**Editorial:**

**Hepcidin and the Anemia of Chronic Disease**

Farid I. Haurani  
Pocono Pines, Pennsylvania

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In recent years, fascinating regulatory agents have been identified that relate to intestinal iron absorption and macrophageal iron release, the primary targets of anemia of chronic disease (ACD). These discoveries provide a molecular understanding of clinical erythrokinetics and explain many previous observations [1,2]. Among the new agents, hepcidin is the most exciting. It was independently discovered by Krause et al [3] and Park et al [4] as a 25 amino acid protein with antibacterial activity, produced in the liver and excreted in the urine. Hepcidin is a type II acute-phase protein similar to ferritin [5].

**Regulation of Hepcidin Production**

Production of hepcidin is regulated by interleukin-6 (IL-6) [6,7]. IL-1, interferon gamma (IFN-γ), and tumor necrosis factor alpha (TNF-α) were considered to be responsible for the inhibition of iron release from the macrophageal system and the hypoferremia of ACD [8]. Aisen’s group [9] showed that none of these agents influenced the release of iron from Kupffer cells that contained iron-labeled erythrocytes. However, when the Kupffer cells were exposed to serum from rats previously injected with turpentine, there was a block in the release of iron from the erythrocytes. The responsible factor was not identified, but it was probably hepcidin.

Patients with type 1α glycogen storage disease and hepcidin-secreting hepatic adenoma develop hypoferremic hypochromic anemia, which is corrected by the surgical removal of the adenoma [10]. Nemeth et al [5] showed that hepcidin mRNA is greatly induced in hepatocytes in vitro by IL-6 but not by IL-1 or TNF-α, indicating that hepcidin, an acute phase reactant type II, plays a key role as a mediator of the anemia of inflammation. On the other hand, Lee et al [11] showed that mice with disrupted IL-6 gene still produced hepcidin transcripts in the liver following endotoxin treatment. Moreover, incubating hepatocytes with IL-6 and IL-1 (alpha and beta) strongly stimulated hepcidin transcription. The authors concluded that IL-1 may play a significant role in the anemia of inflammation by up-regulating hepcidin.

**Increased Production of Hepcidin**

Erythrokinetic studies have shown that practically all patients with ACD, inflammation [12], malignancy [13], or primary defective red cell iron reutilization [14], have poor macrophageal release of iron and severe malabsorption of iron [15]. After simultaneous iv injection of inorganic ⁵⁹Fe and ⁵⁵Fe-tagged hemoglobin solution, erythrokinetic studies revealed normal total erythropoiesis as measured by ⁵⁹Fe-derived plasma iron turnover, normal effective erythropoiesis as measured by ⁵⁹Fe-derived red cell iron utilization, and normal red cell survival using ⁵¹Cr-tagged red cells. On the other hand, ⁵⁵Fe-derived red cell iron reutilization, a measure of iron release from the macrophageal system, was defective and so was iron intestinal absorption (tested by an oral dose of ⁵⁹Fe). The hemoglobin solution was cleared and processed by the macrophageal system. Then the iron released to the circulation became bound to transferrin. Transferrin iron was reutilized by newly formed red cells that eventually appeared in the circulation over a three week period. Their radioactivity in the peripheral blood indicated the red cell iron reutilization. The net result of defective red cell iron reutilization is hypoferremia, anemia, and increased accumulation of ferritin and hemosiderin in the macrophages.
At least in inflammation, it has been shown that increased production of hepcidin is the cause of these events [6,8]. In patients with primary defective red cell iron reutilization syndrome, the anemia responds well to testosterone or danazol (a non-masculinizing testosterone) [17]. Testosterone, in vitro, increases the release of radioactive iron from macrophages laden with 59Fe-tagged red cells [18]. So at what level, if any, does testosterone interact with hepcidin?

**Decreased Production of Hepcidin**

Hepcidin production is diminished in hypoxia and anemia [8]. Patients with mutations in the hepcidin gene have decreased production of hepcidin, which results in a severe form of juvenile hereditary hemochromatosis [19]. Iron overload occurs in the hepatocytes as intestinal iron absorption and macrophageal iron release continue unhampered in the absence of hepcidin. Hepcidin gene knockout mice have an iron overload distribution similar to mice with knockout of hfe (the gene responsible for the HFE intestinal crypt cell receptor) and to humans with hepcidin gene mutations [20,21]. Patients with HFE hemochromatosis or mice with hfe knockout are overloaded with iron and have decreased hepatic expression of hepcidin [22], probably secondary to iron deposition in hepatocytes, which reduces the production of hepcidin and thereby increases intestinal iron absorption.

**How Does Hepcidin Act?**

As previously mentioned, hepcidin production is regulated by IL-6 [6,7] and probably by IL-1 [11]. In turn, hepcidin regulates the protein product (MTP1) of the mtpt1 gene, described by Abboud and Haile [23]. MTP1 is better known as ferroportin [24]. The absorption of reduced iron (ferric reduced to ferrous by ferric reductase) by intestinal apical cells is facilitated through ferroportin. Also through ferroportin, iron is released from the macrophages, pregnant uterus, and other tissues. Before it becomes bound to plasma transferrin, the released iron is oxidized by hephaestin/seruloplasmin. Hepcidin binds and then internalizes ferroportin, thereby rendering it dysfunctional [25]. Mutations of ferroportin are of two types: one type, such as the missense and point deletion in humans, causes impaired function or decreased number of ferroportin receptors, resulting in increased iron macrophageal retention and decreased iron absorption [26,27]. The second type of mutation causes increased number of ferroportin protein molecules, which over power hepcidin and flood the circulation with iron [28]. Inactivation of the HFE receptor of the crypt intestinal cell does not interfere with hepcidin function [29]. Abnormality of this receptor in the intestinal crypt cell is responsible for primary (HFE) hemochromatosis [30].

Is the hypoferremia induced by hepcidin alone responsible for the anemia in ACD? My answer is yes. The bone marrow findings in ACD and simple iron deficiency (SID) are similar except that the iron content is different. Respectively, one is replete of iron in the macrophages of the bone marrow and the other is depleted. In both conditions, erythropoiesis seems inadequately responsive to erythropoietin. Is hypoferremia enough to blunt the action of erythropoietin regardless of its concentration? My answer is yes.

The action of erythropoietin is blunted by hypoferremia in the following clinical situations: Patients with simple iron deficiency secondary to *Ancylostoma duodenale* with intestinal bleeding achieve the highest titers of urinary erythropoietin; so much so that in the past their urine was collected to provide erythropoietin for research use. Yet, such patients have “normal” erythropoiesis. One may call the anemia relatively hypoproliferative compared to thalassemia, another hypocromic anemia but one with iron overload. Other clinical conditions where the action of erythropoietin is blunted in the presence of hypoferremia include hypoferremia complicating pernicious anemia, which changes the megaloblastic erythropoiesis to megaloblastoid, and arrests the response of the anemia to cobalamin. Similarly, iron deficiency arrests the response of the anemia of chronic renal disease to erythropoietin. These two conditions require simultaneous therapy with iron and cobalamin or erythropoietin for anemia to improve.

Basic science evidence supports the clinical observations just mentioned. Although iron is involved in many reactions, the most germane to
this discussion involves an essential enzyme in DNA synthesis, ribonucleotide reductase. This iron-containing enzyme reduces ribose to deoxyribose in DNA synthesis. Le and Richardson [31] showed that iron chelators have high antiproliferative activity, indicating a link between iron metabolism and proliferation. Ponka [32] noted that Robbins and Pederson [33] presented the first convincing evidence for a crucial role of iron in DNA synthesis. When the iron present in the nuclear fractions of HeLa cells was reduced by exposure to an iron chelator, a significant decrease in DNA synthesis ensued [33]. Recently, Liu et al [34] found that mRNA levels of several hundred genes of cardiac cells were affected by iron, including several that were increased in response to oxidative stress. In a human liver cell line, they studied 13 genes that were affected by iron chelation and found that metabolic pathways of 5 of these genes were linked by responsiveness to phorbol ester. Their study demonstrated that the iron-regulated proteome is extraordinarily complex and that definitive understanding of its organization will require global gene approaches [34].

Conclusions

Iron depletion interferes with DNA synthesis and can prevent the proliferation of erythropoiesis. Hypoferremia per se can be responsible for a lack of erythroid precursor compensation of the bone marrow.

It is now generally accepted that “anemia of chronic disease” (ACD) is a misnomer [35,36]. Whereas the term ACD is overly inclusive, the frequently used term, “anemia of inflammation,” is quite exclusive. Conditions other than inflammation can produce this type of anemia.

The author recommends the terms ACD and anemia of inflammation be replaced with “hyperhepcidin anemia” if experimental findings continue to support and expand the central role of hepcidin in the pathogenesis of such anemia.

References


