

# Hepcidin, iron, and COVID-19: is there an erythroid connection?

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Many years ago, it was postulated that the low serum iron that characterized anemia of chronic disease (now called anemia of inflammation) provided protection from the inflammatory conditions and infections with which it was associated by depriving bacteria of iron on which they were dependent or by removing iron that would otherwise be available for the generation of free radicals.<sup>1</sup>

The discovery of the iron regulatory peptide hepcidin provided the mechanism by which inflammation, infection, and other cytokine-mediated processes could shift the iron balance from circulation bound to transferrin to intracellular storage in the reticuloendothelial system and could control iron absorption.<sup>2</sup> Hepcidin, an element of the innate immune system, is regulated by systemic iron levels, by inflammation, and by the degree of erythroid activity in the bone marrow. This latter effect is mediated principally by erythroferrone (ERFE), a product of erythroid precursors that downregulates hepcidin production, allowing increased absorption of iron and mobilization of intracellular iron stores.<sup>3</sup>

The pathologic manifestations of COVID-19 reflect, in part, the consequences of the response of the innate immune system to SARS-CoV-2 infection,<sup>4</sup> and elevated hepcidin levels have been reported in COVID-19.<sup>5</sup> In a paper in this issue of the journal, Delaye, Alarcán, and colleagues<sup>6</sup> examine this phenomenon in light of the effects on ERFE and on growth and differentiation factor-15 (GDF15), another erythroid-secreted mediator with the capacity to downregulate hepcidin production. They observed that hepcidin levels were higher and ERFE/GDF15 levels were lower in patients with COVID-19 and that this difference was more pronounced in patients who were more critically ill. A novel feature of the study design was that patients with COVID-19 were compared with patients with bacterial sepsis rather than with healthy controls. In consequence, both groups of patients had evidence of inflammation (elevated C reactive protein (CRP)) and of red blood cell/iron abnormalities associated with inflammation (elevated ferritin concentration, hypotransferrinemia, and a moderate degree of anemia).

The findings raise questions that require assessment in a larger patient population. As an example, while ferritin, transferrin, iron, and CRP values do not differ with statistical significance between the two groups, median ferritin and CRP concentrations are higher, and median iron and transferrin concentrations are lower, in patients with COVID-19. However, hepcidin, ERFE, and GDF15 levels are strikingly different between the two patient populations, both statistically and in absolute median values and range. Serum soluble transferrin receptor concentrations can be increased by iron deficiency and/or by increased erythroid activity in the marrow and are independent of inflammation.<sup>7</sup> Both of these circumstances would usually be associated with increased ERFE and GDF15 production. It is interesting to note that transferrin receptor concentrations, both median and range, are very similar in both patient groups.

The GDF15 findings are also of great interest. Since the discovery of ERFE, the role of GDF15 in the physiologic regulation of hepcidin production has been questioned. However, it has been proposed that GDF15 plays a specific response in the immune response in COVID-19 that involves its engagement in iron metabolism.<sup>8</sup>

The report by Delaye, Alarcán, and colleagues<sup>6</sup> raises the question of whether the hepcidin/ERFE/GDF15 abnormalities observed reflect non-specific consequences of inflammation as it alters iron metabolism, or as suggested are a specific feature of the pathophysiology of severe COVID-19 syndromes. Creative clinical research, as this paper demonstrates, raises new questions for future investigation.

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