Comment on Cieri et al, page 2865, and Roberto et al, page 2855

A maturing understanding of naive T cells

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In this issue of Blood, Cieri et al and Roberto et al report that recovery of a diverse T-cell receptor (TCR) repertoire following haploidentical hematopoietic stem cell transplantation (haplo-HSCT) using posttransplant cyclophosphamide (pt-Cy) is dependent on T memory stem cells (TSCM) maturing from naive T cells adoptively transferred in the donor graft.1,2

These results considerably advance our understanding of how immune reconstitution occurs in the setting of haplo-HSCT. Historically, due to the increased risk of graft–versus-host disease (GVHD), outcomes for patients requiring allogeneic HSCT (allo-HSCT) have been inferior to results of sibling and matched unrelated donor HSCT. Fortunately, the past decade has seen dramatic advances in alternative donor transplantation, using either umbilical cord blood or haploidentical family donors. These developments are welcome, particularly for patients of minority groups, who are far less likely to find a registry match when lacking a sibling donor.3

Because alloreactive T cells present in a native haploidentical donor graft would rapidly induce lethal GVHD in the recipient, the classic approach to haploidentical transplantation involved rigorously depleting donor T cells from the donor graft ex vivo, typically reducing transferred T cells by ~1000-fold. The modern approach developed by Luznik, Fuchs, and colleagues was inspired by seminal studies, more than a half-century old, demonstrating induction of tolerance by the alkylating agent cyclophosphamide,4 and their own preclinical models of allogeneic transplantation.5 Subsequent human clinical trials demonstrated the feasibility of transplantation of an unmanipulated haploidentical graft if cyclophosphamide was administered to the recipient on days +3 and +4 following donor graft infusion.6

The repercussions from these advances in haplo-HSCT have been widely felt. Following the original publication demonstrating the safety of pt-Cy administration, multiple publications from academic and even private settings have demonstrated the feasibility, safety, and efficacy of this approach in varied subgroups.7 In fact, recent data suggest an increase in haploidentical transplants performed with an attendant decrease in the utilization of cord blood transplantation, despite the lack of head-to-head clinical data demonstrating the superiority of this approach.8 Given its increasing use, significant attention is now being focused on the mechanisms of recipient T-cell recovery after pt-Cy, the subject of these 2 studies.

Gattinoni et al previously identified human early memory-stage T cells with stemlike properties (TSCM) that preferentially facilitated T-cell recovery in immunodeficient mice, similar to their multipotent murine counterparts.9 While expressing classical naive markers (eg, CD45RA, CD62L), human TSCM additionally expressed markers including the tumor necrosis factor receptor superfamily member and cellular death receptor Fas/CD95; in contrast to their true naive counterparts, this subpopulation proved low in the content of recent thymic emigrants and more readily produced cytokines upon polyclonal stimulation.

Recent preclinical and clinical studies have better defined the effects of pt-Cy on both alloreactive and nonalloreactive T-cell subsets. Kanakry et al recently demonstrated that the expression of aldehyde dehydrogenase, known to protect hematopoietic progenitors from the effects of cyclophosphamide, is also responsible for the relative preservation of regulatory T cells (Tregs) in murine and human subjects.10 In murine studies, Ganguly and colleagues further demonstrated that the adoptive transfer of donor Tregs is necessary for the protective effects of pt-Cy against GVHD.11 Additionally, our own murine studies have demonstrated that pt-Cy relatively spares pathogen and cancerspecific T cells expanding under lymphopenic conditions, whereas antigen engagement in the early post-HSCT era drives the preferential deletion of alloreactive T cells.12

To add to this growing understanding of the effects of pt-Cy on immune recovery, the 2 new studies in this issue used parallel conceptual approaches, albeit in the setting of distinct haplo-HSCT subpopulations. Cieri et al studied patients receiving ablative conditioning and peripheral blood stem cell grafts, with recipients receiving, in addition to pt-Cy, mycophenolate mofetil (MMF) and sirolimus for GVHD prophylaxis.1

Roberto et al studied haploidentical recipients who received nonmyeloablative conditioning and marrow grafts, with GVHD prophylaxis consisting of pt-Cy, MMF, and calcineurin inhibition.2 Although the clinical approaches to haplo-HSCT differed, both investigative teams performed serial measurements of naive and TSCM T cells at early points following HSCT, including comprehensive immunophenotypic and functional measures, to assess patterns of immune reconstitution with a focus on early events following the administration of pt-Cy.

The novel and important finding of both studies is that in the early post-HSCT interval, the peripheral lymphoid pool was dominated by TSCM derived from naive donor graft T cells, and that TSCM were directly responsible for the recovery of a diverse TCR repertoire. Both studies used thorough immunophenotypic and functional analyses, which allowed indirect but meaningful conclusions to be drawn not only about TSCM, but also their precursor and derivative lymphoid subsets. The dramatic expansion of TSCM suggests a mechanism for the superiority of the pt-Cy approach to haplo-HSCT over the traditional approach of rigorous T-cell depletion. These studies highlight the importance of TSCM in immune recovery not only after haplo-HSCT, but also in the ontogeny of memory T-cell development more generally.

Although these studies are compelling, important questions remain. It remains possible that the expression of CD95 on naive T cells could be driven by activation events early after HSCT, when tissue injury, cytokine excess, and lymphopenia prevail, leading to a pseudo-TSCM phenotype (just as lymphopenia can push truly naive cells...
deprived of antigen in mice to masquerade as memory cells). Whereas these data suggest that T_{SCM} are critical to memory rediversification in HSCT recipients, the present studies provide few concrete answers regarding how naive-to-T_{SCM} transitions are directed, or how this maturation might be enhanced clinically. Such knowledge might even help us improve outcomes in cord blood transplantation in adults, which is characterized by delayed recovery of functional T-cell responses despite the transfer of uniformly naive T cells, in part due to delays in thymopoietic recovery.13 Although these and other questions remain, our maturing understanding of in vivo T-cell development inspires genuine hope that we will soon have active clinical strategies that may accelerate immune recovery in all allo-HSCT recipients, including those requiring alternative donors.

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**REFERENCES**


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