Next-Generation Biomarkers for Iron Status

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Importance of Measuring the Iron Status and Current Approaches

Iron deficiency is a major cause of anemia worldwide and impacts on child development, pregnancy outcome [1], as well as kidney disease, transplantation medicine, and heart failure. Iron therapy (in the form of tablets, multiple micronutrient sprinkles, food fortifications, and intravenous preparations) can improve the iron status, but is recognized as having potential risks, for example promoting infections, detrimentally destabilizing the gut flora, and possibly increasing the likelihood of transplant rejection [2]. Therefore, it is important to assess the iron status of individuals and populations with a view to appropriately targeting iron therapy to maximize efficacy and reduce unwanted adverse events. Current indices used to diagnose iron deficiency (such as serum ferritin, transferrin saturation, serum transferrin receptor, and zinc protoporphyrin), all suffer from limitations: first, they are all compromised by the presence of other commonly occurring comorbidities (especially inflammation); second, as tests they may lack standardization or are not straightforward to perform, and, third, and in my view most importantly, they do not report accurately the capacity to respond to iron therapy, probably because they are not direct measures of systemic iron-regulatory processes.

Hepcidin – Role and Regulation in Iron Homeostasis

The master controller of systemic iron balance is the liver-secreted peptide hormone hepcidin [3]. Hepcidin inhibits absorption of iron from the diet and prevents recycling of iron by macrophages; in this way, hepcidin determines both the total amount of iron in the body and its tissue distribution. High levels of hepcidin decrease the amount of iron in serum and restrict erythropoiesis; low hepcidin levels allow
absorption from the diet and facilitate the release of iron from tissue stores. The regulation of hepcidin expression is matched to three major competing demands: (i) iron in serum or in the liver switch hepcidin on to prevent absorption and so maintain homeostasis; (ii) infection and inflammation switch hepcidin on so that microbes are starved of the iron they need to thrive, and (iii) blood loss causes profound suppression of hepcidin, to maximize iron availability for the replacement of lost erythrocytes. These three signals all arrive at the promoter of the hepcidin gene in hepatocytes; the balance between the signals controls hepcidin transcription and synthesis, and ultimately determines systemic iron trafficking.

Table 1. Equivalence of indices used to assess the iron status and known molecular regulators of hepcidin

<table>
<thead>
<tr>
<th>Molecular regulators of hepcidin synthesis</th>
<th>Biomarkers used to assess the iron status</th>
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<td>signal regulating hepcidin (direction of regulation)</td>
<td>index of the iron status</td>
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<tr>
<td>BMP6/SMAD signaling (↑)</td>
<td>Liver iron stores</td>
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<tr>
<td>HFE/Tfr2, SMAD signaling (↑)</td>
<td>Iron available in blood</td>
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<tr>
<td>IL-6/STAT3 signaling (↑)</td>
<td>Inflammation</td>
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<tr>
<td>Erythroferrone (↓)</td>
<td>Erythropoietin signaling in bone marrow following blood loss or in thalassemia</td>
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Hepcidin is upregulated by iron: both by iron in the liver, which drives hepcidin transcription through bone morphogenetic protein 6 (BMP6) and SMAD signaling, and by iron in serum bound to transferrin, again via SMAD transcription factors but also requiring HFE and Tfr2. Inflammation stimulates hepcidin synthesis through cytokines, especially IL-6 (although IL-22 and type-I interferon may contribute), and the transcription factor STAT3. Bone marrow demand for iron is communicated to the liver via the erythroblast-secreted hormone erythroferrone, which causes suppression of hepcidin. Commonly used indices of iron status (e.g. C-reactive protein, which is used to assess inflammation but influences the interpretation of serum ferritin concentrations) show a very close relationship with the known factors that control hepcidin, so that attempts to ascertain iron status using a combination of these indices could be viewed as measures of the balance of hepcidin regulation.
Hepcidin – A Next-Generation Biomarker to Guide Iron Therapy

Iron status indices have evolved to incorporate the effect of inflammation (for example by adjusting serum ferritin cutoffs if C-reactive protein is detected) and to reflect bone marrow demand (log ferritin/transferrin receptor ratio), but these components are already integrated into hepcidin regulation. In other words, determining the iron status has been a difficult and empirical exercise that unconsciously has attempted to balance the signals that we now know control hepcidin synthesis (table 1). However, hepcidin also has the significant advantage that is a direct assessment of the capacity of an individual to efficiently absorb oral iron and traffic it to the bone marrow [4]. Hepcidin is not a biomarker of iron deficiency per se, but rather of the combined need for and ability to utilize iron if it is provided. Individuals that are either iron replete or inflamed will have high hepcidin levels and will likely respond poorly to iron. Hepcidin may thus be useful to categorize conditions into iron-responsive and non-iron-responsive types; we have been able support this concept in a large cohort study of African children [5]. Much more work is required to establish hepcidin as a biomarker for iron therapy in the full range of different conditions in which iron has potential benefits (including anemia, heart disease, and renal medicine) but, currently, both theory and available data warrant further investigation.

References