Cytomegalovirus-specific T cells following haploidentical transplants: reshaping a repertoire by half

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Studies addressing the impact of human leukocyte antigen (HLA) disparities on the reconstitution of antigen-specific immunity following allogeneic HLA haploidentical hematopoietic cell transplant (HCT) are very limited. The paper by Tassi *et al.*[1] in this issue of *Haematologica* is the first to analyze the pattern of HLA restrictions exhibited by antigen-specific T cells emerging in a cohort of adult patients following HLA haploidentical transplants for hematologic malignancies. This report provides important new evidence documenting limitations to the repertoire of cytomegalovirus (CMV) epitope-specific HLA-restricted T cells achievable following HLA-haploidentical HCT.

In 1974, Zinkernagel and Doherty[2] first demonstrated that T cells recognize viral antigens only when presented by self major histocompatibility complex (MHC) alleles. Subsequent studies demonstrated that T cells bearing such MHC-restricted antigen-specific receptors (TCR) are positively selected during their development through interactions with cortical epithelial cells in the thymus.[3] Thereafter, they are negatively selected to deplete potentially autoreactive T cells specific for self-peptides presented by MHC alleles expressed by thymic dendritic cells and other antigen-presenting cells. After selection, the surviving, mature but naïve T cells are exported to the periphery and maintained in homeostasis until activated in response to antigenic challenge.[4]

While HLA restriction is now well recognized as a hallmark characteristic of TCRα/β antigen-specific T cells, information regarding the contributions of T cells restricted by shared *versus* donor or host unique alleles to reconstitution of pathogen-specific immunity following HLA partially matched or haploidentical HCT is minimal. Prior studies were almost exclusively focused on reconstitution of T-cell immunity in children with severe combined immunodeficiency diseases (SCID) who had received either T-cell-depleted grafts from an HLA-haploidentical parent or a fully allogeneic fetal liver, usually administered after no or minimal conditioning. Because the thymic epithelium is of host origin and, in murine models, positive selection depends on the interaction of the TCR of T-cell precursors with MHC alleles of thymic cortical epithelial cells,[4] it would be expected that donor-type tetanus toxoid antigen-specific T cells developing in the host thymus would be selectively restricted by HLA alleles shared by donor and host and that T cells restricted by host-unique alleles would not be detected. In fact, T-cell responses to tetanus presented by host-unique HLA alleles were equal to responses to epitopes presented by HLA alleles shared by donor and host.[5,6] However, prior to transplantation, the thymus in infants with SCID is embryonal, without evidence of lymphoid or other hematologic elements. Its development, including corticomedullary differentiation, is only initiated after transplantation. It is thus possible that concomitant differentiation of a functional thymic cortical epithelium, which is induced by prothymocytes,[7] could also be influenced by cells in the donor graft to permit positive selection of developing T cells recognizing host-unique HLA alleles.

In contrast, the CMV-specific T cells analyzed by Tassi *et al.*[1] were from adult recipients of HLA-haploidentical HCT whose thymuses would be fully differentiated from birth to the time of transplant. In these patients, CMV-specific T cells isolated by dextramers selectively recognized epitopes presented by shared or donor-unique HLA alleles. As observed in murine models, no CMV-specific T cells restricted by host-unique HLA alleles were detected, either early or up to 3 years after transplantation, likely reflecting the failure of T-cell progenitors in the graft bearing TCR specific for epitopes presented by donor-unique HLA alleles to be engaged and positively selected by cortical epithelial cells of the host thymus. Furthermore, while CMV-specific T cells restricted by donor-unique HLA alleles (D-restricted CMV-specific T cells) were detected in most patients who received transplants from CMV-seropositive donors, they were detected in only a minority of recipients of transplants from seronegative donors, consistent with D-

restricted CMV-specific T cells being derived from mature T cells in the graft. Furthermore, these T cells expanded later than CMV-specific T cells restricted by shared alleles, persisted for only 6 months and maintained a less differentiated phenotype. In contrast, CMV-specific T cells restricted by shared alleles expanded rapidly in most (but not all) patients, and to a greater degree. They also persisted at a high frequency for ≥1 year and contained more T_{EM} and T_{EMRA} cells. These findings support the authors' hypothesis that the donor CMV-specific T cells restricted by shared HLA alleles are responding to CMV epitopes presented by infected host-type non-hematopoietic cells or residual antigen-presenting cells. They also indicate a primary role for CMV-specific T cells restricted by shared HLA alleles in the initial and sustained control of CMV reactivation after transplantation. However, the proportion of T cells restricted by shared alleles that are derived from T-cell precursors maturing in the host thymus and their repertoire remains to be determined.

Transplants from HLA non-identical unrelated and HLA haploidentical related donors are increasingly invoked for the treatment of patients lacking a matched related or unrelated donor. Such transplants have been associated with higher incidences of CMV infection and associated non-relapse mortality.[8] In part, this increased incidence can be ascribed to graft-*versus*-host disease or the use of more intensive treatment with immunosuppressive drugs to control it, or to impairments to early reconstitution associated with T-cell-depleted grafts, *in vivo* T-cell depletion by pre-transplant antithymocyte globulin or post-transplant cyclophosphamide. However, the findings of Tassi *et al.*[1] raise the possibility that the inability of virus-specific donor T cells to recognize or be primed to epitopes presented by host-unique alleles could also retard or impair development of an effective immune response. We previously described a recipient of a haploidentical HCT with an Epstein-Barr virus (EBV)-positive lymphoma of host origin who failed treatment with donor EBV cytotoxic T lymphocytes that were restricted only by an HLA allele not shared by the patient but responded to third-party EBV cytotoxic T lymphocytes restricted by a shared allele.[9] To what degree such limitations contribute to the heightened risk of CMV or other latent viral infections in haploidentical transplant recipients warrants examination since the repertoire of CMV-specific T cells contracts over time and, in the graft, can be limited to responses to immunodominant viral epitopes presented by a single HLA allele. The repertoire of donor T cells developing in the host thymus may also be constricted by graft-*versus*-host disease and older age.[10] Thus, if epitopes presented by shared alleles are less immunogenic, early recovery of functional CMV-specific T cells may be delayed or inadequate to control disease.

Disclosures
No conflicts of interest to disclose.

Contributions
RJO and ZM co-wrote the editorial.

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