
To the editor:

**Does SPRED1 contribute to leukemogenesis in juvenile myelomonocytic leukemia (JMML)?**

Dr Pasmant and colleagues recently reported a child with a neuro-cardio-facial-cutaneous (NCFC) syndrome caused by a germline SPRED1 mutation.1 The child developed acute myeloid leukemia.1 The relation between the molecular pathology of NCFC syndromes and that of myeloid malignancies in children is well-documented. NCFC syndromes include Costello, Noonan, LEOPARD, and cardiofaciocutaneous syndromes. Endogenous IL-17 contributes to reduced tumor growth and metastasis.

In order to test this possibility, we sequenced the SPRED1 gene in granulocyte DNA from 23 JMML patients without mutations in *PTPN11*, *KRAS*/*NRAS*, or *CBL* and without NF-1 features. The assumption put forward by Dr Pasmant and colleagues, that germline *SPRED1* mutations predispose children to leukemia, is certainly plausible. However, the absence of *SPRED1* mutations in an early childhood leukemia such as JMML indicates that the putative link between *SPRED1* lesions and childhood myeloid malignancies requires further clarification.

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To the editor:

B cells in GVHD: friend or foe?

We were pleased to read the recent review by Shimabukuro-Vornhagen et al., “The role of B cells in the pathogenesis of graft-versus-host disease,” which highlights the importance of B cells after bone marrow transplantation, as B cells have tended to be overlooked as a contributor to transplantation immunology. This review comprehensively describes the use of the humanized chimeric CD20 monoclonal antibody, rituximab, for the prophylaxis and treatment of acute and steroid-refractory chronic graft-versus-host disease (GVHD). Three key observations have been made: (1) the use of rituximab as part of pretransplantation conditioning results in the in vivo depletion of donor B cells after transplantation; (2) pretransplantation rituximab is associated with reduced incidence and severity of acute GVHD in a cohort of patients; and (3) elevated B-cell numbers in donor grafts are associated with the development of both acute and chronic GVHD. Whether B-cell depletion per se is the mechanism underlying reduced GVHD rates, and whether this reflects a direct role of B cells in stimulating allogeneic T-cell expansion and effector function remains unknown.

It is important to also consider the potential nonspecific effects of rituximab therapy on the activation of allogeneic T cells. Nonspecific IgG treatment, such as high-dose intravenous immune globulin, can inhibit interferon-γ (IFN-γ) responses in macrophages via a FcγRIII-dependent mechanism, and induce natural killer cell–mediated antibody-dependent cellular cytotoxicity of dendritic cells (DCs). Apoptotic lymphocytes also have a regulatory effect upon DCs, by down-regulating costimulatory molecules and inducing the production of the immunosuppressive cytokine interleukin-10 (IL-10). In GVHD, these events stimulate the generation and proliferation of regulatory T cells (Tregs), thus suppressing allogeneic T-cell activation.

Both T and B lymphocytes play a role in tolerance induction to autoantigens, whereby CD4+ T cells regulate early allogeneic T-cell activation and expansion, and B cells control their differentiation into effector T cells. Host B cells have also been shown to play a protective role in GVHD, via the secretion of IL-10 after total body irradiation, thus inhibiting allogeneic T-cell expansion and subsequent acute GVHD induction. Donor B cells can also inhibit acute GVHD in a major histocompatibility complex class II– and Treg-dependent manner. Mice receiving BM from B cell–deficient mutant mice (B6.129S1-Il2rgtm1Jfsn/J) developed rapid-onset acute GVHD, contributed by faster donor CD8+ T-cell engraftment and production of IL-2 and IFN-γ (J.E.D., V. Watt, and D.R.S., manuscript in preparation), and indirect alloantigen presentation to CD4+ T cells. This is supported by recent in vitro human data, indicating that activated B cells directly suppress allogeneic CD4+ T-cell proliferation through the expansion of alloantigen-specific suppressor Tregs.

While clinical observations indicate that rituximab has a beneficial effect in the prophylaxis of acute GVHD, it is worth considering that an alternate mechanism of its action may exist over and above simple B-cell depletion. Furthermore, the potential benefit of regulatory B cells may be lost if rituximab is adopted wholesale into pretransplantation conditioning regimens.

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References

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