Hepcidin: inflammation’s iron curtain

Rheumatologists and their patients are the beneficiaries of a recently identified peptide, hepcidin (Table 1). Isolated from human urine and plasma in the year 2000 [11, 12], hepcidin appears to be the long-sought iron-regulatory hormone responsible for the anaemia of chronic disease [3, 4]. It is more than that: it is an acute-phase reactant, responding to infection and inflammation [5]; it is an antimicrobial peptide that disrupts microbial membranes [1, 6]; and it provides an iron-restricted internal milieu inhospitable to microbes [7, 8].

Hepcidin is a 25 amino acid, 2–3 kDa, cationic peptide that has broad antibacterial and antifungal actions [1]. In concert with other antimicrobial peptides, known as defensins and cathelicidins [9], it provides a first line of defence at mucosal barriers [1, 2]. However, more germane for rheumatologists is its control of iron kinetics. Produced by hepatocytes, hepcidin inhibits the intestinal absorption [1, 10], macrophage release [3, 7] and placental passage [10] of iron. Hepcidin mRNA moves with the body’s iron levels, increasing as they increase and decreasing as they decrease [11]. More pertinently, hepcidin rises with infection or inflammation and falls with hypoxia or anaemia [12].

The anaemia of chronic disease has long confounded physicians. It is generally normocytic and normochromic, but may be hypochromic or microcytic [13]. The low serum iron and normal-to-low iron-binding capacity, in conjunction with a high-to-normal serum ferritin level in patients with inflammatory disease, has been perplexing. Also notable has been the shortened red blood cell survival and blunted erythropoietin-induced production of red blood cells. At one time known as the anaemia of infection, it became known, after man’s entry into the age of antibiotics, as the anaemia of chronic disease, and now, perhaps more aptly, it is the anaemia of inflammation.

Iron can be toxic. It catalyses the generation of reactive free radicals [14] and activates NF-κB, the prototypic transcription factor for genes involved in inflammation [15]. At high levels, iron is damaging to tissues. Humans need little dietary iron, 1–2 mg a day sufficing for the average adult male [16]. However, mammals lack a regulated pathway for iron excretion [12], so iron absorption has to sufficing for the average adult male [16]. However, mammals lack a regulated pathway for iron excretion [12], so iron absorption has to

In addition to iron levels and inflammation/infection, there is another factor that affects hepcidin levels: it is anaemia. Along with hypoxia, anaemia overrides the effects of iron and inflammation/infection, reducing levels of hepcidin mRNA [4, 12]. Were this not the case, inflammation, by maintaining high hepcidin levels, would keep the haematocrit dropping. Instead, down-regulation of hepcidin mRNA expression by anaemia produces a new steady state, usually with haematocrits 3–5 points below normal.

In addition to disrupting bacterial membranes, hepcidin provides an inhospitable internal milieu for microbes that successfully enter the bloodstream. Micro-organisms need iron [14]. Bacteria require iron for the production of the superoxide dismutase that protects them from host oxygen radicals [20, 21]. Hepcidin, by inducing macrophage sequestration of iron, robs bacteria of this element. Blood and intracellular bacteria [22] may weaken; biofilms may not develop [7]. Pertinent here is the recent report of an inverse relationship between the incidence of tuberculosis and rheumatoid arthritis (RA) [23], raising the possibility that that the inaccessibility of iron in RA protects from tuberculosis [24].

Palor, weakness and fatigue have been recognized as hallmarks of chronic disease for millennia. Anaemia obviously contributes to the pallor. Less obvious is whether the decrease in serum iron diminishes its availability to myoglobin and the enzymes catalysing the redox reactions required for the generation of energy (cytochromes) sufficiently to contribute to weakness and fatigue. Defensins are antimicrobial peptides produced by cells of epithelial linings [9]. Hepcidin, like defensins, is an antimicrobial peptide that kills on contact. However, because it is produced by the liver, has not been found to have chemotactic properties, and differs structurally from defensins [25], it will likely be classified as an acute-phase reactant [5].

The identification of hepcidin opens the door to therapeutic approaches for several disorders and to proscriptions regarding the use of iron. Recombinant hepcidin may be the ideal therapeutic agent for those with some forms of juvenile haemochromatosis and

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<th>TABLE 1. Dynamics of iron and hepcidin regulation</th>
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<td><strong>Stimulation or down-regulation</strong></td>
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<td><strong>1. Inflammation/infection</strong></td>
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<td><strong>Haemosiderosis</strong></td>
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<td><strong>3. Body Fe ↓</strong></td>
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<td><strong>4. Anaemia, hypoxaemia</strong></td>
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<td><strong>5. Erythropoiesis ↑</strong></td>
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with the less severe but more common form of haemochromatosis caused by mutations in the HFE gene [26]. Hepcidin-induced iron deprivation may prove helpful in preventing the development of resistant bacterial biofilms [10]. For the anaemia of inflammation, often resistant to erythropoietin therapy [27], inhibitors of hepcidin, by releasing sequestered iron, could restore haemoglobin levels and conceivably correct an iron lack in myoglobin and cytochromes as well. Finally, of related interest is a recent report that moderate alcohol intake reduces levels of C-reactive protein and IL-6 [28], the principle chemokine for the generation of hepcidin mRNA, extrapolating to a possible ameliorative role of alcohol in both inflammation and the anaemia of inflammation.

As to proscriptions, iron supplements should be monitored, not only because the resulting increase in hepcidin can fuel antimicrobial engines unnecessarily, but because hepcidin increases macrophage iron sequestration in the synovium as elsewhere. Synovial iron has the propensity to generate oxygen free radicals that have been linked to the chronicity and erosiveness of joint disease in RA [29]. In fact, intramuscular injections of iron have long ago been reported to cause acute flares of joint inflammation in RA [30]. A broader phlogistic potential of iron towards the joint comes from a recent report that iron depletion by serial phlebotomies diminishes recurrences of gouty arthritis [31]. If one adds all of the above to the reported links of iron sufficiency to colon cancer [32], diabetes mellitus [33], chronic hepatitis [34] and atherosclerosis [35], it would seem best to phase out gratuitous iron supplementation altogether.

The discovery of hepcidin provides a thread that ties together the perplexing triad of decreased serum iron, increased macrophage iron and chronic inflammation. In addition, it offers a unique opportunity for determining the effects of iron on disease, the usefulness of hepcidin inhibitors or promoters to control iron kinetics, and the proper means of iron administration. In the aggregate, these will represent a step forward in the treatment of a variety of diseases.

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