Reconstitution of T Cell Immunity after Umbilical Cord Blood Transplantation

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In patients who undergo allogeneic hematopoietic stem cell transplantation, recipient hematopoiesis is rapidly replaced with donor-derived cells. Various approaches have been used to measure the reconstitution of cellular and humoral immunity, as it provides protection against infectious pathogens and effects graft-versus-tumor (GVT) activity. Indicators include restoration of absolute neutrophil and lymphocyte counts; normalization of lymphocyte subset distribution between naïve, memory, effector, and regulatory cells; emergence of recent thymic emigrants; and detection of antigen-specific cellular immunity [1]. In addition, diversity of the T cell repertoire has been measured by spectratyping, an assay that measures the breadth of utilization of individual TCR Vβ genes [2]. Recognizing those aspects of reconstitution that correlate with and are causative for clinical outcomes enables the identification of patients at high risk for infection and the development of approaches to correct deficient elements of immune recovery.

Immune reconstitution is particularly important after umbilical cord blood transplantation (UCBT), given the significant temporal delays in myeloid and lymphoid recovery compared with after standard HLA-matched unrelated stem cell transplantations [3,4]. Many variables have been found to influence immune reconstitution after UCBT, including age of recipient, baseline thymic activity, use of multiple umbilical cord blood products, in vivo T cell depletion with alemtuzumab or antithymocyte globulin, intensity of conditioning, and graft-versus-host-disease (GVHD) prophylaxis. Nevertheless, the relative delay in immune reconstitution is a consistent observation after UCBT, and impaired recovery has been correlated with increased incidence of infection and non-relapse mortality (NRM).

In this issue, Saliba et al. present their analysis of numerical and functional antigen-specific lymphocyte reconstitution after double cord blood transplantation (dUCBT) [5]. One hundred eight adult patients who engrafted after dUCBT were tracked for standard demographic and clinical outcomes to identify predictors of 3-year NRM. Of note, all patients received antithymocyte globulin in their preparative regimen and 70% received a cord blood product expanded ex vivo after coculture with mesenchymal stromal cells. Multivariate analysis demonstrated that absolute lymphocyte count (ALC) at 30 days above or below 150 x 10^9/L was strongly associated with NRM and survival. In 65 recipients, immunophenotyping of peripheral blood mononuclear cells after transplantation revealed early recovery of natural killer cells and B cells followed by delayed recovery of CD4+ and CD8+ T cells with an inverted CD4/CD8 T cell ratio. In a subset of 46 recipients, stimulation of peripheral blood mononuclear cells with peptides representing immunogenic antigens from 6 viruses (cytomegalovirus, Epstein-Barr virus, BK virus, adenovirus, influenza, and respiratory syncytial virus) was used to assess recovery of specific T cell responses against these viral pathogens. ELIspot assays demonstrated slow recovery of viral-specific T cell activity until at least 9 months after dUCBT. Notably, there was no correlation between normalization of ALC, CD4, or CD8 T cell numbers and detection of viral-specific T cell immunity. Nevertheless, a low ALC 30 days after transplantation represents an easy, rapid way of identifying patients at high risk for poor outcomes. Similar results have been demonstrated in patients receiving filgrastim-mobilized peripheral blood stem cell grafts [6]. Identification of these high-risk patients early after transplantation can facilitate closer monitoring and early interventions to mitigate serious infections.

The overarching conclusion of studies on immune reconstitution has been that lack of diversity or skewing of the T cell repertoire increases the risk of infections, NRM, death, and potentially GVHD [7,8]. Adoptive therapy with virus-specific T cells or other T cell populations expanded ex vivo can provide protection against specific pathogens but may not be sufficient to robustly augment T cell repertoire diversity. Achieving a truly diverse T cell population will likely impact the balance between GVT and GVHD responses and determine long-term outcomes after UCBT. Measurements of total and naïve lymphocytes, viral-specific T cells, and recent thymic emigrants after hematopoietic stem cell transplantation (Figure 1A,B) are all surrogate markers for T cell diversity.

It is now possible to quantify T cell repertoire diversity by next-generation sequencing of PCR-amplified products representing the highly polymorphic CDR3 regions of individual T cells (Figure 1C) [9,10]. This approach can identify individual TCR gene rearrangements in millions of T cells and provides a direct measurement of the TCR Vβ repertoire. It is also possible to track individual T cell clones in serial samples and quantify their expansion or loss. In preliminary studies, NRM and survival have been shown to correlate with early T cell repertoire diversity after UCBT [11,12]. This approach may provide a more comprehensive profile of immune reconstitution and, when combined with sequencing of the TCRs chain, may predict immunity to specific pathogens and enable antigen-discovery in patients with GVHD or GVT.

With continued development and refinement of this approach, monitoring T cell diversity and specificity in this.

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detailed manner may be used to identify patients at high risk for serious infections and to evaluate the results of future therapies designed to enhance immune reconstitution.

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REFERENCES