, leading to internalization and degradation of the transporter (7), thus reducing the amount of iron entering the plasma. Conversely, when plasma or tissue iron levels decrease or when iron requirements increase (as in states of hypoxia), hepcidin expression is suppressed, allowing increased FPN levels and greater efflux of iron into the circulation. Thus, the hepcidin-FPN axis is a key component of a negative feedback loop that maintains plasma iron concentrations within a narrow physiologic range. However, it is important to note that in young animals – suckling rodents and 4-6 month old human infants – intestinal absorption of iron may be insensitive to regulation by hepcidin, possibly as a way of maximizing uptake of the metal from breast milk (8-11).

DYSREGULATION OF IRON METABOLISM BY INFLAMMATION

The major factor responsible for altered iron metabolism in inflammatory states is increased expression of hepcidin (12). The abnormally elevated levels of hepcidin lead to intracellular sequestration and decreased absorption of iron as a result of down-regulation of FPN expression on macrophages and enterocytes, respectively. Plasma iron levels fall, usually within hours of the inflammatory stimulus (13,14), and if the hypoferremia persists, it can impair erythropoiesis and other processes that are dependent on iron.

There has been a great deal of interest in clarifying the molecular pathways that connect inflammation to the increased expression of hepcidin (Figure 2). The cytokine interleukin (IL)-6 has emerged as one of the most important mediators of this up-regulation. Studies with cultured hepatocytes, wild-type and knockout mice and human volunteers have shown that IL-6 is sufficient to induce hepcidin expression, and is required for hepcidin up-regulation in response to inflammatory stimuli such as endotoxin or turpentine (13,15). Subsequent experiments have confirmed IL-6-dependent up-regulation of hepcidin in mouse models of inflammatory bowel disease (IBD) and systemic bacterial, viral and parasitic infection (16-18). The importance of IL-6 in the elevated hepcidin levels associated with human inflammatory diseases is highlighted by the good correlation between serum or urine hepcidin levels and serum IL-6 concentrations in IBD, and by the fact that anti-IL-6 treatment in rheumatoid arthritis is associated with a decline in circulating hepcidin (19-22). Mechanistic experiments have demonstrated that IL-6 acts by binding to its receptor gp130 on hepatocytes, thereby activating signals that phosphorylate the transcription factor signal transducer and activator of transcription 3 (STAT3), which binds to the promoter of the hepcidin gene and increases its expression (15,23-25). Cytokines other than IL-6, such as IL-1 and IL-22, have been shown to be involved in hepcidin up-regulation in cultured cells and in mice, but the relevance of these observations to the pathophysiology of inflammatory states is yet to be determined (26-28). Tumor necrosis factor α (TNF α) is another cytokine that is often elevated in inflammatory conditions, but its role in hepcidin expression is unclear. TNF α has been shown to inhibit hepcidin expression when added to cultured hepatocyte cell lines and has also been shown to have an inhibitory effect on hepcidin expression in two different mouse models of IBD (13,29). However, anti-TNF α therapy in human rheumatoid arthritis has been shown to be associated with decreases in hepcidin levels (21). Further work will be required to clarify this discrepancy. Besides cytokines, other inflammation-associated factors, such as oxidative and endoplasmic reticulum stress and direct stimulation of pattern recognition receptors, may also contribute to increased hepcidin expression, at least in mice (30-33). Recent experiments have suggested that the composition of the intestinal microbiota may influence hepcidin expression in mouse models of IBD, possibly by altering the cytokine milieu associated with intestinal inflammation (34).

In addition to IL-6 and the other inflammatory mediators described above, activators of the bone morphogenetic protein (BMP) receptors are also involved in the increased hepcidin expression associated with inflammatory conditions. Soluble forms of BMP co-receptors, as well as inhibitors of BMP signal transduction, have been shown to suppress hepcidin up-regulation in mouse models of IBD and bacterial infection (16,35). One of the BMP receptor ligands that appears to play a role in the inflammation-induced elevation of hepcidin is activin B. This member of the transforming growth factor β super-family is highly up-regulated in an IL-6-independent manner in the livers of mice treated with endotoxin, and is capable of inducing hepcidin expression when added to mouse hepatocytes and human hepatoma cells (36). Interestingly, the expression of activins has been shown to be increased in conditions such as IBD, rheumatoid arthritis and sepsis (37). BMP receptor stimulation by ligands such as activin B leads to the activation of the transcription factor small-mothers

against decapentaplegic 4 (SMAD4), which cooperates with STAT3 and is required for IL-6-induced hepcidin up-regulation (38,39).

Not all inflammation-associated events induce increased hepcidin expression. Besides the possible inhibitory effect of TNF α mentioned above, the increased erythropoietic activity that can accompany inflammation can also decrease hepcidin levels, probably as a result of RBC precursors releasing factors that suppress hepcidin expression (34,40). Some components of the microbiota may also have an inhibitory effect on the production of hepcidin (34). Thus, the net level of hepcidin during inflammation is likely to reflect the combined influence of factors that alter expression either positively or negatively.

Mechanisms that do not involve up-regulation of hepcidin may also contribute to the hypoferrremia of inflammation. Injection of mice with polyinosinic:polycytidylic acid, a ligand for the pattern recognition receptor Toll-like receptor 3, has been shown to cause a prompt decrease in serum iron concentration without a significant increase in hepcidin expression in the liver or spleen (41). It is not clear how the hypoferrremia occurs under these circumstances but it may involve down-regulation of FPN mRNA levels.

Measurement of serum or urine levels of bioactive hepcidin can be a useful tool in the diagnosis of the hypoferrremia and anemia associated with inflammation. Several methods are now available for this purpose, including enzyme-linked immunosorbent assays and mass spectrometry-based approaches (42). There is considerable variability in the hepcidin concentrations obtained with the different methods, even when using comparable samples, making further standardization essential before the tests can be implemented clinically (43). Nevertheless, serum or urine hepcidin levels have been shown to be significantly elevated in a number of human inflammatory conditions, including IBD, rheumatoid arthritis, malaria, human immunodeficiency virus infection and neonatal sepsis (19-22,44-47).

MANAGEMENT OF INFLAMMATION-ASSOCIATED HYPOFERRREMIA

Treatment of the underlying inflammatory condition will restore normal iron homeostasis and is all that is required in situations where the hypoferrremia and associated anemia are mild. However, more severe cases of AI reduce quality of life and benefit from specific treatment, as has been demonstrated in studies of rheumatoid arthritis, cancer and chronic renal failure (48-50). When intervention is called for, the general therapeutic strategies include iron supplementation, interference with the hepcidin-FPN axis and, in the case of anemia associated with chronic kidney disease, use of erythropoiesis stimulating agents (5,51). Oral iron supplements can be used but may be poorly effective because of the decreased intestinal absorption caused by elevated hepcidin levels. The impaired absorption can lead to elevation of iron concentrations in the intestinal lumen, which may alter the gut microbiota and exacerbate intestinal inflammation (52). Intravenous iron therapy is effective at correcting the functional iron deficiency associated with increased hepcidin expression, but supraphysiologic levels of iron can further up-regulate hepcidin and worsen the dysregulation of iron homeostasis by decreasing FPN expression (5). Because iron can promote the growth and virulence of some pathogens, it has been suggested that iron supplementation may increase the incidence or severity of infections, particularly in iron

replete individuals. This is a concern that has been supported by some studies, but several others have indicated that iron supplementation does not increase infectious disease morbidity (53-56).

Interfering with the hepcidin-FPN axis constitutes a rational form of therapy that is directed at correcting the basic pathophysiology of the hypoferremia associated with inflammation. Several reagents targeting this axis are in various stages of development or evaluation (5,51) and include those that (a) inhibit hepcidin expression (antibodies that block IL-6 or the IL-6 receptor, inhibitors of IL-6 signaling, antibodies, soluble receptors and other molecules that block or sequester BMPs, inhibitors of BMP signaling, anti-sense oligonucleotides and short interfering RNAs directed against the hepcidin transcript, vitamin D), (b) block hepcidin (anti-hepcidin antibodies, proteins and aptamers that bind hepcidin), and (c) prevent hepcidin from down-regulating FPN (anti-FPN antibodies, thiol modifier compounds, cardiac glycosides).

CONCLUSION

Extensive basic research into the mechanisms that regulate iron metabolism has resulted in a solid understanding of the pathophysiology of the hypoferremia associated with inflammatory states, which in turn has allowed the development of rational therapeutic strategies. Application of these novel forms of treatment, and others that will undoubtedly emerge with further elucidation of the fine details of hepcidin and FPN function and regulation, will make it easier for the clinician to correct the abnormalities of iron homeostasis caused by inflammatory diseases.

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ABBREVIATIONS

AI	Anemia of inflammation
BMP	Bone morphogenetic protein
FPN	Ferroportin
IBD	Inflammatory bowel disease
IL	Interleukin
Nramp	Natural resistance-associated macrophage protein
RBC	Red blood cells
SMAD	Small-mothers against decapentaplegic
STAT	Signal transducer and activator of transcription
TNF	Tumor necrosis factor

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Figure 1. Mechanisms that regulate iron homeostasis under normal conditions

Iron recycled from RBCs (Red Blood Cells) or absorbed from the diet is transported by Nramp2 (Natural resistance-associated macrophage protein-2) and FPN (Ferroportin) into the blood, where it circulates bound to transferrin. Circulating levels of iron are regulated by controlling the amount of FPN expressed on the plasma membrane, a function that is carried out by the peptide hormone hepcidin, which is secreted by the liver in response to changes in iron status and iron requirements.

Figure 2. The major factors contributing to hypoferremia during inflammation

Inflammatory stimuli such as IL-6 (Interleukin-6), other cytokines, activin B, BMPs (Bone morphogenetic proteins), endoplasmic reticulum (ER) and oxidative stress, and pattern recognition receptor ligands activate STAT3 (Signal transducer and activator of transcription-3), SMAD4 (Small-mothers against decapentaplegic-4) and other transcription (Tx) factors to induce increased expression of hepcidin, leading to downregulation of FPN (Ferroportin) and consequent hypoferremia. Inflammatory mediators may also act directly to cause decreased expression of FPN. For clarity, inflammation-associated factors that inhibit hepcidin expression have not been shown.