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Regulation of Iron Metabolism by Hepcidin Under Conditions of Inflammation

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Abstract

Iron is a redox-active metal required as a cofactor in multiple metalloproteins essential for a host of life processes. The metal is highly toxic when present in excess and must be strictly regulated to prevent tissue and organ damage. Hepcidin, a molecule first characterized as an antimicrobial peptide, plays a critical role in the regulation of iron homeostasis. Multiple stimuli positively influence the expression of hepcidin, including iron, inflammation and infection by pathogens. In this minireview, we will discuss how inflammation regulates hepcidin transcription, allowing for sufficient concentrations of iron for organismal needs while sequestering the metal from infectious pathogens.

Iron is crucial for many life functions in both eukaryotic hosts and prokaryotic pathogens. Due to its ability to readily accept or donate electrons, iron is a valuable cofactor in proteins essential in metabolic processes. However, when left unsupervised, iron can also react with oxygen to generate radical oxygen species that can damage all facets of a cell, leading to tissue damage and eventual organ failure. Therefore, it is crucial for organisms to maintain strict control over iron uptake and distribution to assure appropriate amounts for life requirements, yet regulate and sequester it tightly to prevent oxidative stress or microbial proliferation during infection. Herein, we will present an overview of how iron balance is maintained in vertebrate organisms and discuss the role of hepcidin, the master regulator of iron metabolism, in iron regulation during inflammation and infection.

General iron homeostasis

Each day the average human must absorb 1-2mg of iron from the diet to offset unregulated losses from general bleeding, menstruation, or the sloughing of epithelial cells. Iron is a critical cofactor required for DNA synthesis, mitochondrial respiration and various signaling pathways. Most crucially, almost 25 mg of iron per day is required for hemoglobin synthesis and the replacement of an estimated 200 billion red blood cells (RBC). The vast majority of this iron pool is acquired through the recycling of senescent erythrocytes by macrophages of the reticuloendothelial compartment. Whole body iron homeostasis is thought to occur completely at the level of iron absorption, as no physiologically regulated means of iron excretion has been elucidated. Hence, influx of iron from the diet, and recycling of iron from aged or damaged RBC's, must be closely regulated to prevent iron-restricted erythropoiesis resulting in anemia or excess iron loading and subsequent tissue damage caused by the generation of radical oxygen species. Proper distribution of circulating iron to tissues such as the brain, heart and skeletal muscle is crucial for the prevention of human disease states.

Non-heme dietary reduced iron is admitted into the body through divalent metal transporter 1 (*DMT1, Slc11a2*) (1,2), an iron transporter located on the apical membrane of duodenal enterocytes located in the first section of the small intestine (Figure 1). After uptake into villus enterocytes, the iron may take two different paths. A fraction of the

reduced iron may be oxidized and securely sequestered in ferritin. Alternatively, iron may be transferred across the basolateral membrane by ferroportin (3-5) where it is oxidized to the ferric state by the membrane-bound multicopper ferroxidase hephaestin, or the homologous soluble ferroxidase ceruloplasmin (6,7). Oxidized iron is then loaded onto Transferrin (TF), a soluble protein in the blood that securely transports and distributes iron to downstream tissues.

As previously noted, reticuloendothelial macrophages phagocytose senescent RBC's, harvesting the heme and returning almost 25mg of iron into circulation each day. Like duodenal enterocytes and hepatocytes of the liver, macrophages of the RBC recycling compartment also employ ferroportin to export recovered iron into the general circulation (Figure 1). Iron export, both from epithelial cells of the duodenum and macrophages within the RBC recycling compartment, is rate controlling for total body iron flux; consequently, ferroportin expression must be closely regulated to assure sufficient iron for erythropoiesis and prevent excess tissue iron accumulation. Ferroportin expression is regulated post-translationally by its ligand hepcidin, the master-regulator of iron metabolism.

Role of hepcidin in iron metabolism

In 1994 Finch (8) postulated that soluble regulators of systemic iron metabolism, the "stores regulators", exist and that these hormones are essential for the maintenance of appropriate iron balance. However, it was not until 2000 that hepcidin, originally termed LEAP-1 (liver expressed antimicrobial protein 1), was characterized as a defensin-like, liver-expressed, 25-residue antimicrobial peptide with four disulfide bonds (9). Simultaneous work in mice and humans demonstrated that hepcidin expression increases concomitantly with serum and tissue iron levels and is excreted in the urine (10,11). Deletion of the hepcidin locus in mice demonstrated that animals lacking hepcidin have severe iron overload (12,13); conversely, overexpression of hepcidin leads to severe iron deficiency (14,15).

Hepcidin acts as a negative regulator of iron release from cells (Figure 1), binding to ferroportin, the only known iron exporter, and causing the internalization and degradation of the transporter (16). Administration of synthetic exogenous hepcidin (17) leads to hypoferremia, a state of diminished TF-bound iron in the serum, and eventual iron deficiency. Interestingly, specific mutations in human ferroportin (18) prevent transporter binding to its ligand hepcidin, leading to iron overload and confirming the key function of this iron regulatory mechanism. In total, an increase in hepcidin expression leads to elevated iron storage in RBC recycling macrophages and hepatocytes, and limits uptake from dietary sources. Conversely, diminished hepcidin expression permits more non-heme iron to be released from internal liver and macrophage stores and increases iron transfer through intestinal epithelial cells, effectively controlling the bioavailable iron supply.

Regulation of hepcidin through the Bone Morphogenetic Protein (BMP)/SMAD signaling pathway

Hepcidin is only regulated at the transcriptional level and expression is inhibited by anemia, hypoxia (19) and ineffective erythropoiesis (20), and stimulated by iron loading and inflammation. Multiple lines of inquiry have demonstrated that members of the TGF-β superfamily, including bone morphogenetic protein (BMP) receptors, associated BMP ligands and the cytoplasmic SMAD transcription factors (homologs of the Caenorhabditis elegans protein *SMA* and the Drosophila protein mothers against decapentaplegic (*MAD*)) play a central role in transcriptionally regulating hepcidin expression (Figure 2). Hemojuvelin (*HJV*) is a BMP co-receptor (21) required for appropriate iron metabolism that is expressed primarily in liver, heart and skeletal muscle (22). Loss of HJV causes severe cases of iron loading in humans termed Juvenile Hemochromatosis (22) and mouse models

confirmed that ablation of *HJV* (23,24), specifically in hepatocytes (25,26), leads to extreme iron overload due to depressed hepatic hepcidin expression. Furthermore, the ligand BMP-6 is essential for appropriate HJV-mediated hepcidin expression (27,28) and serine/threonine type I, predominately ALK3 (29), and type II, ActRIIA and BMPRII (30) receptors are required for transmission of this signal. Stimulation of these receptors leads to phosphorylation of SMAD1/5/8 transcription factors. Earlier work demonstrated that loss of SMAD4 (31), the primary common mediator SMAD (co-SMAD) which binds to activated SMAD1/5/8, results in iron overload and decreased hepcidin expression. Finally, BMP-responsive elements are found in the hepcidin promoter and are critical for appropriate hepcidin regulation (32,33). This data, in aggregate, establishes that the BMP-SMAD signaling pathway plays a central role in the transcriptional regulation of hepcidin.

Regulation of BMP/SMAD-pathway signaling by iron sensors is complex and not completely understood and dysregulation of this system can lead to human disease. Although loss of multiple members of the iron sensing mechanism including *HFE* (34), the classic hereditary hemochromatosis gene, and *TFR2* (transferrin receptor 2) (35), a homolog of the iron uptake receptor TFR1, are known to diminish hepcidin expression leading to excess iron absorption, how they interact with the BMP/SMAD signaling complex is uncertain. HFE binds to transferrin receptor 1 (*TFR1*), sharing a binding site on the receptor with transferrin (*TF*) (36). One model asserts that increasing transferrin saturation displaces HFE from TFR1, leading to increased hepcidin expression (37). Although work *in vitro* has demonstrated that HFE, TFR2 and HJV may form a stable complex that functions to regulate hepcidin expression through HJV (38), other data suggests that this interaction is dispensible or works through a different mechanism (39,40). To this end, recent work has demonstrated that HFE directly interacts with ALK3, stabilizing the receptor on the cell surface and helping transduce a signal for hepcidin transcriptional regulation (41). Further research will be required to fully comprehend how these proteins, as well as other effectors of BMP/SMAD signaling, work together to regulate hepcidin expression.

Regulation of hepcidin by inflammation

A large number of plant and animal tissues contain antimicrobial peptides involved in host defense. Due to its eight cysteine residues and defensin-like structure, hepcidin was originally postulated to be a liver-generated member of this large protein family. In fact, the peptide has both antifungal and antimicrobial activities (11). Importantly, it was noted that murine hepcidin transciption surges upon treatment with lipopolysaccharide (LPS) (10) or turpentine (19). LPS is an endotoxin and the major component of the outer membrane of Gram-negative bacteria, and as such, is an extremely potent pathogen-derived inflammatory signal. Toll-like receptor 4 (TLR4), a member of the TLR family which plays a fundamental role in pathogen recognition and activation of innate immunity, is the receptor for LPS (42). Turpenes are thought to play a protective role in conifers and turpentine has long been known to initiate inflammatory responses in mammals. Taken together, these investigations suggested that the hepcidin peptide was likely regulated by both inflammation and infection.

Inflammatory cytokines are generated in response to infection by iron-dependent invading pathogens. Particular molecular patterns are recognized by specific receptor familes (TLR's) and cytokines are released to instigate an immune repsonse. This response can stimulate an acute hypoferremia, inhibiting pathogen growth and prolifferation. Several cytokines, including primarily interleukin-6 (IL-6) (43), but also IL-1 (44), IL-22 (45) and interferon α (46) have been shown to positively upregulate hepcidin expression. This is mediated by signal transducer and activator of transcription 3 (STAT3) signalling (47,48), and loss of STAT3 specifically in the liver prevents hepcidin regulation by cytokine stimulation

(49). In the current model, IL-6 binds to the gp130 protein receptor complex (50) instigating a janus kinase 1/2 (JAK1/2) tyrosine kinase mediated phosphorylation of the transcription factor STAT3. Activated STAT3 then translocates to the nucleus and binds to the STAT3-responsive element on the proximal hepcidin promoter inducing hepcidin transcription (Figure 2).

More recently, ALK3, the primary type I receptor BMP receptor involved in hepcidin regulation, was shown to be crucial for IL-6-mediated hepcidin induction (51). Furthermore, activin B, a member of the TGF-β superfamily, is involved in response to inflammation in an IL-6 independent manner (52). Upon treatment with LPS, expression of the activin β(B)-subunit is significantly increased and this leads to a rise in SMAD1/5/8 phosphorylation and subsequent hepcidin induction. Importantly, IL-6 is known to be crucial for the response to common bacterial or viral infections or to pathogen-derived molecules in mice (53). Interestingly, cytokine induction, and the resulting increase in hepcidin expression by inflammation, also leads to decreased numbers of erythroid progenitors (54), possibly helping to match the diminished amount of iron available for erythropoiesis. Finally, upon infection activated inflammatory cells undergo an oxidative burst that results in the release of large amounts of reactive oxygen species which help to kill invading microbes. Neutrophils generate H_2O_2 when activated and work in cell culture has shown that low levels of H_2O_2 stimulation contributes to hepatic hepcidin induction through STAT3 (55).

There is also some suggestion that inflammatory signals may modulate iron metabolism without the need for hepcidin induction. Animals with complete genetic ablation of hepcidin and treated with LPS have diminished ferroportin expression in the duodenum and spleen leading to slightly decreased plasma iron (56). Furthermore, TLR's are key components in the innate immune system and are required for the induction of the adaptive immunity response. They are normally expressed in sentinel cells such as tissue macrophages and recognize pathogen-derived molecules. Stimulation of TLR2 and -6 receptors (Figure 3) reduces ferroportin expression in mouse bone marrow-derived macrophages, liver and spleen independently of hepcidin (57). Ferroportin containing a C326C mutation is known to be resistant to hepcidin-mediated degradation (18). Injection with two separate TLR2/6 ligands down-regulated ferroportin and induced hypoferremia in mice containing the C326C mutation. These data suggest that there may be multiple pathways by which organisms attempt to withhold iron from invading pathogens during periods of inflammation, but further research is essential to better understand these additional inflammatory responses leading to hypoferremia.

Cooperation between BMP/SMAD and JAK1/2-STAT3 inflammatory signalling pathway

Increasing weight of evidence suggests that essential crosstalk exists between the BMP/SMAD and JAK1/2-STAT3 inflammatory signalling pathway (Figure 2). SMAD4 is the co-SMAD necessary for dimerization with phosphorylated SMAD1/5/8 and subsequent hepcidin induction. Early studies suggested that mice lacking Smad4 are unable to induce hepcidin expression after treatment with LPS (31). Pharmacological intervention with dorsomorphin, LDN-193189, or other specific small-molecule inhibitors of the BMP pathway (58-60), are able to attentuate hepcidin expression in rodents treated with inflammatory agents. Loss of HFE and TFR2, either alone or in combination, leads to inappropriately phosphorylated SMAD1/5/8 and supressed hepcidin expression (39,61-63). Mice lacking HFE (64) or both HFE and TFR2 (65) are able to mount an appropriate immune response to LPS, but do not elevate hepcidin production nor develop hypoferremia. Furthermore, concomitant stimulation of both the BMP/SMAD and JAK1/2-STAT3 pathways in rodents causes, at minimum, additive, and also in some experiments synergistic, affects upon

upregulation of hepcidin (59,66,67). In toto, this research suggests that the BMP/SMAD and JAK1/2-STAT3 signaling pathways impinge on one other, leading to increased hepcidin expression under conditions of infection or inflammation.

Role of hepcidin in the anemia of inflammation

The anemia of chronic disease (68), now commonly termed the anemia of inflammation, is known to occur in settings of infection by microbial pathogens, in inflammatory, autoimmune conditions such as arthritis or lupus, in chronic kidney disease or as a result of cancer. The mild to moderate anemia is normocytic and normochromic with a reduced number of erythrocytes; however, patients may progress to a more serious condition with microcytic and hypochromic red blood cells over the course of a long, serious illness. In most cases, iron is retained within macrophages of the reticuloendothelial system, leading to inappropriately low availability of iron bound transferrin required for erythropoiesis. In these inflammatory states, release of cytokines leads to elevated hepcidin expression, diminishing ferroportin on the surface of enterocytes, recycling macrophages and hepatocytes, sequestering iron in storage sites and diminishing iron uptake from the diet. One of the first studies to demonstrate the involvement of hepcidin in this condition showed that patients with glycogen storage disease (GSD) type 1a, a population that spontaneously develops large adenomas in the liver and the anemia of inflammation, have elevated hepcidin expression. The observed anemia ameliorated upon resection of the adenomas (69).

Anemia of inflammation and infection

Historically, the anemia of inflammation in humans was most readily observed and understood in the context of infection with pathogenic organisms. The hypoferremia associated with infection was first noted over 70 years ago by Cartwright and colleagues and was hypothesized to sequester iron in tissues to prevent transfer to invading microbes. Based on the overwhelming weight of evidence, this response is primarily due to the upregulation of hepcidin. Interestingly, hepcidin regulation by infection was first noted in sea bass (70) where a massive induction of hepcidin occurs after bacterial infection. Subsequently, it was demonstrated that patients with various causes of anemia of inflammation or infection had elevated urinary hepcidin excretion (71). Furthermore, humans treated with Il-6 (43) or with LPS (72) have elevated hepcidin expression leading to an acute hypoferremia.

Significant data demonstrates that hepcidin-mediated iron regulation plays a crucial role in the interaction between human hosts and their microbial pathogens. For example, hepcidin is induced in malarial infection (73), a disease that is estimated to kill 600,000 people every year. The relevance of hepcidin, and its role in the treatment and outcome of infection by this human scourge, has been reviewed extensively elsewhere (74). Furthermore, the crucially important nature of hepcidin in host defense was starkly illustrated by a laboratory accident. Attenuated strains of *Yersinia pestis* lacking a high-pathogenicity island involved in iron uptake are commonly employed in vaccine research. A researcher with an undiagnosed case of hereditary hemochromatosis caused by a mutation in *HFE*, a disease where inappropriately low hepcidin expression leads to elevated total body iron body burden, died after developing a case of septicimic plague (75). Of note, the upregulation of hepcidin and resulting acute hypoferremia may not be a universal phenomenon in pathogen infection. For example, hepcidin is induced upon HIV-1 infection, but not by infection with hepatitis B or C, in humans (76). This suggests that the hepcidin-mediated iron sequestration in infection may be pathogen, tissue and inflammation-response specific.

The vast majority of hepcidin is expressed by hepatocytes of the liver. However, immune cells at the site of infection produce small concentrations of the peptide (77), likely through a TLR4-dependent mechanism (78). Furthermore, treatment of monocytes from

anemia of inflammation patients with IL-6 or LPS induced a more robust hepcidin induction than in controls, and this leads to diminished ferroportin expression and a decrease in iron export in an autocrine manner (79). Taken together, this implies that hepcidin production at the site of infection may lead to localized iron sequestration and prevent iron theft by pathogens; however, further research is required to understand this response to microbial invasion.

It appears that a regulatory pathway facilitates the amelioration of inflammation-mediated anemia once infection has resolved (Figure 4). Recent investigation has uncovered erythroferrone (ERFE), a hormone produced by erythroblasts in response to erythropoietin, which mediates hepcidin suppression during early stages of stress erythropoiesis (80). Significantly, ERFE also appears to play a role in the recovery of organisms from the anemia of inflammation (81). Heat killed *Brucella abortus* (HKBA) is known to induce an amemia of inflammation response in rodents (82,83). Mice lacking ERFE have both a more severe and prolonged anemia, and more greatly elevated hepcidin expression, as compared to wild type animals upon exposure to HKBA. Elevated hepcidin expression causes depressed serum iron available for erythropoiesis in HKBA treated mice. Increased ERFE expression appears to suppress the deleterious effects of iron sequestration during infection or the anemia of inflammation, and as such, may be a possible target for therapeutic intervention in disorders with chronic inflammation.

Other causes of the anemia of inflammation

The anemia of inflammation has also been linked with chronic kidney disease (CKD), a disorder most commonly caused by diabetes and high blood pressure, and cancer. Patients with CKD are known to present with anemia during the course of their illness and have elevated hepcidin expression (84). Hepcidin is also greatly increased in multiple myeloma, a plasma cell malignancy that is thought to account for a large percentage of hematologic cancers (85). Hepcidin induction in this cancer requires BMP2, another BMP/SMAD pathway ligand, and the inflammatory cytokine IL-6 (67). Furthermore, recent work demonstrated that hepcidin is elevated in breast cancer patients and diminished tumor expression of ferroportin promotes breast cancer growth (86,87). Finally, patients with the most advanced cancers have the lowest RBC hemoglobin concentration and hemoglobin measurements are conversely correlated with inflammatory markers and hepcidin (88). This research indicates that efficacious treatment of CKD, and a number of distinct malignancies, requires not only directed therapy toward each disease, but also appropriate management of patient iron status.

Interestingly, anemia is widespread in elderly populations even though iron is not normally diet limited. This anemia has been attributed to low grade inflammation; however, the cause of this inflammation is often not explained by infection, CKD or cancer and has been termed the unexplained anemia of the elderly (UAE). Studies in aged mice demonstrate that IL-6 and hepcidin are not directly required for aging-related anemia; however, mice lacking these genes have improved erythropioiesis later in life (89). More recent work has demonstrated that patients with UAE, all of whom have no known history of chronic inflammatory disease, do in fact have features of low grade inflammation including elevated IL-6 expression (90).

Finally, endoplasmic reticulum (ER) stress induces multiple pathways that are collectively known as the unfolded protein response. Toxins, misfolded proteins, disruption of ER homeostasis and inflammation are all known to generate ER stress. ER stress was directly linked to the acute inflammatory response when it was demonstrated that the ER stress-activated transcription factor CREBH (cyclic AMP response element–binding protein H) responds to induction by both LPS and IL-6 (91). Importantly, hepcidin expression can be modulated by the transcription factors CHOP, C/EBPa, and CREBH which bind to specific binding sites on the hepcidin promoter (92,93).

Conclusions

Hepcidin is the master regulator of vertebrate iron metabolism and homeostasis. Expression of hepcidin is modulated by multiple signaling pathways, and upregulation of the anti-microbial peptide is triggered by elevated iron status, inflammation and infection. Inflammatory-mediated induction of hepcidin is thought to occur through the combined efforts of the BMP/SMAD and JAK1/2-STAT3 signaling pathways. Stimulation of hepcidin expression during episodes of inflammation and infection greatly decreases bioavailable iron to invading pathogens; however, this may cause iron-restricted erythropoeisis in the host. Accordingly, there is a constant struggle within a host to meet organismal iron demands for heme production while preventing iron theft by invading infectious agents. This balance is primarily maintained by the attenuation of hepcidin production.

Moving forward, much of the research concerning hepcidin and its link to various human disease states will need to be completed in animal models. Accordingly, new rodent models of cancer (94) and infection (82,83) have been recently generated. These model systems will be essential for dissecting the more intricate interactions between hepcidin regulation and changes in iron homeostasis induced by inflammation or infection.

Furthermore, the intimate link between hepcidin regulation, iron metabolism and human health suggests that therapeutic manipulation of hepcidin is an essential future goal. To that end, neutralizing hepcidin antibodies (95), small-molecule inhibitors of the BMP/SMAD pathway (59), siRNA (96) and antisense oligonucleotide (97) technology or hepcidin mimetics (minihepcidins) (98) have been employed to inhibit, or induce hepcidin expression, respectively. Additional work will be necessary to determine the most efficacious methods of hepcidin modulation in clinical settings.

The direct measurement of hepcidin protein in both rodent models of human disease, and in patients themselves, is vital for further investigation and treatment of the anemia of inflammation. Moreover, determination of the therapeutic efficacy of hepcidin modulation requires specific, non-invasive measurements of the ligand which can be ascertained over the course of treatment. Several methods have been proposed to directly measure the peptide in easily accesible body fluids. Human serum or urine hepcidin can be measured by enzyme linked immunosorbent assays (ELISA) (84) or time of flight mass spectroscopy (99). Recently, a highly specific ELISA assay has been generated that quantitatively measures hepcidin in mouse serum or urine under conditions where hepcidin is greatly elevated or repressed (100).

Although our undertanding of how inflammation regulates hepcidin expression, and by extension modulates vertebrate iron metabolism, is rapidly increasing, many pertinent questions yet remain. For example, do other regulatory pathways exist that influence hepcidin expression during inflammatory events? Are there additional mechanisms that modify iron flux under acute inflammatory conditions without the need for hepcidin? Finally, and perhaps most importantly, how do we best modify hepcidin expression in patients with the anemia of inflammation? Significant further research will be required to answer these questions and identify novel therapeutic approaches for the safe and effective treatment of affected individuals.

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Figure Legends

Figure 1. Role of the hepcidin/ferroportin axis in iron metabolism
Divalent metal transporter 1 is required for the uptake of dietary iron through duodenal epithelial cells. Hepcidin is predominately produced by hepatocytes of the liver. Stimulation of hepcidin production by elevated iron, inflammation or infection causes ferroportin to be internalized and degraded in red blood cell recycling macrophages, duodenal enterocytes of the large intestine or hepatocytes themselves. In this manner, iron can be sequestered in ferritin within these cells, lowering iron concetration in the serum and preventing iron overload or theft of iron by invading pathogens. The opposite is also true. Iron-restricted erythropoeisis leads to a diminishment of hepcidin, elevated numbers of ferroportin transporters on iron exporting cells and increased serum iron availability for red blood cell maturation.

Figure 2. Regulation of hepcidin expression by iron and inflammation.
Increasing saturation of transferrin (TF), and subsequent binding to transferrin receptor 1 (TFR1), causes HFE to be released from a complex with TFR1. HFE is postulated to interact with TFR2 and hemojuvelin (HJV), a BMP co-receptor, to stimulate SMAD1/5/8 phosphorylation, dimerization with SMAD4 and elevation of hepcidin transcription. The ligand BMP6 is thought to play a key role in this process. HFE also interacts with ALK3, a Type I BMP receptor, and stabilizes it on the cell membrane. During periods of inflammation or infection, the cytokine

interleukin 6 (IL-6) is produced, activating the STAT3 signaling pathway to promote transcription of hepcidin through a gp-130-, JAK1/2-mediated pathway. Both the phsophorylated SMAD1/5/8-SMAD4 heterodimer and STAT3 transcription factors have known binding sites in the hepcidin promoter and the two pathways are believed to work together in hepcidin regulation. Other inflammation-mediated stimulatory signals may act to positively stimulate hepcidin expression.

Figure 3. Hepcidin-independent, inflammation-mediated regulation of ferroportin.
Stimulation of Toll-like receptors (TLR) 2 or 6 by the ligands FSL1 or PAM3CSK4 causes diminished ferroportin mRNA and protein expression in bone marrow derived macrophages, liver or spleen. This occurs through TLR2/6 heterodimers or TLR2 homodimers. Decreased ferroportin expression leads to an acute hypoferremia that may procede or complement the hepcidin-mediated decrease in bioavailable iron during inflammatory conditions. Further research is necessary to determine whether this pathway supresses ferroportin mRNA expression by diminishing transcription or through increased mRNA degradation.

Figure 4. A model for erythroferrone-mediated recovery from the anemia of inflammation.
Hypoxia is sensed in the kidney and erythropoietin levels are increased through an IRP1-HIF2α signalling pathway. Elevated erythropoietin causes a JAK2/STAT5 phosphorylation cascade leading to the production of erythroferrone (ERFE) in early erythroblasts. Circulating erythroferrone supresses hepcidin production in hepatocytes leading to elevated ferroportin expression and augmenting serum iron availability for red blood cell maturation.

Figure 1

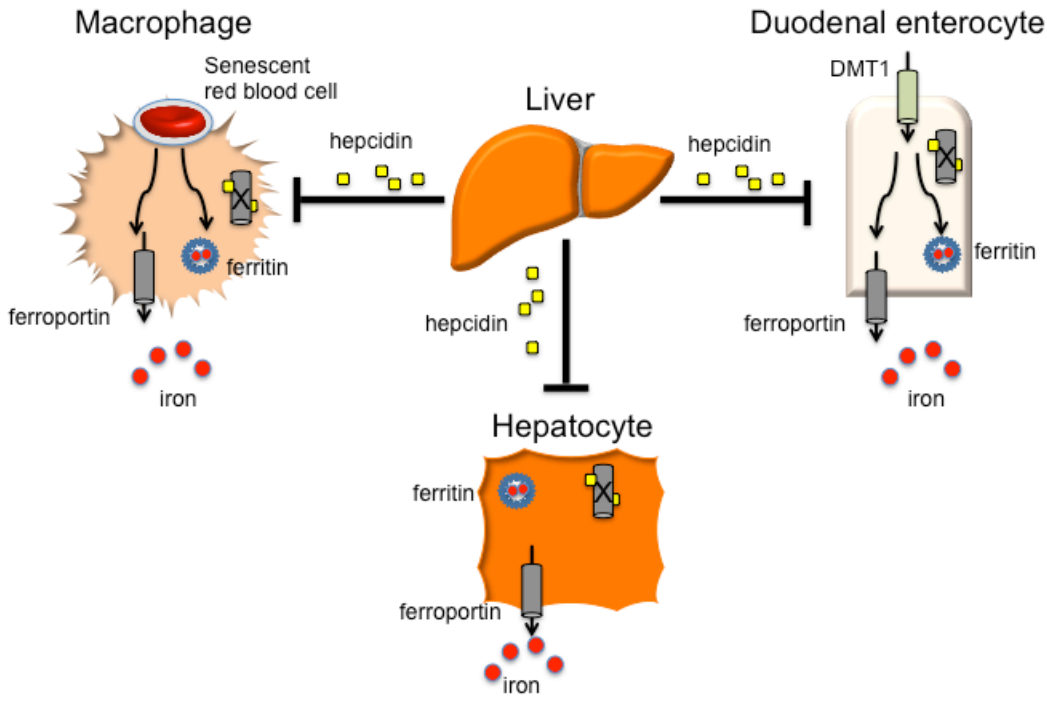


Figure 2

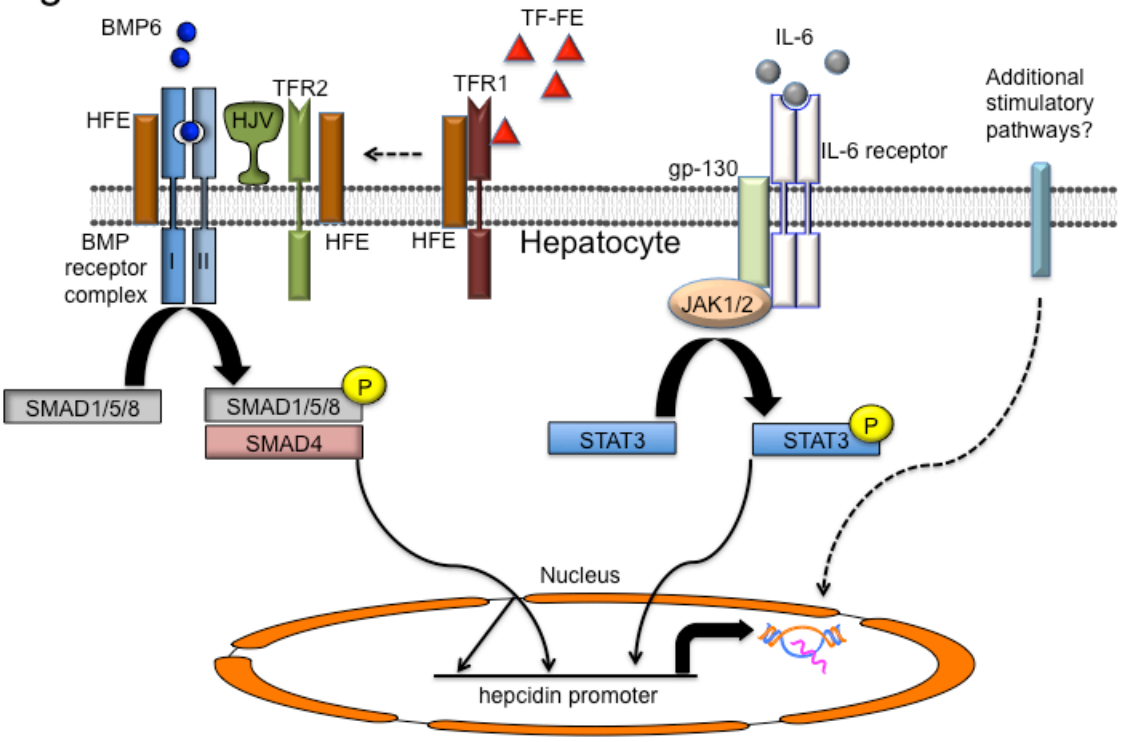


Figure 3

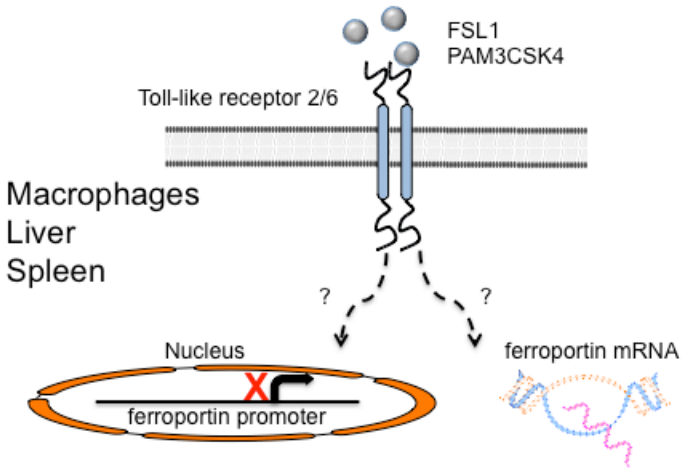
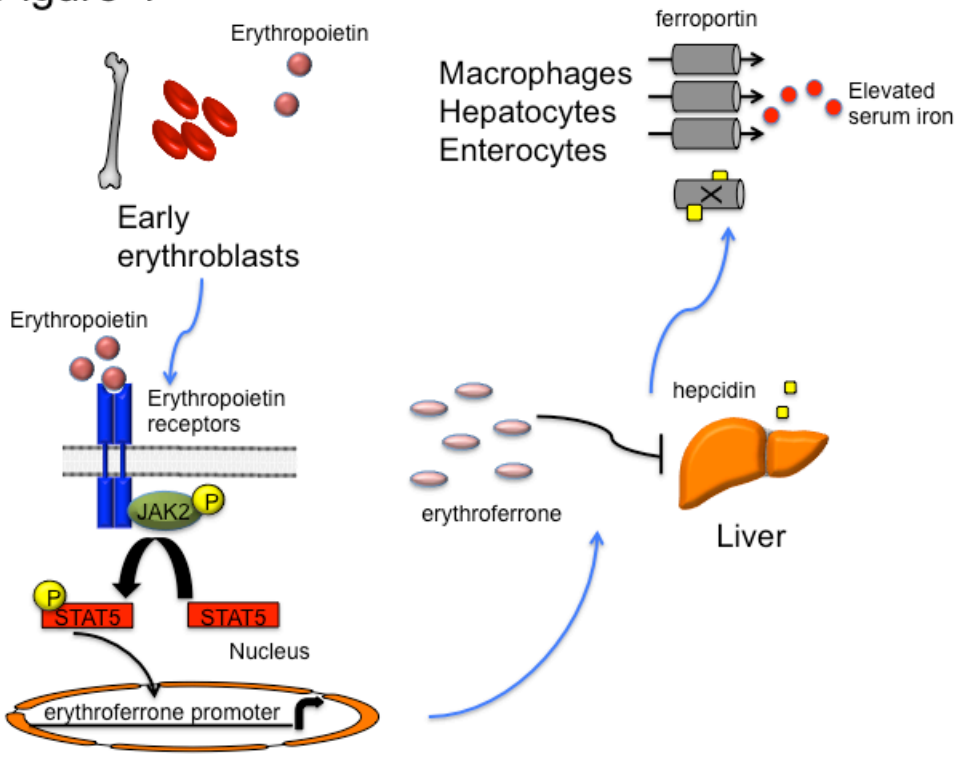


Figure 4



Minireview:

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Paul J Schmidt

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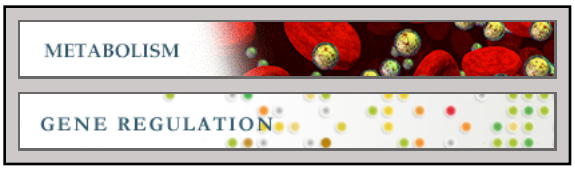

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