group could ultimately help to open another front in the battle to cure AML.

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Comment on Ulyanova et al, page 975

Anchoring at an island to relieve stress

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In this issue of Blood, Ulyanova and colleagues present a systematic analysis of the role of β1 integrins in erythropoiesis and demonstrate that α6β1 integrin is a critical requirement for mounting successful stress erythropoiesis.1

Stress erythropoiesis is increasingly recognized as more than simply an expansion of steady-state erythropoiesis. Rather, it is a process arising from unique progenitor cells with distinct quantitative and qualitative cytokine requirements. Increased erythropoietin (Epo) levels resulting from kidney hypoxia due to anemia, initiate the response of stress erythropoiesis. A progenitor, named stress burst-forming unit-erythroid (BFU-E) and found in the spleen but not in bone marrow of mice subjected to erythropoietic stress, has been identified as able to produce erythroid colonies when exposed to high Epo concentrations with no additional in vitro requirement for stem cell factor (SCF) or interleukin-3, in contrast to bone marrow BFU-E.2 Stress BFU-E are stimulated to expand by bone morphogenetic protein 4 (BMP4) produced in the spleen in response to hypoxia. Erythropoietic stress leads to mobilization of bone marrow progenitors which home to the spleen and differentiate into stress BFU-E, under the influence of BMP4 and Hedgehog signaling.3 Nevertheless, homeostatic erythropoietic pathways like SCF–c-kit and glucocorticoid receptor–mediated signaling are also vital for successful stress erythropoietic response in vivo.4,5 Stress erythropoiesis has been shown to be impaired in gene-targeted mouse models where steady-state erythropoiesis is fairly normal, like in mice with deficiency of growth arrest–specific gene 6 (Gas6)6 or conditional deletion of focal adhesion kinase (FAK).7 On the other hand, stress erythropoiesis in the splenic microenvironment can be successful in cases where homeostatic erythropoiesis in the bone marrow is pathologic, like in deficiency of Rac1 and Rac2 GTPTases.8

The interactions of erythroid progenitors and precursors with macrophages and extracellular matrix components such as fibronectin and laminin within erythroblastic islands are critical for optimal proliferation, survival, differentiation, and terminal maturation into red blood cells.9 α6β1 and α5β1 integrins are the main erythroid cell receptors that interact with fibronectin. Whereas α5β1 mediates adhesion to several sites on fibronectin, α6β1 binds predominantly to the Arg-Gly-Asp (RGD) domain. α5 expression is noted to be higher in early erythroblasts, whereas α6 is widely expressed throughout nucleated erythroid cells. VCAM-1 represents the major and preferred ligand for α6β1 in stroma cells. The role of these integrins and their ligands in erythropoiesis has been extensively studied by in vitro and in vivo assays, frequently with contradictory results. In this issue, Ulyanova and colleagues offer a resolution to these conflicts, using a systematic in vivo genetic approach to analyze the erythropoietic phenotype after conditional deletion of β1, α6, or VCAM-1 in hematopoietic tissues of adult mice.1 β1 deletion produces β1Δ/Δ mice which demonstrate deficiency of α6β1 and compensatory over-expression of α5β1 in erythroid cells. α6Δ/Δ mice are deficient in α6β1 and α5β1; but not

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αβ1) in hematopoietic cells. β1Δ/Δ, αΔ/Δ, and VCAM-1Δ/Δ mice have normal homeostatic erythropoiesis. Ulyanova and colleagues proceed to examine their stress erythropoiesis response to phenylhydrazine (PHZ). The survival of β1Δ/Δ mice is severely compromised due to their inability to mount successful life-saving splenic stress erythropoiesis, despite having a robust response to PHZ in the bone marrow regarding progenitor cell expansion and mobilization to peripheral blood. BFU-E, stress BFU-E, and CFU-E are all drastically diminished in β1Δ/Δ spleen, associated with increased apoptosis in splenic erythroblasts. To determine whether the phenotype observed is due to β1 integrin deficiency in erythroid or stroma cells, Ulyanova and colleagues used irradiated wild-type recipient mice transplanted with β1Δ/Δ donor cells. These mice demonstrate similar although slightly improved phenotypic response, indicating that the absence of αβ1 integrins in the erythroid progenitors after interaction with ligands on the stroma cells and matrix components of the erythropoietic niche and what are the gene expression patterns they induce in combination or distinctly? Are the RGD-dependent interaction and αβ1-mediated signaling potential targets to decrease stress erythropoiesis in conditions where stress-induced extramedullary erythropoiesis may cause more harm than benefit, like in thalassemias? Answers to these questions would further our understanding of the molecular control of erythropoiesis in health and disease and direct these findings toward future clinical applications.

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Comment on Corash et al, page 1014

Breathing easy with pathogen inactivation

James P. AuBuchon | PUGET SOUND BLOOD CENTER

In this issue of Blood, Corash and colleagues report the results of a blinded expert analysis of patient experiences in the SPRINT trial of transfusion of pathogen-inactivated platelets and document the lack of any pulmonary toxicity of this approach to providing safer platelet transfusion. Because of the recognition of the HIV threat almost 3 decades ago, the sought-after “holy grail” in blood transfusion has been pathogen inactivation (PI), a treatment that would renders residual or undetected pathogens in the unit noninfectious. Success with PI in plasma-protein derivatives reopened the potential for use in hemophiliacs without the fear that a patient’s next treatment might transmit a fatal disease. Multiple means of treating plasma for transfusion have been developed as well and have been widely adopted in Europe. (Although one of these remains licensed in the United States, none are currently marketed.) Inactivating pathogens in cellular blood components has proven more difficult to achieve and even more difficult for US regulatory authorities to accept. Red blood cells are the most frequently transfused component (16 million units annually in...
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