Commentary

Inflammation, Hemolysis, and Erythropoiesis Lead to Competitive Regulation of Hepcidin and Possibly Systemic Iron Status in Sickle Cell Disease

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Sickle cell disease is a common, recessively inherited hemoglobin disorder affecting populations in malaria-endemic regions. It is associated with acute and chronic complications and a reduced life expectancy. Approximately 300,000 affected children are born annually worldwide [1] with 80% of African-born SCD patients dying in childhood [2]. The most common and most severe form of SCD is a consequence of inherited β^S mutation. Homozygous hemoglobin S leads to polymerization when deoxygenated, damaging RBC membranes, causing cellular desiccation, adhesiveness and rigidity, leading to hemolysis, vaso-occlusion, and inflammation, which together result in anemia, vasculopathy, recurrent painful crises, and multiple end-organ damage (i.e. brain, kidney, lung, and bone).

Anemia in SCD is multi-factorial. Causes include hemolysis, ineffective erythropoiesis, impaired iron utilization, insufficient erythropoietin responsiveness, and low oxygen affinity [3]. The mainstay of therapy is RBC transfusion to correct anemia and decrease the proportion of hemoglobin S-containing RBCs, improving oxygen carrying capacity and reducing the tendency to propagate vaso-occlusion. Chronic RBC transfusion results in iron overload, requiring iron chelation therapy but can be mitigated by exchange rather than simple transition approaches.

With the exception of RBC transfusion indications to prevent neurologic complications of SCD in childhood, much of the standard therapy in SCD is based on empiric evidence and physiological principles. Thus, an improved understanding of the pathophysiology of anemia in SCD is likely to yield more specific indications for RBC transfusion to manage SCD in adulthood. Furthermore, an enhanced understanding of iron metabolism and hepcidin regulation in SCD may pave the way for novel therapeutic approaches. Thus, a manuscript by Lee et al. in this issue is particularly timely, leading the way to capitalize on the recent expansion of knowledge within the iron field.

Because hepcidin is enhanced by iron and inflammation and suppressed by hypoxia and erythropoiesis, distinguishing the relative contribution of these effects in SCD, in which each of these factors is altered, is complicated. Because nutritional iron deficiency is common in Tanzanian children [4] and iron deficiency has been associated with cognitive impairment, even in non-anemic children [5], using hepcidin to quantify the degree of iron restriction in children with SCD is thoughtful and potentially instructive. Recently, iron restriction has been shown to not only lower hemolysis but also improve anemia in SCD mice [6] and multiple case reports reveal potential benefits of iron restriction on clinical outcomes in SCD patients [7]. Thus, identifying a component of systemic iron restriction/deficiency in SCD either provides 1) a novel and potentially treatable defect, the management of which may reduce the severity of anemia in children and adolescents with SCD, or 2) support for the paradoxical protective effect of iron deficiency in SCD as in non-sickle cell related anemia in African children [8].

In EBioMedicine, Lee and colleagues investigate potential predictors of severe anemia in SCD, specifically exploring correlation between hepcidin and severity of anemia in SCD and factors impacting this correlation [9]. By examining archived plasma samples previously collected from a relatively large and homogenous SCD patient population, for whom important hematological data was already available, and performing additional iron- and erythropoiesis-related measurements, the authors aim to stratify severity of anemia in SCD and use hepcidin to determine if any component of iron deficiency compounds anemia in SCD. It is important to point out that the authors used logistic regression to report adjusted odds ratios rather than relative risk regression. Odds and risk are similar when the prevalence of an outcome is rare, however in this case, low hemoglobin, the outcome variable, was present in 50% of patients. While we can still use these results to determine which associations were statistically significant, the relative risks associated with each variable would be much smaller than the odds ratios that the authors report.

The data demonstrate that hepcidin is relatively decreased in more severely anemic SCD children and does not identify a correlation with erythropoiesis- or inflammation-related markers. However, multiple important elements are missing to provide definitive confirmation of this data. For example, the current results are insufficient to conclude that iron status as a whole, not just hepcidin concentration, correlates with anemia severity in SCD. Furthermore, although serum erythropoietin concentration is presented as a surrogate of erythropoietic activity, erythroferrone, the purported erythroid regulator of hepcidin, was not
quantified. A more robust analysis of erythropoietin responsiveness, would further inform an erythropoiesis-dependent correlation between decreased hepcidin and severity of anemia in SCD. Lastly, the manuscript neglects to assess contribution of intestinal hypoxia to hepcidin suppression [8]. The effect of hypoxia on iron absorption may be both hepcidin-dependent and independent in light of the additional effect of hypoxia on the import of iron into duodenal enterocytes via DMT1 [10], thus dissociating hepcidin concentration from other parameters of systemic iron status. For example, the additional evaluation of duodenal hypoxia (e.g. as measured by HIF expression and/or concentration in duodenal mucosa of biopsy specimens) may enhance our understanding of correlation, or lack thereof, between hepcidin expression and severity of anemia in SCD.

In the complex interplay between inflammation, hemolysis, and erythropoiesis, competitive regulation of hepcidin as well as its complete or partial consequences on systemic iron status in SCD remains difficult to interpret. While Lee and colleagues demonstrate that hepcidin levels correlate with clinically important measures of anemia in their cohort, more nuanced investigations are now indicated to clarify what these findings mean about systemic iron status and its relationship with disease severity in SCD.

Disclosure

The authors declared no conflicts of interest.

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