To the editor:

Decreased hepcidin expression in murine β-thalassemia is associated with suppression of Bmp/Smad signaling

β-thalassemia is a genetic disorder of hemoglobin production characterized by ineffective erythropoiesis and anemia.1 Iron overload, a major source of morbidity, results from inappropriately low expression of the gene encoding hepcidin (Hamp1).1 Hamp1 controls plasma iron concentration by facilitating the degradation of the iron efflux protein ferroportin.2 In healthy individuals, hepcidin is transcriptionally responsive to iron via bone morphogenetic protein (Bmp)/Smad pathway-mediated phosphorylation of Smad 1,5,8.3 Phosphorylated Smad 1,5,8 is an essential component of the transcriptional complex that induces Hamp1 expression in response to iron.4 We investigated the...
relationship between iron status, Bmp-Smad signaling, and Hamp1 expression in mouse models of β-thalassemia intermedia (th3/+ and major (th3/th3).  

Wild-type (wt) C57BL/6 mice were placed on a high iron diet to match the elevated liver iron concentrations (LICs) observed in th3/+ mice (Figure 1A). The severity of iron overload in th3/th3 was even higher, by 5-fold, relative to iron-loaded wt mice (Figure 1A). Dietary iron loading of wt mice resulted in the expected increase in Hamp1 and Bmp6 expression (measured by quantitative RT-PCR). However, despite the similarly elevated LICs in th3/+ mice, neither Bmp6 nor Hamp1 expression was significantly and proportionally increased. Moreover, the highly iron loaded th3/th3 mice demonstrated a decrease in expression of both Bmp6 and Hamp1. Thus, relative to hepatic iron load, expression of these genes is significantly decreased in both β-thalassemia models (Figure 1B). Furthermore, hepatic phosphorylated Smad 1,5,8 protein concentration is significantly increased in iron-loaded wt mice (Figure 1C). When normalized to LIC, our data reveal significantly increased phosphorylated Smad 1,5,8 in th3/+ and th3/th3 samples compared with wt and wt fed a high-iron diet (Figure 1D). These results present strong evidence of a blunted relationship between LIC and Bmp6 mRNA expression in β-thalassemic mice.

No prior studies have examined Bmp6 expression or Smad signaling in models of β-thalassemia. Suppressed Hamp1 transcription relative to the degree of iron overload in β-thalassemic mice has been postulated to occur as a consequence of expanded or ineffective erythropoiesis and effects of certain erythroid factors (eg, GDF15 or TWSG1) on hepatocellular hepcidin expression. This observation supports the proposal that different erythroid signals regulate hepcidin in normal and ineffective erythropoiesis. Whether or not as a consequence of an erythroid factor, our findings demonstrate that in β-thalassemic mice the normal relationship between iron status and liver Bmp6 mRNA expression is blunted. This dysregulation results in low Hamp1 levels relative to iron stores and excess iron absorption relative to tissue demands. Continued exploration of the mechanisms underlying blunted Bmp/Smad signaling in β-thalassemia will enhance understanding of the iron overload that is central to the pathophysiology of this disease.

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