Blood and bones
Osteoblastic HIF signaling regulates erythropoiesis

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Abbreviations: Epo, erythropoietin; HIF, hypoxia-inducible factor; PHD, prolyl hydroxylase; PHI, prolyl hydroxylase inhibitor; VHL, von Hippel-Lindau

Erythropoietin (EPO) is a glycoprotein that is critical for the regulation of red blood cell production. During embryonic development, Epo is mainly expressed in the fetal liver. However, as hematopoiesis switches sites from the fetal liver to the bone marrow, peritubular interstitial cells of the kidney support EPO production. Epo expression is tightly regulated by spatial, temporal and environmental cues. Clinically, the regulation of EPO is critical as overproduction of EPO results in anemia associated with an increase in EPO expression and development of polycythemia. While overproduction of EPO results in the development of polycythemia, hypoxic response provides exciting possibilities for the treatment of oxygen-deprivation related disorders such as anemia.

In Volume 149, Issue 1 of Cell, Rankin et al. discovered a previously unidentified source of endogenous Epo capable of stimulating erythropoiesis (Fig. 1). In their studies, a Cre-loxP approach was used to inactivate VHL and, thus, constitutively activate HIF signaling, specifically in cells of the osteoblastic lineage. Augmented HIF activity in osteoblasts resulted in enhanced erythropoiesis marked by the development of severe polycythemia by 8 weeks of age in 100% of mutant mice. The development of polycythemia occurred in an EPO-dependent manner and was associated with an increase in EPO expression in bone and decreased EPO expression in the kidney. Elevated bone EPO expression occurred in a HIF-2α-dependent manner, demonstrating that HIF-2α expression in osteoblasts drives EPO expression in bone. In the endogenous setting, Rankin et al. found that bone and primary osteoblasts cultures from neonatal mice also expressed Epo in a HIF-2α dependent manner. Studies investigating the endogenous role of EPO in bone are eagerly awaited, as homeostatic erythropoiesis was maintained in HIF-2α-deficient mice.

The discovery that osteoblasts have the capacity to regulate Epo expression in bone and, in turn, to directly modulate erythropoiesis raises the exciting possibility that manipulation of HIF signaling in osteoblasts may prove beneficial for the treatment of anemia. In support of this hypothesis, Rankin et al. demonstrated that mice with constitutive HIF activity in osteoblasts were indeed protected against hemolytic anemia. To examine the potential clinical implications of their findings, Rankin and colleges generated a second murine model in which all three PHD isofoms were specifically inactivated in cells of the osteoblastic lineage. These mice also developed polycythemia associated with upregulation of Epo in bone tissue. Furthermore, exposure of the bone marrow microenvironment to pan PHD inhibitors was sufficient to induce Epo expression in the bone. These findings highlight the therapeutic potential of targeting the PHD/VHL/HIF signaling pathway in osteoblasts for the treatment of anemia.

The genetic and pharmacological data from these studies have important clinical implications for the treatment of anemia in the context of renal insufficiency. Pharmacological manipulation of the HIF signaling pathway through the inhibition of prolyl hydroxylases enzymes represents a novel treatment option, as

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these small-molecule inhibitors are less costly and more easily administered than recombinant EPO. Several classes of PHD inhibitors (PHI) are currently in clinical trials for the treatment of renal anemia. However, the mechanisms by which PHIs protect against renal anemia are not fully understood. It is postulated in patients suffering from renal failure, PHIs activate HIF-2α within the liver leading to the reactivation of hepatic Epo production. The studies performed by Rankin et al. identify a previously unknown source of Epo, raising an intriguing hypothesis that osteoblastic Epo could also contribute to the clinical benefits seen in these patients. As the bone marrow serves as the major site of post-natal erythropoiesis, the ability to directly modulate erythropoiesis through osteoblastic expression of EPO indicates that PHD inhibition within bone tissue could be an effective and efficient therapeutic modality for those suffering from renal anemia. In light of these recent findings, it will be important to evaluate the relative contribution of hepatic vs. osteoblastic Epo production in the context of renal insufficiency for those patients receiving treatment with PHIs.

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Figure 1. EPO production for the regulation of erythropoiesis occurs in the fetal liver and adult kidney. Rankin and Wu et al. demonstrate that manipulation of the PHD/VHL/HIF signaling pathway in osteoblasts elevates the erythroid lineage in the local hematopoietic environment and protects from anemia through modulation of EPO expression in bone. These findings implicate osteoblasts in bone as a novel source of endogenous EPO to stimulate erythropoiesis. The image depicts the regulation of erythropoiesis by an osteoblast with augmented HIF activity. Rankin and colleagues demonstrate that osteoblasts (shown attached to the bone surface) secrete EPO (green), which stimulates erythroid progenitor (purple) proliferation and differentiation in the bone marrow microenvironment. Artwork by Butch Colyear.