Ineffective Erythropoiesis: Anemia and Iron Overload

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KEYWORDS

- Erythroblastic island • Hepcidin and iron homeostasis
- Stress and ineffective erythropoiesis • Iron overload

KEY POINTS

- Stress erythropoiesis (SE) is characterized by an imbalance in erythroid proliferation and differentiation under increased demands of erythrocyte generation and tissue oxygenation.
- β-thalassemia represents a chronic state of SE, called ineffective erythropoiesis (IE), exhibiting an expansion of erythroid-progenitor pool and deposition of alpha chains on erythrocyte membranes, causing cell death and anemia. Concurrently, there is a decrease in hepcidin expression and a subsequent state of iron overload.
- There are substantial investigative efforts to target increased iron absorption under IE, by genetic and pharmacologic agents. There are also avenues for targeting cell-contact and signaling within erythroblastic islands under SE for therapeutic benefits.

Erythrocytes are the primary carrier of oxygen in vertebrate systems. The oxygen-carrying capacity of erythrocytes stems from their key constituent heme, capable of binding to iron and delivering oxygen to tissue through circulating red blood cells (RBCs). As a result, erythropoiesis and iron levels are tightly linked in mammalian

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systems in order to maintain a healthy balance of iron utilization for the generation of new erythroblasts and iron recycling from senescent erythrocytes.

Iron has unique properties that make it crucial to the functioning of the mammalian physiologic system. One such property is its interconversion from the ferric (Fe^{3+}) to the ferrous (Fe^{2+}) form.[1] Although this makes iron an essential component of oxygen-carrying proteins like hemoglobin and myoglobin, as well as many redox enzymes, it also allows iron to generate harmful oxidative radicals.[2] This dichotomous nature of iron functioning requires this element to be tightly regulated. Loss of this regulation is the underlying cause of many disorders, with symptoms ranging from anemia to hemochromatosis (iron overload). Although many of these disorders have been identified and some characterized, their underlying molecular mechanisms have only recently begun to be elucidated.

ERYTHROPOIESIS AND THE ERYTHROBLASTIC ISLAND

Erythropoiesis occurs in specialized niches within the bone marrow and the spleen consisting of a central nursing macrophage surrounded by erythroid cells in different stages of differentiation. Although the first erythroblastic island was observed by Bessis and colleagues[3] through electron micrographs, long-term liquid cultures of bone marrow cells have also been used to generate erythroblastic islands in vitro. Erythroblastic islands have also been isolated and cultured from the spleens of phlebotomized mice, whereby the central stromal macrophage extended cytoplasmic processes to surrounding erythroblasts with the erythrobalsts also exhibiting differentiation.[4] Moreover, cell-to-cell adhesion has been shown to be a key factor regulating erythroid differentiation in an erythroblastic island. Adhesion within an erythroblastic island is not only mediated by the erythroblast macrophage protein, as demonstrated extensively using knock-out mice of this protein that are embryonic lethal, but also by the intracellular adhesion molecule-4 (ICAM-4) such that mice lacking ICAM-4 shows significantly reduced erythroblastic islands.[5] Furthermore, blocking the interaction between ICAM-4 on erythroid cells and α-V integrin on macrophages results in a marked reduction of erythroblastic islands.[6] Interaction between vascular cell adhesion protein 1 (VCAM-1) and Beta-1 integrin has also been implicated in erythroid macrophage contact within the erythroblastic island[7] (**Fig. 1**).

Erythropoiesis within erythroblastic islands consists of multiple developmental stages. Erythroid progenitor proliferation begins as multipotent hematopoietic stem cells proliferate and differentiate into the burst-forming unit-erythroid stage, which in turn gives rise to the colony-forming unit-erythroid. Terminal erythroid differentiation begins at the proerythroblast stage. This stage undergoes 3 consecutive mitoses to generate basophilic erythroblast followed by polychromatic erythroblast and then orthochromatic erythroblasts. The orthochromatic cells expel their nuclei to generate reticulocytes, which undergo further changes to give rise to erythrocytes or RBCs.[8] The different stages of terminal erythroid differentiation have been elucidated both by sequencing of RNA and by morphology.[9]

Hepcidin and Iron Homeostasis

Hepcidin (HAMP) is considered a key regulatory molecule of systemic iron homeostasis, produced primarily by hepatocytes.[10,11] HAMP acts as a negative regulator of iron availability by preventing the export of iron from duodenal enterocytes, hepatocytes, macrophages, and placental trophoblasts. High levels of HAMP trigger hypoferremia, as evidenced by studies whereby a single dose of 50 ug of HAMP in mice caused a rapid decrease in serum iron in 1 hour. HAMP carries out this negative regulation of