Anemia, Ineffective Erythropoiesis, and Hepcidin: Interacting Factors in Abnormal Iron Metabolism Leading to Iron Overload in β-Thalassemia

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KEYWORDS

• β-Thalassemia • Ineffective erythropoiesis • Iron overload
• Splenomegaly • Hepcidin • Jak2

β-THALASSEMIA
Genetic Causes, Consequences and Pleiotropic Effects

As discussed in more detail in the overview by Sankaran and Nathan elsewhere in this issue, β-thalassemia is an inherited disorder characterized by mutations in the gene encoding β-globin that lead to the quantitative reduction or, in the most severe cases, the total absence of β-globin synthesis in human erythroid cells. As a consequence, α-globin chains accumulate in excess, forming aggregates that impair erythroid cell maturation, which ultimately leads to a chronic hemolytic anemia and ineffective

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erythropoiesis (IE) (**Fig. 1**). The severity of the clinical manifestations in β-thalassemia varies widely, ranging from patients that are almost asymptomatic to individuals who suffer from severe anemia and require regular blood transfusion to sustain life.[1–6] In general, the clinical severity of the disease correlates with the size of the free α-chain pool and the degree of imbalance between the production of α- and β-like globin chains.

The α/β globin chain imbalance is responsible for the hemolysis of red blood cells (RBCs) and for the premature death (apoptosis) of erythroid precursors in the bone marrow and at extramedullary sites (see **Fig. 1**). The α-globin chain aggregates form inclusion bodies responsible for oxidative stress and membrane damage within RBCs and immature developing erythroblasts. These events are followed by the premature death of many late erythroid precursors in the bone marrow and spleen. Together, these phenomena are designated as IE. The anemia and resulting hypoxia lead to a dramatic increase in serum erythropoietin (Epo) levels in an attempt to compensate for the reduced oxygen-carrying capacity. The marked increase in Epo stimulation, if it is not inhibited by proper transfusion therapy, can lead to uncontrolled expansion of erythroid precursors in the marrow as well as in other sites, such as the spleen and liver, leading to extramedullary hematopoiesis (EMH) (see **Fig. 1**).

The defect in hemoglobin synthesis that occurs in β-thalassemia leads to the development of pleiotropic effects on different body compartments. For example, one of the consequences of IE and EMH is splenomegaly (see **Fig. 1**). The abnormal and damaged RBCs that are produced in β-thalassemia are sequestered by the reticuloendothelial system in the spleen, causing its enlargement. This enlargement leads to increased sequestration of RBCs, including transfused RBCs, in the spleen, with worsening of the anemia and an increase in transfusion requirement. Increased Epo synthesis is also reflected in marrow expansion, leading to bone marrow hyperplasia, bone deformities, and osteopenia (see **Fig. 1**), which contribute to increased morbidity as the disease progresses.[7]

However, iron overload is the principal and multifaceted complication of β-thalassemia. Physiologically, it is caused by an increased absorption of iron from the gastrointestinal (GI) tract as a consequence of IE, and is greatly aggravated by chronic transfusion therapy. Thus, transfusion-independent individuals with thalassemia

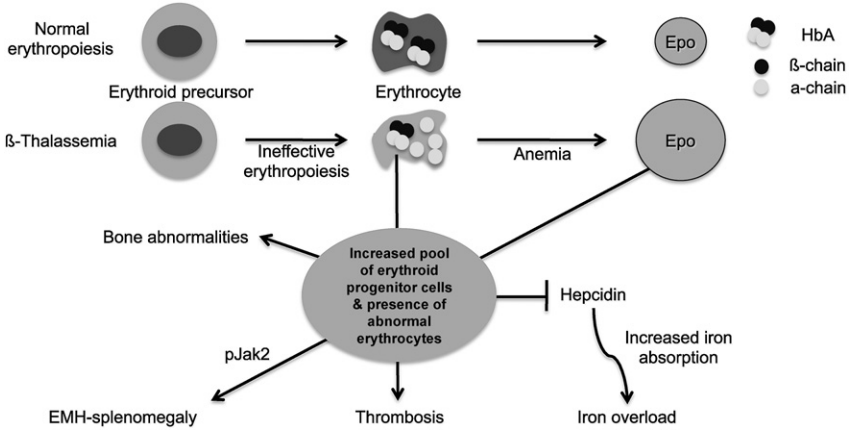

Fig. 1. Consequences of IE and abnormal erythrocyte production. Lines ending with an arrow indicate activation. Lines ending with a line indicate repression.