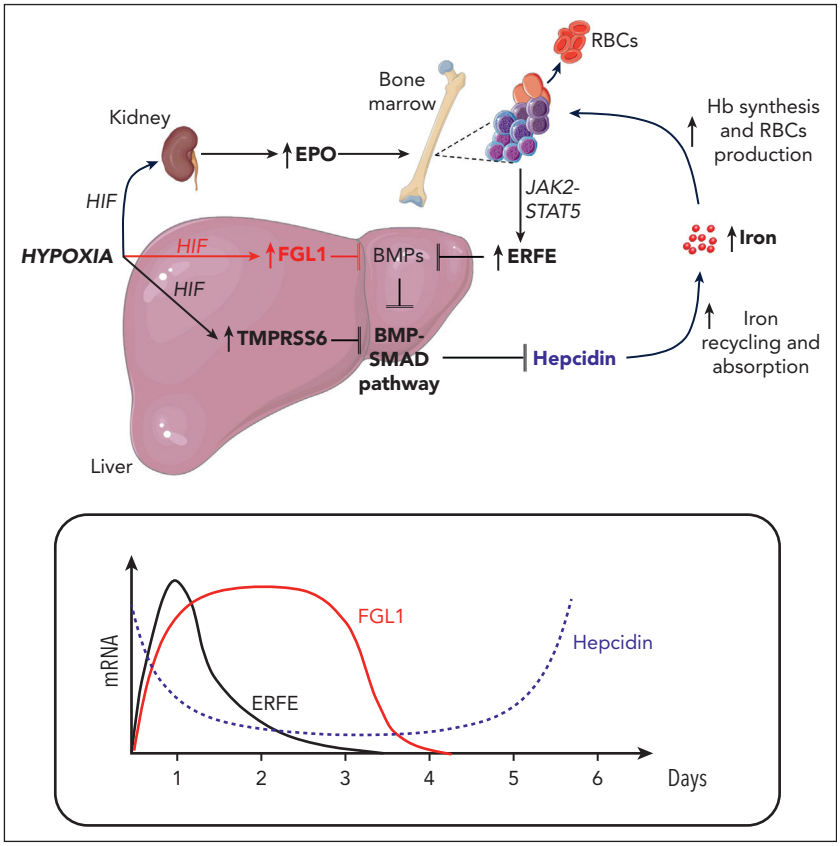

Under hypoxia (experimentally induced by controlled bleeding), the kidney increases production of EPO, a growth factor that stimulates proliferation of erythroid precursors and their differentiation into mature RBCs, whereas the liver upregulates the serine protease TMPRSS6 to decrease the BMP-SMAD pathway and hepcidin expression. In erythroid precursors, activation of the EPO-dependent signaling pathway, mediated by JAK2-STAT5, increases the production of ERFE, a secreted protein that inhibits the BMP-SMAD pathway and hepcidin by sequestering the BMP ligand BMP6. ERFE reaches its maximum concentration within 24 hours (lower panel) after bleeding. The liver plays a crucial role in the hypoxia-mediated inhibition of the BMP-SMAD pathway and hepcidin through the upregulation of the newly identified "erythroid regulator" FGL1. Like ERFE, FGL1 acts upstream of the BMP-SMAD signaling by sequestering BMP6. However, the timing of FGL1 expression is delayed compared with ERFE and reaches its maximum level 1 to 3 days after bleeding. Reduced production of hepcidin promotes iron recycling and uptake of dietary iron by stabilizing the sole iron exporter ferroportin at the cell membrane of macrophages and enterocytes, respectively, thereby increasing iron entry into the bloodstream. The coordinated activity of ERFE and FGL1, which ensures efficient hepcidin downregulation (lower panel), provides all the iron required by erythroid cells for hemoglobin synthesis and RBC production. HIF, hypoxia-inducible factor.

selective degradation of target RNAs by binding to the asialoglycoprotein receptor highly expressed on hepatocytes.

Future studies and novel tools are required to prove the relevance of FGL1 in human physiology and disease. However, the evidence that FGL1 shares 82% identity between human and mouse suggests that its function is also conserved.

With the identification of FGL1, Sardo and colleagues add another piece to the complex regulation of hepcidin; suggest a further link between hypoxia, iron regulation, and metabolism; and offer another potential target to be explored in the treatment of diseases characterized by a dysregulated cross talk between erythropoiesis and iron metabolism.

Conflict-of-interest disclosure: The author declares no competing financial interests. ■

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THROMBOSIS AND HEMOSTASIS

Comment on Shi et al, page 1293

Sickle cell anemia: hepatic macrophages to the rescue

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In this issue of *Blood*, Shi et al[1] demonstrate the importance of hepatic macrophages in the clearance of a disintegrin and metalloproteinase with thrombospondin type 1 motif, member 13 (ADAMTS13)-cleaved von

Willebrand factor (VWF) in mice with sickle cell anemia (SCA). The authors discovered that the resulting short VWF fragments adhere to erythrocytes, and insufficient phagocytosis of these fragments fuels the aggressiveness of vaso-occlusive episodes associated with SCA.

Sickle cell disease is an inherited disorder due to a single mutation in the β-globin gene.[2] Yet, as the authors remind us, SCA "is a systemic disease with complex, incompletely elucidated pathologies." For example, macrophage clearance of SCA erythrocytes is essential to prevent hemolysis and limit tissue damage and inflammatory processes caused by released heme.[3] Macrophages are a diverse population, and Shi et al sought to identify the particular macrophage type(s) involved in the complex pathologic process(es) of SCA. Using single-cell RNA sequencing and fluorescence in situ transcriptome techniques, the authors identified a significant presence of hepatic macrophages within the vessel wall, particularly in SCA mouse liver compared with normal mouse liver. Several macrophage populations, including Kupffer-cell receptor marker (C-type lectin receptor, *Clec4f*) and a few macrophage scavenger receptors (*Macro*) were shown to have enhanced erythrophagocytosis and macrophage phagocytosis activity, thus reducing tissue damage in the SCA mouse liver.

VWF promotes vaso-occlusive events (VOEs) and thromboinflammation in SCA.[4,5] VWF is elevated in individuals with SCA, and its clearance by macrophages is obviously important.[6] The authors found that the *Clef4fMacro* macrophage subset was most active in VWF clearance. Removal of VWF by these macrophages is preceded by ADAMTS13 proteolytic cleavage of VWF; the importance of this process is highlighted by the fact that administering recombinant ADAMTS13 alleviates VOEs,[7] and dysregulation of the VWF–ADAMTS13 axis promotes SCA pathogenesis.[8] Further, cleavage requires desialylation of VWF in the liver, thereby supporting the role of sialyation by hepatic macrophages in this process.

Cleaved VWF assembles into higher- and lower-molecular-weight multimers.[9] In their study, Shi et al identified a new pathologic activity of the lower-molecular-weight VWF. The lower-molecular-weight fragments bind to sickle erythrocytes and exacerbate VOEs if these fragments are not cleared from the circulation. Ac2-26, a peptide derived from Annexin A1, stimulates the phagocytosis activity of bone marrow macrophages. Shi et al showed that Ac2-26 increased colocalization of VWF with macrophages and reduced vaso-occlusion, a finding that suggests a "new therapeutic option for the treatment of VOE."

In conclusion, targeting macrophages as innovative therapeutic approaches for SCA may pave the way to further our knowledge of the complexity of this disease.

Conflict-of-interest disclosure: The authors declare no competing financial interests. ■

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