Correspondence

To the editor:

Angioimmunoblastic T-cell lymphoma: a neoplasm of germinal-center T-helper cells?

We have read the paper by Kim et al1 recently published in Blood with great interest. The study reports the gene-expression profile of germinal-center T-helper (GC-Th) cells and identifies genes differentially expressed by G-C-Th cells compared with other T-cell subsets.

The germinal center microenvironment not only is an essential niche for generation of B-cell response, but also is considered to be critical in the development of most human lymphoid neoplasms. Although most lymphomas originating from germinal-center lymphocytes are B-cell lymphomas, it has been suggested recently that some peripheral T-cell lymphomas,2 in particular angioimmunoblastic T-cell lymphoma (AITL), may arise from GC-Th cells.3,4 AITL is a relatively infrequent disease accounting for 1% to 2% of all lymphomas. Typically, the tumor cells of AITL have a T-helper–cell phenotype expressing CD3, CD4, and frequently CD10, similar to a subset of normal GC-Th cells.5 In early lymph-node involvement by AITL, the neoplastic T cells preferentially occupy the B-cell follicles and immediate perifollicular area, sometimes mimicking a follicular lymphoma of B-cell origin.6,5 This suggests that the follicle-center microenvironment is critical for tumor development.

In the Kim et al1 study, one of the most highly up-regulated genes in the GC-Th cell subset was CXCL13, a chemokine critical for B-cell entry into germinal centers.6 Based on this observation, we investigated the expression of CXCL13 in AITL. We stained paraffin sections of 29 AITL lymph-node biopsies using a monoclonal antibody against CXCL13 (Clone 53610; R&D Systems, Minneapolis, MN) and standard immunohistochemical methods. All cases were previously characterized by immunohistochemical studies that documented expression of CD3 and CD4 by the tumor cells. CD10 was expressed in 22 cases. We observed striking cytoplasmic expression of CXCL13 by the vast majority of the tumor cells (> 80%) in 25 (86%) of 29 AITL cases studied. The tumor cells both within the follicles and in the interfollicular areas stained with similar intensity. All 22 cases expressing CD10 also expressed CXCL13 (Figure 1). In addition, a subset of the macrophages and follicular dendritic cells (FDCs) was labeled by CXCL13.

The expression of CXCL13 by AITL provides another piece of evidence linking the tumor cells to GC-Th cells. Increased CXCL13 message in AITL was also detected by transcription-profiling studies using cDNA chips designed to detect chemokine-gene expression.7 Kim et al1 also reported selective up-regulation of several transcription factors in GC-Th cells. One of these was Bcl-6, which, like CXCL13, is overexpressed in AITL.8

These observations are important in several respects. One of the downstream effects of CXCL13 expression is induction and proliferation of FDCs, probably via stimulation of lymphotixin-alpha production by B cells.6 Of interest, the proliferation of FDCs is a morphologic hallmark of AITL and is considered to be a requirement for histologic diagnosis.9 Another attribute of AITL is the presence of dysregulated B-cell growth. In early stages, this is primarily seen as follicular hyperplasia1,5; in later stages, a more immunoblastic and plasmacytic expansion with hypergammaglobulinaemia occurs.3,10 As CXCL13 is a critical factor in B-cell recruitment and activation, it may also be responsible for some of the B-cell abnormalities seen in AITL. Marked immune dysregulation, rather than aggressive tumor growth, is thought to be the main clinical problem in AITL, and there are attempts to treat this disease using immunomodulatory approaches.11,12 The information gained by studying normal follicle-center T cells may be helpful in the development of targeted immunomodulatory treatment strategies for this otherwise-fatal condition. The study by Kim et al1 elegantly

Figure 1. CXCL13 expression in AITL. (A) High-power view of AITL lymph-node biopsy. Typical clusters of tumor cells with clear/pale cytoplasm are present. There is marked microvascular proliferation in the background (hematoxylin and eosin [H&E]). (B) The tumor cells are positive for CD3 (immunoperoxidase). (C) There is variable expression of CD10 (immunoperoxidase). (D) The tumor-cell clusters show strong cytoplasmic expression of CXCL13 with marked paranuclear enhancement (inset, immunoperoxidase). Images were visualized under an Olympus BX51 microscope equipped with UPlanFL ×40 (main panels) or ×65 (inset) objective lenses and WH 10 × 22 eyepiece (Olympus, Tokyo, Japan). Images were captured with an Olympus DP70 camera and processed with Adobe PhotoShop 7.0 software (Adobe Systems, San Jose, CA).
To the editor:

**Interferon γ (IFN-γ) polymorphism in posttransplantation lymphoproliferative disease**

Injecting severe combined immunodeficient (SCID) mice with severe combined immunodeficient (SCID) mice with primary blood mononuclear cells (PBMCs) from Epstein-Barr virus (EBV)-positive donors regularly produces EBV-positive B-lymphoproliferative disease, which closely resembles posttransplantation lymphoproliferative disease (PTLD) in humans. In a recent paper in Blood, Dierksheide et al presented interesting data showing that tumor development in SCID mice correlates with an adenosine (A)/thymidine (T) polymorphism at position +874 in the IFNG gene. Their data suggest that an A/A phenotype in the PBMC donor significantly associates with rapid, high-incidence tumor development. As a consequence of these results, the authors speculate that the A/A IFNG gene phenotype confers a predisposition to PTLD. They report finding a significantly higher proportion (58%) of 12 PTLD patients exhibiting the A/A phenotype than non-PTLD transplant controls (27%).

We have analyzed the identical IFNG polymorphism in blood samples from 37 patients with PTLD and 109 controls (patients who had not developed PTLD 5 years after transplantation). Patients with PTLD had received transplants of the following: liver with or without small bowel (n = 17), hemato poetic stem cells (n = 1), lung (n = 1), kidney (n = 10), and heart (n = 8). PTLD was diagnosed by clinical, morphologic, and immunophenotypic criteria. EBV positivity was assessed by in situ hybridization for EBV-encoded small RNAs (EBERs) or immunocytochemical staining for EBV nuclear antigen (EBNA) and latent membrane protein 1 (LMP1). Thirty five (95%) of 37 tumors were EBV positive. IFNG sequences were amplified from extracted DNA by polymerase chain reaction (PCR), and products visualized by ultraviolet light on agarose gels containing ethidium bromide, as described by Pravica et al. Statistical analysis was performed using Fisher exact test.

We found no significant difference in the incidence of IFNG polymorphic types between our PTLD patients and controls (Table 1): A/A was present in 32% of patients and 31% of controls; A/T, in 46% of patients and 41% of controls; and T/T, in 22% of patients and 28% of controls. Additional analysis of “early” (diagnosed < 1 year after transplantation; 35%) and “late” (diagnosed > 1 year after transplantation; 65%) cases separately did not demonstrate an association. Furthermore, there was no difference between the patients or controls and 181 healthy controls (A/A in 33%, A/T in 47%, and T/T in 20%).

PTLD is a histologically diverse tumor with a multifactorial pathogenesis. Intense immunosuppression and EBV seronegativity are the major risk factors. The A/A IFNG polymorphism is associated with low IFN-γ production, and Dierksheide et al and VanBuskirk et al postulate that low IFN-γ levels increase susceptibility of EBV-specific cytotoxic T lymphocytes to immunosuppression, thereby predisposing an individual to PTLD.

Our results presented here contrast those of Dierksheide et al and VanBuskirk et al in failing to show a significant increase of the A/A IFNG polymorphism in PTLD. This may, in part, be explained by the disparity in patient groups; their patients were all renal transplant recipients, whereas ours were more diverse (above). However, the discrepancy in results is most likely due to the small number of patients analyzed by Dierksheide et al and VanBuskirk.

| Table 1. Incidence of interferon γ + 874 A/T polymorphism in PTLD patients and controls |
|----------------------------------------|------------------|------------------|------------------|
|                                        | A/A polymorphism | No A/A polymorphism | Total   |
| Patients with PTLD, no. (%)            | 12 (32)          | 25 (68)           | 37 (100)        |
| Posttransplantation controls without PTLD, no. (%) | 34 (31) | 75 (69) | 109 (100)        |
| Healthy controls, no. (%)              | 60 (33)          | 121 (67)          | 181 (100)       |
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