breakthrough. It has to be remarked that an excellent clinical efficacy can be achieved irrespective of this residual complement activity, eventually raising the question whether the abolishment of this residual activity is a goal to be pursued for improving the results of current anticomplement treatment.

With their study, Peffault de Latour et al provide a reliable way to monitor therapeutic complement inhibition. Given that residual anemia in PNH patients on eculizumab may be due to different (but possibly concomitant) causes (residual intravascular hemolysis due to PK or PD breakthrough, bone marrow failure, C3-mediated extravascular hemolysis),[10] these findings are useful to drive therapeutic decisions (see figure). Indeed, only PNH patients showing recurrent residual CH50 activity may benefit from modification of the treatment schedule (ie, increased doses or reduced administration intervals). This mechanistic demonstration of residual terminal complement activity is extremely interesting even in the context of the development of second-generation complement inhibitors. Indeed, a number of novel complement therapeutics are in preclinical and clinical investigations[8-10]; they may intercept complement at the level of its terminal effector components (eg, C5 inhibitors) or target the proximal activating complement. The latter include broad C3 inhibitors (eg, compstatin)[9] and pathway-specific modulators of the initial complement activation (eg, alternative pathway inhibitors targeting complement factor B and factor I, or factor H-based engineered proteins).[8] In the future scenario of a multioption complement inhibition, the assays proposed by Peffault de Latour et al will be pivotal to identify patients who may benefit from a second-line treatment with other terminal complement inhibitors and patients who better qualify for an upstream targeted intervention aiming to treat C3-mediated extravascular hemolysis (see figure).

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Comment on Shah et al, page 784

The off-target effects of nonspecific NK cells

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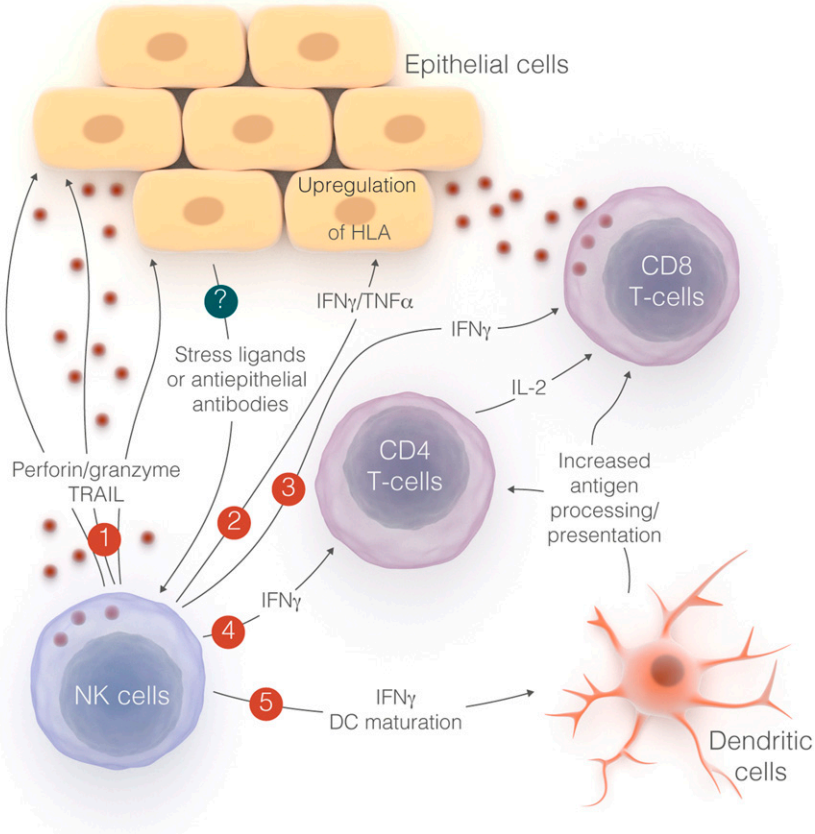
In this issue of *Blood*, Shah et al describe the onset of severe acute graft-versus-host disease (GVHD) in 5 of 9 patients who received infusions of ex vivo expanded donor natural killer (NK) cells after HLA-matched hematopoietic stem cell transplantation (HSCT).[1]

Despite conducting a small phase 1 trial with significant diversity in patients, donors, products, and treatment, the authors provide careful correlative studies that suggest exacerbation of subclinical T-cell–mediated skin and gut graft-versus-host as a possible mechanism. By carefully evaluating the manufacturing process, characteristics of the NK-cell and stem cell products, and patient pathology, the authors demonstrate a previously unrecognized potential for NK cells to have a profound effect in promoting GVHD in this context.

This clinical trial used CD34 selection and CD3 depletion of the starting apheresis product to deliver a very low dose of T cells in both the stem cell graft and NK cell product, enabling a posttransplant period without immune-suppressive drugs that would interfere with NK-cell function. T-cell doses were $<2 \times 10^4$/kg in the stem cell graft and $<2 \times 10^3$/kg in the NK-cell infusion. NK-cell doses were also very low compared with previously published trials; subjects received only 10^5 to 10^6/kg.

That NK cells can discriminate between healthy and malignant cells despite lacking antigen specificity, separating graft-versus-leukemia (GVL) from GVHD, is especially striking in the setting of HLA mismatch, where NK cells appear to have the most pronounced effect. More strikingly, NK cells may mediate a GVL effect while simultaneously mediating a decrease in GVHD, perhaps because missing self alone is insufficient, and normal tissues do not express the requisite activating ligands to induce an NK-cell response. Genetic determinants of NK-cell function may have value in predicting GVHD in the transplant setting,[2,3] but rapid NK-cell reconstitution[4] and higher NK-cell graft content[5] are associated with decreased GVHD. Moreover, hundreds of patients treated in clinical trials infusing NK cells derived by apheresis and T-cell depletion have shown no infusion-related dose-limiting toxicity or evidence of GVHD exacerbation, whether delivered after high-dose chemotherapy[6] or after mismatched HSCT.[7]



Possible mechanisms of NK cell–mediated acute GVHD. Subclinical GVHD triggers NK cell activation through unknown mechanisms (denoted by "?"), perhaps involving antiepithelial antibodies or expression of stress ligands induced by local inflammation. The resulting NK-cell responses may be targeted directly at epithelial cells (1), or may indirectly activate adaptive immune mechanisms that exacerbate T-cell–mediated GVHD (2-5). Professional illustration by Luk Cox.

Thus, the GVHD seen in this report is quite unexpected.

Possible factors in the current report that may help explain the unexpected GVHD rates include the timing of NK-cell infusion (8-35 days after transplant), the lack of posttransplant immunosuppression, or the hyperactivation of the NK cells, which were expanded on interleukin 15-secreting feeder cells. It is important to note that all 4 patients receiving unrelated donor transplants developed GVHD compared with only 1 of 5 patients receiving related donor transplants, further implicating a T-cell etiology mediated by minor antigens that was somehow exacerbated by the infused NK cells.

This then raises several possible mechanisms to explain the observed GVHD. As shown in the figure, subclinical dermal or mucosal inflammation may increase stress ligands, rendering epithelium susceptible to recognition by NK cells, causing (1) a direct effect via lysis or indirect activation of adaptive immunity through (2) cytokine-mediated upregulation of HLA for T-cell recognition, (3) stimulation of cytotoxic T cells, (4) activation of helper T cells, or (5) maturation of dendritic cells for enhanced antigen presentation or crosspresentation.

Whichever the case, these findings force us to recognize the potential potency of NK cells and to consider that GVL is no longer discretely separated from GVHD for NK cells. Further understanding of this mechanism is essential for understanding GVHD and the future of adoptive cell therapy with NK cells.

Conflict-of-interest disclosure: The author declares no competing financial interests. ■

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● ● ● LYMPHOID NEOPLASIA

Comment on Pawlyn et al, page 831

Blind men and an elephant

Shaji Kumar MAYO CLINIC

In this issue of *Blood*, Pawlyn et al examine the prognostic implications of overlapping chromosomal abnormalities in multiple myeloma (MM), demonstrating that coexistence of hyperdiploidy does not mitigate the impact of high-risk abnormalities.[1]

The story of the blind men and an elephant originated in the Indian subcontinent and describes a group of blind men coming to different conclusions about how an elephant looks like by feeling different parts of the animal. The parable