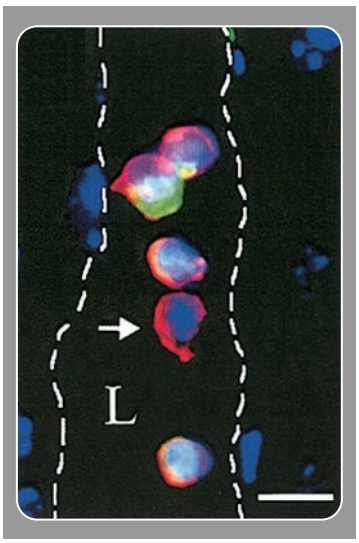
inside blood

Hemangioblasts in adults?

The intimate association between developing vascular endothelial and hematopoietic cells was noted almost a century ago. Based on microscopic analyses of chick embryos, it was hypothesized that these lineages share a common progenitor, the "hemangioblast." Since then, it has become apparent that the earliest detectable mesodermal progenitors of blood and endothelial cells in a variety of vertebrate embryos express many of the same genes, and mutations in some of these affect normal development of both cell types. The most compelling evidence for the hemangioblast has come from the mouse embryonic stem (ES) cell differentiation system, where "blast colonies" formed in culture in the presence of vascular endothelial growth factor (VEGF) have the potential to develop to hematopoietic, endothelial, and smooth muscle cells.



Identification of blast colony–forming cells in embryos has presented technical challenges, but some success has been reported.[1]

It has generally been assumed that the hemangioblast is a transient cell restricted to the blood islands of the yolk sac and, perhaps, to some regions of the embryo proper. But might hemangioblasts be present in adult tissues? The presence of endothelial progenitor cells (EPCs) in circulating blood hinted that this might be the case. Grant et al evaluated the endothelial potential of highly enriched hematopoietic stem cells (HSCs) using a retinal neovascularization model in the mouse.[2] Transplanted green fluorescent protein (GFP)–expressing c-kit$^+$Sca-1$^+$Lin^{neg} (GFP$^+$ KSL) cells from bone marrow could contribute to long-term multilineage hematopoietic engraftment and to neovascularization in retinas of recipient animals subjected to acute ischemic injury and treatment with exogenous VEGF. Engraftment arose from serially transplantable (self-renewing) donor cells. However, the low hematopoietic and vascular engraftment by single cells (3/80 recipients) left some doubts about whether the same cell gives rise to both lineages.

In this issue of *Blood*, Bailey and colleagues (page 13) have shown that transplanted GFP$^+$ KSL HSCs from bone marrow can contribute to long-term multilineage hematopoiesis and can differentiate rapidly into functional endothelial cells in many adult tissues. Endothelial engraftment persists for many months, can be serially transplanted, exhibits several features of functional endothelium, and does not arise by cell fusion. Importantly, hemangioblast activity was demonstrated at the clonal level. The physiologic relevance of these interesting findings remains to be determined, however, as irradiation of recipient animals was required to attain vascular engraftment.

Also in this issue of *Blood*, Cogle and colleagues (page 133) have demonstrated that human CD34$^+$ cells from umbilical cord blood can contribute to retinal neovascularization in a nonobese diabetic (NOD)/*scid* xenograft model. Endothelial engraftment occurred in myeloablated recipients following laser-mediated ischemic damage and local administration of VEGF. For technical reasons discussed by the authors, it was not possible to determine whether the observed engraftment was clonal or to demonstrate self-renewal. It will be important to address these fundamental questions to prove that human CD34$^+$ cord blood cells contain hemangioblasts. Nevertheless, this work is significant because it raises the hope of using HSCs to achieve vascular repair in human patients.

What are the roles played, under normal physiologic as well as pathologic conditions, by bone-marrow–derived versus circulating versus locally resident EPCs, in vascular tissue homeostasis? What is the relationship between these cells and the hemangioblast activity identified in embryonic systems? Functional adult hemangioblast activity has been defined on the basis of repopulation of the hematopoietic system and blood vessel regeneration. Do the engrafted endothelial cells observed in the transplantation studies arise directly from HSCs, from a bipotential hemangioblast, or from some other cell type? The reports from Bailey et al and Cogle et al are sure to stimulate further investigations into the characteristics of the stem/progenitor cell(s) that can engraft into adult endothelium.

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1. Palis J, Kennedy M, Keller G. Hemangioblast development during mammalian embryogenesis [abstract]. Blood. 2000;96:68a.
2. Grant MB, May WS, Caballero S, et al. Adult hematopoietic stem cells provide functional hemangioblast activity during retinal neovascularization. Nat Med. 2002;8:607-612.

Light at the end of the VOD tunnel?

Reduced-intensity allogeneic transplants have become widely used to reduce treatment-related morbidity and mortality (TRM) while maintaining an immunologic (graft versus tumor) response against host tumor cells. These regimens have primarily been used for older patients, those with more indolent diseases, such as chronic lymphocytic leukemia or low-grade lymphoma, and

those with underlying organ dysfunction. It is hypothesized that this strategy will make allotransplantation feasible for patients in this latter category who would not be candidates for myeloablative regimens.

This issue contains a report by Hogan and colleagues (page 78) that studied the impact of one reduced-intensity regimen, low-dose total body irradiation (TBI), with or without fludarabine, on hepatic toxicity, the most common cause of fatal regimen-related toxicity after ablative transplant preparation. Hepatic veno-occlusive disease (VOD), also known as sinusoidal obstruction syndrome (SOS), is characterized by fluid retention, painful hepatomegaly, and jaundice. VOD/SOS is more common in patients with active liver inflammation who undergo transplantation, in those who receive more intensive conditioning, and in the setting of active infection during the peritransplantation period.

In their article, Hogan et al describe the incidence, severity, and outcome of hepatic toxicity in 193 consecutive patients prepared for allogeneic transplantation using 200 cGy total body irradiation, with or without fludarabine, and who received cyclosporine and mycophenolate mofetil for postgrafting immunosuppression. Of the patients, 26% developed hyperbilirubinemia (bilirubin levels of 68.4 μM [4 mg/dL] or higher) by day 200 (compared with 48% in a historical group of 1149 patients who underwent transplantation using an ablative regimen), but in none was this due to VOD/SOS. Graft-versus-host disease (GVHD), or cholangitis lenta, was the most common cause of jaundice in these patients. Survival was superior in patients with normal or minimally elevated bilirubin levels and in those whose bilirubin level exceeded 68.4 μM (4 mg/dL) within the first 28 days compared with patients whose bilirubin level reached 68.4 μM (4 mg/dL) after day 28. Among patients with bilirubin levels of 68.4 μM (4 mg/dL) or higher, those with aggressive histologies were more likely to die than those with more indolent disease. Patients who received fludarabine with their preparative regimen were more likely to develop hyperbilirubinemia, although fludarabine was not an independent risk factor for death. There were 3 patients, all with chronic liver disease at the time of transplantation, who died of liver failure.

What does this report show us? First, it shows that allotransplantations can be performed without patients developing VOD/SOS. We must remember, however, that 200 cGy TBI (± fludarabine) is only one of many nonmyeloablative regimens and that VOD/SOS has been reported after conditioning using other reduced-intensity programs. Second, it demonstrates that patients with chronic and pre-existing liver disease remain at high risk for early death and that reduced-intensity preparation does not protect them. It also makes clear that hyperbilirubinemia beyond day 28 is associated with an adverse outcome even in the absence of VOD/SOS and independent of the relative intensity of the regimen. The utility of this marker in predicting overall survival was sufficiently strong to make it both important to look for and discouraging to find in any patient undergoing a reduced intensity allograft. Finally, while Hogan and colleagues have provided important data indicating that this approach significantly reduces regimen-related hepatic toxicity, assessing the effect of nonablative transplantations on long-term outcome will require longer follow-up as well as improved treatment or prevention of other complications such a relapse, GVHD, and infection.

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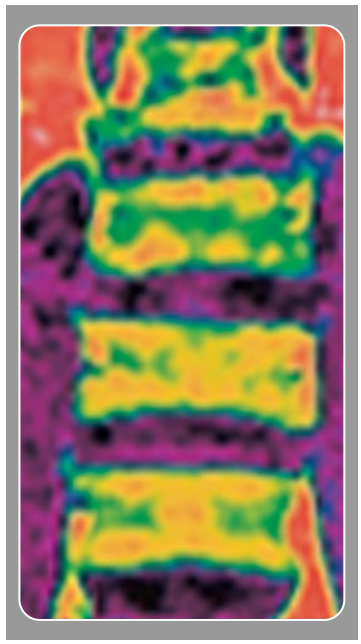
Surrogate markers for lysosomal storage

Enzyme replacement therapy (ERT) for lysosomal storage disorders (LSDs) is safe and effective treatment. It was first developed for Gaucher disease (GD), a disorder in which the bone marrow and the tissue macrophages derived from it play a central role in its pathogenesis. Currently, ERT is being developed for other LSDs following the blueprint developed for GD. This approach uses receptor-mediated endocytosis of glycoprotein lysosomes/enzymes by naturally occurring lectins.[1] Successful clinical trials resulted in new enzyme therapies becoming available a few months ago for patients with Fabry disease and mucopolysaccharidoses I.

The development of enzyme replacement therapy for GD prompted several research groups to identify biochemical markers to allow the clinician to monitor the disease



and make the appropriate dosing decisions. Currently, chitotriosidase, angiotensin-converting enzyme, and tartrate-resistant acid phosphatase are the most commonly used surrogate markers to monitor disease progression and response to ERT in GD patients. Chitotriosidase is a good marker for this purpose because it is specific for GD and shows a dramatic response after initiation of therapy, decreasing an average of 50% after the first 3 months of treatment and by 80% after one year. The usefulness of chitotriosidase is limited to a small degree by a recessively inherited 24-bp deletion that is present in 5% to 6% of the population.[2] Treating physicians would