To the editor:

Vascular complications after splenectomy for hematologic disorders

In a recent issue of Blood, Crary and Buchanan published the most perceptive and comprehensive review to date on thrombotic vascular complications arising with functional or surgical asplenia in patients with hematologic, and especially hemolytic, disorders.1 Their overview of the literature presents a great deal of food for thought regarding the apparent role of splenic function in protecting against thromboembolic disease, including venous thrombosis, pulmonary thromboembolism, and even arteriosclerosis and pulmonary hypertension. As the authors describe, these risks are reported even in subjects without hematologic disease who undergo splenectomy, but chronic hemolytic disease may compound this risk. I would like to point out 2 important additional pathophysiologic links.

The authors discuss the paradox that the incidence of arteriosclerotic events is lower in hereditary spherocytosis patients with intact spleens compared with their hematologically unaffected first degree relatives, and this low risk of arteriosclerosis is shared with patients with sickle cell disease. Crary and Buchanan propose a protective effect of hemolysis, mediated possibly by the lower serum cholesterol level seen in several forms of anemia.2 Importantly, clearance of hemoglobin-haptoglobin or heme-hemopexin complexes by CD163- and CD91-expressing reticuloendothelial macrophages triggers induction of hemeoxygenase-1 (HO-1), an enzyme that performs the first committed step in heme catabolism.3 Besides producing carbon monoxide, a molecule with putative antiapoptotic, anti-inflammatory, and antiproliferative properties, HO-1 itself has similar protective functions, as do its metabolic products, biliverdin and bilirubin. I would suggest that part of the paradoxical protective benefit of hemolytic anemia against coronary arteriosclerosis in patients in part involves this induction of HO-1 and production of carbon monoxide, biliverdin, and bilirubin. Supporting this idea, HO-1 gene transfer experiments in mice protect against the development of arteriosclerosis.4

In patients with chronic hemolysis, I agree with Crary and Buchanan that loss of splenic function shifts the predominant site of hemolysis from extravascular to intravascular. More specifically, Westernan and colleagues have observed that plasma hemoglobin and microparticle levels are higher in splenectomized thalassemia patients than those with intact splenic function.5 Although in a nonrandomized study such as this, splenectomy might simply be a marker of patients who underwent splenectomy due to more severe disease, the findings are fully consistent with a delay in hemolysis, but with a proposed shift of site of hemolysis to intravascular, causing plasma hemoglobin levels to rise. The significance of this shift lies in the pathologic effect of plasma hemoglobin, which is documented to scavenge nitric oxide. This decreased nitric oxide bioavailability promotes a generalized vasculopathy phenotype of vasoconstriction, smooth muscle proliferation, and activation of adhesiveness of platelets and endothelial cells, with particular affinity to the pulmonary vasculature.6 Furthermore, microparticles are believed to be prothrombogenic.7

I would like to commend Drs Crary and Buchanan for their valuable contribution to the literature on vascular disease and splenic function. Blood readers should also be aware of the emerging biology of heme-induced HO-1 vasculoprotection and of splenectomy-associated shifts of hemolysis promoting a state of relative nitric oxide deficiency. It is likely that these proposed mechanisms are one part of a multifactorial pathobiology linking asplenia and vasculopathy.

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References


To the editor:

Restoration of the human stem cell niche after stem cell transplantation

Recently, Dominici et al very elegantly demonstrated restoration of the osteoblastic hematopoietic stem cell (HSC) niche after lethal marrow radioablation in mice.1 Based on their data, the authors propose a model in which radiation induced an increase in stromal cell-derived factor 1α (SDF-1α), causing the attraction of CXCR4-positive megakaryocytes that survived radiation. A concomitant
An increase in platelet-derived growth factor-β (PDGF-β) and basic fibroblast growth factor (bFGF) levels, known to promote osteoblast proliferation, leads to restoration of the HSC niche as demonstrated by local engraftment of transplanted HSCs. The effect of radiation on bone marrow (BM) SDF-1α levels in human subjects is unknown. Moreover, data on SDF-1α levels following nonmyeloablative regimens, which are increasingly used in clinical practice, are lacking.

We determined SDF-1α levels in BM and peripheral blood (PB) of 5 patients who underwent an allogeneic stem cell transplantation. Samples were taken on the first day of the conditioning regimen and on the day of stem cell infusion (Figure 1A). Indeed, we were able to show a significant 2.8-fold increase (± 1.8 SD, P = .04, Figure 1B) in BM SDF-1α levels in patients with hematologic malignancies, being treated with nonmyeloablative or myeloablative conditioning regimens. A similar although less pronounced increase in PB SDF-1α levels was observed (1.7 ± 1.1, Figure 1B). In agreement with the findings of Dominici et al in animals, the increase in protein levels was found to be the result of induction of SDF-1α gene expression, as BM SDF-1α mRNA copies increased a mean of approximately 40-fold, correlating with the increase in SDF-1 BM protein levels (r = 0.92; P = .03).

Interestingly, there were indications that the increase in SDF-1α was dependent on the type of conditioning regimen. In the sole patient being mildly conditioned with fludarabine/low-dose TBI no increase in bone marrow SDF-1α mRNA was found, corresponding with only a minor increase in BM SDF-1 protein levels (from 6.0 to 7.5 ng/mL, see outlier at Tx, Figure 1B). In this single patient, platelets did not recover more than 100 × 10^9/L in 100 days. In contrast, the other 4 patients, showing a more pronounced increase in BM SDF-1α mRNA (2.0- to 104.0-fold increase) and protein levels (1.4- to 5.2-fold increase), recovered completely within 20 days. This observation supports the hypothesis of Dominici et al that bone marrow SDF-1α levels improve stem cell engraftment. To substantiate the observation that conditioning with fludarabine/low-dose TBI has only limited effects, we studied PB SDF-1α levels in an
additional group of 7 patients and confirmed that there was no increase PB SDF-1x protein levels (n = 7, P = .24). In contrast, the more dose-intense nonmyeloablative regimen with fludarabine/cyclophosphamide did increase PB SDF-1x protein levels (1.7-± 0.6-fold increase; n = 7, P = .02), as did myeloablative regimens (1.6-± 0.6-fold increase, n = 8, P = .05).

Our data indicate that the key regulatory role of SDF-1x in restoration of the murine stem cell niche as found by Dominici et al can be translated to both the myeloablative and nonmyeloablative clinical transplantation setting in humans. Whether the type of nonmyeloablative conditioning matters warrants further research. However, our data suggest that reassessment of the agents used in conditioning regimens might improve stem cell engraftment efficiency. This may be especially relevant when limited numbers of stem cells are available, as in cord blood transplantations.

Response
Optimizing the niche conditions for maximal stem cell engraftment: human and animal model data

We appreciate the comments from Dr Zweegman and colleagues, who contribute important new data supporting our recent publication.1 While animal models are ideal to uncover the biologic basis of pathologic observations and therapeutic interventions, whether such scientific findings, in reality, apply to patients is always an open question. The exceptional human data of Zweegman et al corroborate our murine findings and suggest that the novel mechanisms we describe may, in fact, apply to clinical hematopoietic cell transplantation.

More than 50 years after the introduction of animal models of marrow radioablation/hematopoietic cell infusion2 and the first clinical bone marrow transplantation,3 our study and the human data of Dr Zweegman et al suggest the mechanisms by which the marrow microenvironment responds to the damaging effects of marrow ablation to favor the stem cell engraftment. We hypothesized that the damage to the hematopoietic stem cell osteoblastic niche is the driving force underlying the restoration, and the data of Zweegman et al support that notion by showing that lower intensity regimens, which may be less damaging to the niche, have a lesser effect on stromal cell–derived factor–1 production. The homing/engraftment of transplanted donor hematopoietic cells may be diminished after nonmyeloablative conditioning regimens, which may affect the long-term outcome of these patients. Our murine model highlights the complexity of the cellular interactions within the stem cell engraftment involving not only stromal cell–derived factor–1 and hematopoietic stem cells, but cells such as the osteoblasts and megakaryocytes and other cytokines, such as platelet-derived growth factor–β and basic fibroblast growth factor.

Future work must define the relationship between conditioning intensity, niche damage and niche restoration in an effort to optimize the niche conditions for maximal stem cell engraftment. A complete understanding of niche damage/restoration may allow targeting the niche restoration and expansion to foster stem cell engraftment after reduced intensity and nonmyeloablative conditioning regimens, which could expand the indications for this reduced toxicity approach. In addition, such targeting therapy may lessen the minimum required cell dose for routine successful cord blood transplantation, which would expand the use of this valuable source.

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