Most importantly, no hematopoietic stem/progenitor cell functional assays were included in the studies by Calado et al. Although it is logical that increasing TERT activity would increase hematopoietic stem/progenitor cell function, no direct studies addressed this critical question. Understanding whether androgen/estradiol-induced TERT activation also occurs in hematopoietic stem/progenitors is crucial because it is loss of these cells that is at the crux of genetic and acquired bone marrow failure conditions. Whereas the investigators used bone marrow CD34+ cells, which are enriched for stem/progenitors, this cell population is very heterogeneous. They contain a low frequency of stem/progenitor cells. In addition, pharmacologic doses of hormones were used in their studies. It is unclear whether the concentrations of the hormones used are achieved clinically. Therefore, future clinical studies assessing TERT activity in peripheral blood cells from patients before and after androgen therapy would be very interesting. Moreover, comparing increased TERT activity in patients who have a hematologic response after androgen therapy with patients who are androgen nonresponders and have no change in TERT activity would provide considerable evidence that the novel mechanism identified by these authors is evident in vivo.

Given the data presented by Calado et al, it is intriguing to speculate whether other tissue-specific stem/progenitor cells may enhance TERT activity in response to endogenously produced hormones. As one example, it is well established that premenopausal women have lower rates of cardiovascular disease compared with men, although those rates increase after menopause when estrogen levels are lower, coinciding with lower telomere lengths in hematopoietic cells.3,4 Could stem/progenitor cells of the vascular system also be dependent on estrogen to activate TERT, thereby enhancing cell lifespan, survival, and proliferation? Many similar provocative questions regarding aging and cancer arise from the studies by Calado et al, an attribute ascribed to groundbreaking scientific investigation.

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Immunobiology

Comment on van Halteren et al, page 2263

Tolerance: pregnancy matters

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In this issue of Blood, van Halteren and colleagues demonstrate that not only antigen-specific CD8+ CTLs, but also antigen-specific CD8+ Tregs can emerge during pregnancy and persist over time when mother and offspring differ for minor histocompatibility antigens.1 The relative ratio between these 2 populations, either promoting aggression against allogeneic tissues or tumor cells or tolerance toward alloantigens, is of potential great relevance in the context of HSCT.

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is largely used for treating patients affected by many malignant hematologic disorders.2 The success of allo-HSCT is strictly dependent on the balance between the detrimental, sometimes fatal, attack of donor immune cells against normal recipient’s tissues (ie, graft-versus-host disease [GVHD]) and the favorable reaction of donor lymphocytes toward malignant cells (ie, graft-versus-tumor [GVT] effect). While a large part of the GVT effect is related to the occurrence of GVHD, there is clear evidence that a selective effect of donor adaptive immunity on tumor cells can occur after allo-HSCT even without GVHD.3 This specific GVT effect is thought to be either directed against antigens with a tissue-restricted distribution (on hematopoietic cells in case of hematologic malignancies) or specifically preferentially expressed on tumor cells.4

Minor histocompatibility antigens (mHAg) are polymorphic peptides encoded by genes located throughout the human genome, which can be presented by the major histocompatibility complex (MHC) molecules and recognized as a foreign antigen by T lymphocytes of a certain donor.5 These peptides can induce both donor–anti-host GVHD and GVT reactions, depending on their expression on both the nonhematopoietic cells and on normal and malignant hematopoietic cells of the recipient, respectively. The ultimate goal of allo-HSCT—based immunotherapy is to maximize the GVT response while mitigating collateral damage to normal tissues by GVHD. Dissecting the role of different mHAg in the elicitation of these effects has also been an area of active investigation in recent years.

Pregnancy is characterized by a bidirectional trafficking of both fetal and maternal cells, leading to different levels of microchimerism both in the mother and in the offspring. These circulating cells may stimulate reciprocal immune sensitization, resulting in the generation of mHAg-specific cytotoxic T lymphocytes (CTLs).6 For example, this phenomenon accounts for the increased risk of immune complications and transplantation-related mortality, observed when a parous female is used as allo-HSCT donor for a male recipient.7 In their article in this issue of Blood, van Halteren and colleagues provide sound evidence that mHAg-specific CD8+ regulatory T cells (Treg) can also emerge during pregnancy and persist for many years. Although the precise mechanism leading to the preferential emergence of either mHAg-specific CD8+ CTLs or Treg remains obscure deserving further investigation, this observation may have relevant clinical implications in allo-HSCT from both HLA-matched and disparate donors. Indeed, in donor/recipient allo-HSCT pairs differing for mHAg, either severe acute GVHD or a potent GVT effect could be predicted to occur if the donor shows a prevalence of mHAg-specific CD8+ CTLs.
Conversely, donors with prevalence of mHAg-specific CD8⁺ Tregs should represent a safeguard toward the risk of life-threatening GVHD, although potentially increasing the risk of leukemia relapse as a blunting effect of Tregs 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 application when less cumbersome and more standardized in vitro methods become available for a precise and reliable identification of either CTLs or Tregs. For the time being, this piece of information, together with the demonstration that during pregnancy a preferential induction of CD4⁺ Tregs 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 Tregs. Cellular adaptive 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⁺ Tregs 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.

Conflict-of-interest disclosure: The author declares no competing financial interests.

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8. Mold JE, Michaelsson J, Burt TD, et al. Maternal/fetal interactions, but there is no doubt that more transfusions reflect more severe underlying diseases. Desmarets 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 allogeneic proliferation 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 MHC-compatible marrow transplant. These transfusions had the same effect as leukocyte-reduced RBC transfusions and BMT rejection

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In this issue, Desmarets 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, hepatits from blood-borne infections, and that more transfusions reflect more severe underlying diseases.

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