et al previously reported that adult murine bone marrow HSCs possess functional hemangio-
blast activity in adult HSCs. See the complete figure in the article beginning on page 1916.

Chronic vascular injury in eNOS gfp chimeras induces widespread hemangio-
blast activity from adult HSCs. See the complete figure in the article beginning on page 1916.

et al previously reported that adult murine bone marrow HSCs possess functional hemangio-
blast activity in the injured murine retina.

In this issue of Blood, Guthrie and colleagues examined the role of the nitric oxide (NO) pathway in modulating vessel repair by transplanted populations of green fluorescence protein–expressing (gfp+) bone marrow cells. Recipient mice deficient in inducible nitric oxide synthase (iNOS−/−) or endothelial nitric oxide synthase (eNOS−/−) received transplants of congenic marrow gfp+ cells enriched for HSCs. At 3 months following transplantation, an adeno-associated viral vector expressing VEGF was injected into the vitreous of the test eye of each host. One month later, laser photocoagulation of the venous vessels juxtaposed to the optic nerve was performed leading to an ischemic injury to nearly one half of the treated retina. The non–laser-treated eye served as a control for each subject. Consistent with prior observations, the gfp+ HSC-enriched cells contributed to new vessel formation in the laser-treated, but not the control, eye of normal congenic hosts. Similarly, gfp+ HSC-enriched cells contributed to new vessel formation in the iNOS−/− hosts only in the laser-injured retina, with little contribution in the contralateral non–laser-treated retina. Surprisingly, gfp+ HSC-enriched cells robustly contributed to neovascularization in both test and control eyes of eNOS−/− hosts, and gfp+ cells populated large and small ves-
sels in all tissues examined. This result was in stark contrast to the paucity of gfp+ cell contributions to systemic vascular tissues in the wild-type and iNOS−/− hosts. Thus, eNOS−/− mice appear to display a systemic vascular dysfunction where marrow-derived progenitor cells are extensively recruited and incorporated into the vessels.

Though the mechanism remains to be elucidated, Guthrie and colleagues propose that eNOS deficiency may lead to a compensatory overexpression of vascular iNOS leading to pathologic vascular endothelial cell turnover. This is an interesting and testable hypothesis that may lead to novel insights into the mechanism of EPC mobilization and engraftment in certain neangiogenic sites. Further studies defining the ontogeny of the vascular dysfunction, kinetics of EPC turnover, and types of cells that rescue eNOS−/− vessels will be challenging and informative.

REFERENCES

Comment on Selleri et al, page 2198

Soluble urokinase activator receptor (suPAR) in stem cell mobilization

Elaine Marie Sloand National Institutes of Health

Selleri et al demonstrate that healthy donors given granulocyte–colony-stimulating factor (G-CSF) have increases in plasma soluble plasminogen activator receptor (suPAR) levels, which in turn induces chemotaxis of CD34 cells. Selleri et al’s findings help better define the complicated mechanism of stem cell mobilization by G-CSF and point to a wide role for uPAR in cell surface adhesion and recognition.

G-CSF, stem cell factor (SCF), and high-dose cyclophosphamide increase peripheral blood CD34 counts in stem cell donors prior to leukapheresis. Nevertheless, 14% of patients receiving G-CSF for the purpose of autologous donation and 4% for allogeneic donors fail to mobilize. Most of what we know about stem cell mobilization is derived from animal models. Adhesion molecules such as VLA-4 and P/E selectins, chemokines, their cognate ligands (stromal derived growth factor 1 [SDF-1] and CXCR4), and proteolytic en-
zymes such as elastase and cathepsin G all appear to play a part in facilitating mobilization and homing of hematopoietic stem cells.

Membrane-associated uPAR is a glycosylphosphatidylinositol-anchored (GPI)-an-
chored protein, first identified as a high-affinity cellular receptor for the inactive proenzyme prourokinase plasminogen activator (uPA); uPAR is believed to increase generation of plasmin, either by increasing the catalytic activity of uPA or by facilitating juxtaposition of this enzyme with membrane-associated plasminogen. The uPAR is composed of 3 do-
 mains, the first required for generation of plasmin and the third attached to the cell membrane by a GPI anchor. Urokinase plasminogen activ-
ator receptor is expressed as a differentiation antigen on cells of the myelomonocytic lineage and as an activation antigen on monocytes, T lymphocytes, and probably platelets. In addi-
tion to its role in plasminogen activation, uPAR appears to mediate cell-to-cell and cell-
to-extracellular matrix adhesion. Some evidence suggests that paroxysmal nocturnal hemoglobinuria (PNH) neutrophils, lacking GPI-anchored protein, are deficient in chemotactic
activity, a feature that has been attributed to the absence of uPAR.

When uPAR is cleaved at the GPI anchor by endogenous phospholipase D, soluble uPAR (suPAR) is released from the cell membrane. Plasma levels of suPAR are increased in metastatic carcinoma where it has been used to monitor disease activity. Plasma levels are also increased in PNH patients who lack the GPI-anchored proteins in affected hematopoietic clones. In this study, Selleri et al demonstrate that suPAR is released in vitro after G-CSF treatment and attribute this to membrane shedding of up-regulated membrane uPAR on immature granulocytes and monocytes, although these cells also have substantial pools of intracellular suPAR. They go on to show that soluble uPAR induces chemotaxis of CD34 cells and down-regulates CXCR4, a chemokine receptor important in retaining stem cells in the bone marrow.

Although the authors speculate that suPAR has therapeutic potential in patients failing to mobilize following G-CSF treatment, suPAR has been reported to antagonize fibrinolysis in vitro, and the potential toxicities of suPAR need to be clarified. Nevertheless, even if suPAR turns out to have no clinical application, it may yet provide a tool for the study of hematopoietic stem cell mobilization and homing.

REFERENCES
Soluble urokinase activator receptor (suPAR) in stem cell mobilization

Elaine Marie Sloand