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**Comment on Shi et al, page 2988**

**Trouble in the niche? Send in a statin**

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In this issue of *Blood*, Shi et al report on functional deficits of marrow endothelial progenitor cells (EPCs) in patients with poor graft function (PGF) after allotransplant which could be improved in vitro with atorvastatin exposure.¹ PGF is estimated to occur in about 5% to 27% of allografts and contributes to morbidity and mortality.² PGF is to be distinguished from graft failure, which is often due to a low transplanted nucleated cell dose or to alloreactive immune responses mediated by residual host immunity. Graft failure is therefore seen most commonly in cases of HLA disparity between donor and host.³ In contrast to graft failure, PGF is characterized by full donor chimerism, and it can also be primary or secondary. It is often associated with postallograft effects of viral infections, of conditioning regimens, of drugs toxic to marrow, or of graft-versus-host disease (GVHD). In some cases, it has been associated with inflammatory mediators such as interferon-γ or tumor necrosis factor-α, which could also impact cells of the marrow microenvironment as well as hematopoietic stem and progenitor cells.²

Shi et al have expanded upon their previous work⁴ which demonstrated reduced numbers of marrow EPCs in PGF cases in an attempt to define functional changes in EPCs and possible ways to overcome quantitative and functional deficits. Twenty-six cases of PGF with 100% donor chimerism were identified from 578 allogeneic transplants performed at a single center, and matched controls with good graft function (GGF) were selected from the same recipient cohort using case-control sampling with matching for pertinent variables.

Strengths of this work are that GGF and PGF were carefully defined, well-matched contemporary controls were used, and patients with relapse or severe acute or chronic GVHD were excluded.

EPCs were isolated from each of these cohorts from light-density marrow cells cultured in medium supportive of endothelial cells for 7 days and identified through CD34, CD133, and CD309 (vascular endothelial growth factor receptor-2 [VEGFR-2]) expression. EPCs from patients with PGF had fewer cells with expression of Dil-acetylated low-density lipoprotein and *Ulex europaeus* agglutinin-1, and migration and tube formation capabilities were reduced. Intracellular reactive oxygen species (ROS) expression and apoptosis were higher in those EPCs from PGF vs GGF patients.

Given the functional alterations noted in EPCs from subjects with PGF, Shi et al took cues from prior work demonstrating that atorvastatin, a 3-hydroxy-3-methylglutaryl coenzyme A (HMGCoA) reductase inhibitor is able to improve function of EPCs in other vascular diseases⁵ and that p38 MAPK, one of the family of the mitogen-activated serine/threonine protein kinases, can regulate EPC dysfunction and can be modulated by HMGCoA reductase inhibitors such as *...*
EPCs may be perivascular or sinusoidal, but unlike the case in murine marrow where systems that demonstrate a role for EPCs in posttransplant poor graft function after allogeneic hematopoietic stem cell transplantation, in cases of PGF where donor chimerism is complete, other treatment modalities are needed. Hematopoietic growth factor administration is often ineffective, and immune-modulatory therapies have also met with limited success thus far. The observation of Shi et al that the EPC component of the niche is dysfunctional and can be modulated through inhibition of the p38 MAPK pathway via atorvastatin is a beginning step toward understanding this multifaceted problem and one that offers a potential therapeutic approach for future examination.

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REFERENCES


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Comment on Aljitawi et al, page 3000

A breath of fresh air for umbilical cord blood

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In this issue of Blood, Aljitawi et al demonstrate for the first time that erythropoietin (EPO) signaling directly inhibits hematopoietic stem and progenitor cell (HSPC) migration and that an acute and transient reduction in peripheral EPO levels, via hyperbaric oxygen (HBO) therapy just before transplant, is safe and can enhance hematopoietic engraftment in patients undergoing umbilical cord blood transplantation (UCBT).1

Since the first UCBT was performed successfully nearly 30 years ago to treat a patient with Fanconi anemia,2 umbilical cord blood (UCB) has provided a rich source of HSPCs, in addition to bone marrow and mobilized peripheral blood (mPB), for
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