molecule to enrich HSCs in adult mice, and higher surface expression of CD150 on HSCs was previously shown to correlate with myeloid differentiation bias. Transplantation assays were performed to examine the self-renewal and lineage reconstitution activities of CD86− HSCs. Shimazu and colleagues found that CD86− HSCs could reconstitute myeloid lineages; however, their ability to reconstitute lymphoid lineage was diminished. Indeed, some mice receiving CD86− HSCs were devoid of donor lymphoid lineages.

The authors tested the effects of deletion of CD86, and showed that CD86 itself does not affect the lineage-reconstitution ability of HSCs. Conditional ablation of the ets-family transcription factor PU.1 in mice established that the expression of CD86 on HSCs requires PU.1. It remains to be determined whether down-regulation of PU.1 expression contributes to the myeloid bias of CD86− HSCs, or whether other mechanisms are involved. Identifying the responsible mechanisms is an important area of future investigation.

Interestingly, although CD86− HSCs accumulate with age, the authors found that small numbers of myeloid-biased HSCs exist even in young, healthy mice. It is unknown whether this reflects exposure of HSCs to TLR ligands or other products of the normal microbiome, and whether such CD86− HSCs might be absent in germ-free mice. It is also unclear whether accumulation of such lineage-biased or lineage-restricted HSCs might have adaptive significance. For example, age-related declines in lymphopoiesis have been previously suggested to reduce susceptibility to lymphoid-lineage cancers. It will be interesting to determine whether CD86− HSCs are less susceptible to the transforming effects of oncogenes that drive cancers of B and T cells. The discovery that CD86 can be used as a marker to identify HSCs with reduced lymphoid developmental potential means that these and related questions can now be better addressed.

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REFERENCES

Donor natural killer (NK) T cells in hematopoietic cell transplants suppress graft-versus-host disease (GVHD) that is induced by donor CD4+ and CD8+ conventional T (Tcon) cells. The T-cell antigen receptors (TCR) of the Tcon cells recognize class I and class II MHC receptors associated with peptides, and the NK T cells recognize CD1d receptors associated with glycolipids on the surface of antigen presenting cells (APCs). Professional illustration by Alice Y. Chen.
unique features. First, iNKT cells have an invariant T-cell antigen receptor (TCR) α chain that allows their identification in mice and humans by the presence of the invariant TCR by immunofluorescent staining. Second, the invariant TCR on the iNKT cell recognizes a nonpolymorphic antigen-presenting molecule, CD1d, associated with self or microbial glycolipids instead of recognizing highly polymorphic MHC class I and II molecules that present foreign peptides to conventional CD4+ and CD8+ T cells (see figure). Third, on activation iNKT cells can secrete large amounts of Th1 or Th2 type cytokines, depending on the antigen-presenting cells and their environment that can enhance or suppress immune-mediated reactions by conventional T cells. Invariant NKT cells can be further subdivided into CD4+ and CD4− (CD4+ CD8−) subsets, and the study by Chaidos et al identified the donor CD4+ iNKT cell in the hematopoietic cell graft as the key predictor for reduced acute GVHD.

The first observations that donor NKT cells in a bone marrow transplant suppress GVHD were made in mouse studies reported in 1999 in which selective deletion of the CD4+ iNKT cells from the marrow transplant resulted in high levels of acute GVHD, and the add-back of these cells protected against GVHD. Before this study, all T-cell subsets in marrow transplants were thought to contribute to GVHD. Host iNKT cells also protect against GVHD. The lymphoid tissues and spleen of murine marrow transplant recipients given nonmyeloablative conditioning with total lymphoid irradiation and anti–T-cell antibodies become enriched for host iNKT cells and these mice were protected from GVHD after bone marrow transplantation, whereas iNKT knockout mice conditioned in the same manner died from lethal GVHD. The enrichment of iNKT cells after total lymphoid irradiation was also reported in clinical studies that showed marked protection against GVHD.

In the preclinical models, suppressive donor and host iNKT cells produced both IFN-γ and IL-4, yet GVHD suppression was dependent on IL-4 production in both cases because experiments using IL-4 knockout donor or recipient mice died from GVHD. The important role of IL-4 in the suppression of GVHD by mouse iNKT cells was also reported in a recent study in which purified donor iNKT cells from the spleen were added to marrow transplants spiked with GVHD-inducing conventional T cells. In the murine models, the IL-4 secretion by iNKT cells promoted expansion of IL-10–secreting donor CD4+ CD25+ FoxP3+ T regulatory cells and polarized donor T cells toward a Th2 phenotype thereby reducing injury in the target tissues of GVHD (skin, liver, and gut). It is noteworthy that the cytokine-dependent mechanism of GVHD protection by the donor or host iNKT cells did not affect donor CD8+ T-cell cytolytic function and graft antitumor activity was preserved.

The report by Chaidos et al validates in humans the finding from murine models of bone marrow transplantation that iNKT cells in the donor graft protect against GVHD. However, the mechanism of GVHD protection in humans is incompletely defined. Chaidos et al reported that in vitro assays using human donor iNKT cells inhibited the immune response of conventional T cells to alloantigens, and the CD4+ iNKT cells induced cytolysis of antigen presenting cells (dendritic cells). These results point to another mechanism by which iNKT cells can suppress GVHD in addition to the cytokine-dependent pathways. However, in view of the rarity of CD4+ iNKT cells in humans (less than 1 in 1000) and the high ratio of effector NKT cells to target dendritic cells required for the in vitro cytolysis assays, the cytokine pathway is more likely to contribute to GVHD protection in vivo. Although the exact mechanism(s) by which the rare iNKT cells modify the immune responses of the numerous conventional T cells is not fully defined, the report by Chaidos et al is an important clinical advance in support of the role of regulatory T cells suppressing GVHD, and will likely spark interest in developing clinical protocols in which purified donor NKT cells are infused into transplant recipients to prevent or treat GVHD.

Conflict-of-interest disclosure: The authors declare no competing financial interests.

REFERENCES
Rare cells predict GVHD
Samuel Strober and Robert Lowsky