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GVHD protection? ThiNK iNKT cells

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In this issue of Blood, Rubio et al report that posttransplant invariant NKT (iNKT) cell recovery is inversely correlated with the risk of developing GVHD after stem cell transplantation.1

Allogeneic hematopoietic stem cell transplantation (HSCT) remains the best curative therapy for many patients with hematologic malignancies and/or marrow failure states. While significant advances in transplant conditioning and supportive care have resulted in a dramatic decrease in early mortality and have facilitated an expansion in the application of HSCT worldwide, significant challenges remain. Paramount among these is the conundrum of GVHD. We now know that the allogeneic donor graft contains T cells that induce GVHD that may result in nonrelapse mortality after HSCT, but may also mediate graft-versus-tumor responses that are critical for the elimination of chemotherapy-resistant cancer cells. Indeed, immunosuppression required to prevent and/or treat GVHD after HSCT may impair antitumor immunity, in addition to delaying the recovery of functional immune responses to pathogens.

The rise of quantitative immunology, facilitated by advances in flow cytometry and the resulting ability to identify fine subsets of lymphoid cells in mice and in humans, has yielded important, and clinically promising, insights into alloreactivity. The identification by Sakaguchi and colleagues of CD4+/CD25+ regulatory T cells re-opened a field of exploration into lymphoid subsets capable of controlling autoimmunity and alloreactivity.2 Sequential murine and human studies have resulted in clinical trials that have established that adoptive immunotherapy using regulatory T cells is safe, feasible, and likely to have therapeutic benefit.3 Conceptually, we have opened the door to a world where more selective immunosuppression is accomplished by manipulating the suppressors in vivo or ex vivo, and not merely by targeting the effectors of alloreactive T-cell responses.

In the present study, Rubio and colleagues focus their attention on the relatively rare lymphoid subset called iNKT cells.1 Like regulatory T cells, iNKT cells are a T-cell subset that is found in mice and in humans, and appear to be capable of controlling autoimmunity and alloreactivity in models of disease, including GVHD. As recently reviewed by Berzins et al,4 these cells are distinct from most peripheral T cells in that they express an invariant T-cell receptor (Va24-Ja18 in humans), are selected by the nonclassical HLA molecule CD1d, and can be activated by glycolipids such as α-galactosylceramide. In mice, iNKT cells are estimated to comprise approximately 0.2% to 0.5% of the lymphocyte population, and vary substantially in frequency by site, with much higher relative frequencies found in organs like the liver, where they may comprise up to 30% to 50% of hepatic T cells.5 In humans, iNKT cells are even more rare (eg, 0.01% to 0.1% of human peripheral blood mononuclear cells), and our understanding of tissue distributions is limited.4

The interest in iNKT cells in the setting of HSCT was triggered by the initial report by Zeng et al demonstrating reciprocal regulation of GVHD in mice demonstrating that an NKT subset could suppress alloreactivity, mediated at least in part by IL-4 production.3 Subsequent studies in murine models using more precise phenotypic characterization of iNKT cells confirmed this observation and additionally demonstrated the importance of cross-talk between iNKT cells and CD4+/CD25+ regulatory T cells.6,7 It was also demonstrated that host iNKT cells were radioreistant, which inspired the development of nonmyeloablative conditioning regimens incorporating both total lymphoid irradiation and anti-thymocyte globulin to facilitate relative enrichment of iNKT cells in humans.8 Despite the significance of these observations in murine models and translational human studies, our understanding of the role of naturally occurring donor graft and recovering iNKT populations in HSCT recipients remains incomplete.

Recently in Blood, Chaidos et al reported that lower donor graft NKT cell numbers predicted the incidence of severe recipient acute GVHD, even when other important predictors of GVHD were examined in multivariate modeling.9 The present study by Rubio and colleagues extends these findings by examining iNKT recovery in 71 recipients of allogeneic HSCT in relation to clinical outcomes, including the incidence of GVHD, relapse, and overall survival.1 Strikingly, the ratio of iNKT cells to other T cells, when higher than 1:1000, remained a predictor of lower GVHD incidence, even after multivariate modeling.1

Subsets of patients with a high iNKT:T ratio were found to have reduced nonrelapse mortality rates and a higher actuarial probability of overall survival. In a small subset of patients, iNKT cells were isolated and expanded, demonstrating the ability of these cells to produce expected cytokines, including IFNγ and IL-4.1 In addition, chimerism analyses performed in 5 patients demonstrated that iNKT cells observed were of donor (rather than host) origin, contrasting that seen in murine models where radioreistant host iNKT cells survived and mediated GVHD protection.1 These results provide confirmation that a relatively rare subset of peripheral lymphoid cells may have potent immunoregulatory functions.

These findings, while compelling, require further confirmation, and some limitations of this study are worth noting. The transplanted group was relatively heterogeneous, with respect to important variables including disease, remission status, donor type, and conditioning.1 As discussed above, the relative number of iNKT cells in humans is broadly variable and the ability to assess rare populations by flow at early time points dictates that such results be considered with caution. Some critical analyses, such as assessment of chimerism and functional studies, were performed only in minor subsets, while others (eg, assessment of recovering regulatory T cells, given predicted cross-talk with iNKT cells) were not included.1

Despite these caveats, Rubio and colleagues have helped to extend an interesting line of investigation into a rare cellular subset with therapeutic potential. The ability to expand these cells, either ex vivo via graft engineering or in vivo with drugs designed to mimic natural expansion via glycolipids, may yield novel therapies. Given that more than
25 years have elapsed since Storb et al established combination therapies using calcineurin inhibition and antimetabolites as a standard of care in GVHD prevention,10 translational studies like this one that may herald novel immunomodulatory strategies are welcome.

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REFERENCES


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