Conversely, donors with prevalence of mHAg-specific CD8+ Treg, should represent a safeguard toward the risk of life-threatening GVHD, although potentially increasing the risk of leukemia relapse as a blunting effect of Treg against tumor cells has been recognized as one of the mechanisms of immune escape. It is reasonable that this specific balance be of greater clinical relevance in the context of unmanipulated allo-HSCT and when the donor is HLA-matched rather than disparate with the recipient.

The intriguing immunobiologic translations deriving from the results reported by van Halteren et al will find routine clinical applicability when less cumbersome and more standardized in vitro methods become available for a precise and reliable identification of either CTLs or Treg. For the time being, this piece of information, together with the demonstration that during pregnancy a preferential induction of CD4+ Treg lymphocytes occurs in fetal lymph nodes and spleen, contributes to biologically explain the clinical advantages deriving from using either the mother as donor in T cell–depleted, haploidentical transplantations or an HLA-mismatched sibling disparate for noninherited maternal antigens.

There is one last potential translation for the evaluation of the balance between mHAg-specific CTLs or Treg. Cellular adoptive immunotherapy based on the use of mHAg-specific CTLs directed against hematopoietic tissue–restricted antigens, such as HA-1 and HA-2, has been proposed for preventing/treating leukemia relapse occurring after an allograft. It is evident that the data produced by van Halteren et al render the evaluation of the presence of these mHAg-specific CD8+ Treg in the donor more than opportune to optimize the chance of success of adoptive cell therapy.

There is still much more to learn about tolerogenic versus immunogenic fetal/maternal interactions, but there is no doubt that pregnancy and allo-HSCT share commonalities.

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Comment on Desmares et al, page 2315

RBC transfusion and BMT rejection

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In this issue, Desmares and colleagues examine whether transfused RBCs themselves participate in priming the immune response against subsequent allogeneic BMT.

An early conundrum in clinical transplantation was that previous red blood cell (RBC) transfusions may reduce the risk of solid organ transplant rejection but increase the risk of bone marrow graft failure in patients undergoing bone marrow transplantation (BMT) for aplastic anemia. Because RBCs do not express the major histocompatibility complex (MHC), the hypothesis was that leukocytes present in the blood products were responsible for alloimmunization causing marrow graft rejection. Studies in the canine model demonstrated that leukocyte depletion of RBC products mitigated the alloimmunization by transfusions and permitted engraftment. It is therefore good practice to transfuse patients who are candidates for BMT exclusively with leukocyte-reduced blood products. Although leukocyte depletion reduced the risk of graft failure associated with previous transfusion, the risk has not been eliminated, particularly in the setting of reduced-intensity preparative regimens for patients with hemoglobinopathies. In addition to alloimmunization, other explanations for poorer outcomes in patients with extensive transfusion histories include iron overload, hepatitis from blood-borne infections, and that more transfusions reflect more severe underlying diseases.

Desmares et al have re-examined this issue recognizing that, in addition to the classic, direct pathway of minor antigen presentation by donor white blood cells (WBCs), recipient antigen-presenting cells may take up and present donor minor histocompatibility antigens (mHAs). This indirect pathway could be responsible for graft rejection. They hypothesize that if RBCs express mHAs that are also expressed on marrow stem cells, RBCs may contribute to alloimmunization of the recipient and lead to resistance to marrow engraftment. In their murine model, as in the canine model and in clinical BMT, leukocyte reduction increases the threshold number of RBC transfusions needed to cause rejection.

To test the indirect pathway of mHA presentation, they substituted leukocyte-reduced RBCs from a strain congenic to the marrow donors, but differing in MHC, so MHC-restricted T-cell responses to minor antigens presented by residual donor leukocytes would be irrelevant to the subsequent MHCrecompatible marrow transplant. These transfusions had the same effect as leukocyte-reduced
RBCs from the marrow donor strain, suggesting mHA presentation by recipient antigen-presenting cells and not by residual leukocytes within the RBC products. Conversely, when the donor mice differ from the recipient mice only by the H-Y mHAs, which are expressed in WBCs (but not RBCs), leukocyte depletion almost completely prevents subsequent rejection. Thus, a clinically relevant degree of leukocyte depletion is enough to mitigate direct mHA presentation. Finaly, the authors demonstrate that RBC transfusion from a mouse strain engineered to express an alloantigen exclusively on RBCs can induce antigen-specific CD8 T-cell proliferation, independent of leukocyte reduction. This finding confirms that epitopes from mHAs on transfused RBCs can be cross-presented in the indirect pathway.

If recipient antigen-presenting cells can cross-present mHAs expressed on RBCs themselves to create an immunologic barrier to subsequent BMT, then even total leukocyte depletion cannot prevent alloimmunization by repeated RBC transfusion. What next? If we are not prepared to perform BMT earlier in the management of the disease, perhaps elucidation of the cellular mechanisms of this alloimmune response may allow its prevention by immunomodulation during transfusion. Identification of the mHAs relevant for clinical BMT may allow selection of RBC donors or processing of blood products in a manner that prevents alloimmunity cross-reactive with the prospective marrow donor’s stem cells. This line of research is important for the goal of developing the least toxic BMT methods that can produce durable engraftment of normal hematopoietic cells in patients with nonmalignant disorders.

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**TRANSPLANTATION**

Comment on Dominici et al, page 2333

The osteoblastic niche following TBI

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In this issue of *Blood*, Dominici and colleagues use a murine model to demonstrate that after lethal TBI, there is a transient significant increase in the number of host osteoblasts accompanied by a maintenance of megakaryocytes, which produce multiple key cytokines known to regulate osteogenesis.1

The fate of endosteal stem cell niches after preparative ablation for bone marrow transplantation (BMT) regarding their ability to accommodate and regulate engrafting donor hematopoietic stem cells (HSCs) remains unclear. Yet, it is critical to understand this variable for the optimal success of clinical stem cell transplantation. These data are used to suggest an increase in the size of the niche available for engrafting transplanted HSCs.

Whereas bone marrow transplantation has been successfully used to treat hematologic diseases for many decades, the effects of the preparative ablation on the microenvironment into which HSCs are landing have not been thoroughly investigated. Important factors could include both the severity and