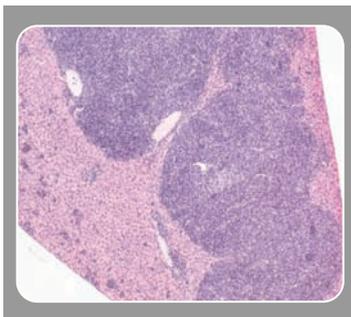


T cells in mouse follicular lymphoma

Common B-cell non-Hodgkin lymphomas (B-NHLs) arise by malignant transformation of defective germinal center (GC)-stage B cells.¹ These include follicular lymphoma (FL) and more aggressive Burkitt (or Burkitt-variant) and diffuse large B-cell lymphomas. A characteristic t(14;18) is detected in over 80% of FL, which causes overexpression of the *BCL2* cell survival gene by rearrangements with immunoglobulin (Ig) heavy chain locus control elements. Initially indolent, FL may transform to a more aggressive tumor with increasingly complex cytogenetics over time.

FL is also the most common B-cell lymphoma naturally arising in old mice and in *Eμ-Pim-1* transgenic mice. White pulp expansions of sIgM⁺/B220⁺/CD19⁺ GC B cells usually begin in the spleen and may contain large (centroblasts, immunoblasts), small (centrocytes), or a mixture of large and small tumor cells that lose the usual GC spatial relationships. Unlike human FL, naturally occurring mouse FLs are not associated with *Bcl2* gene overexpression and do not display a typical follicular pattern. Despite several attempts, a *BCL2*-based model of FL has not been generated in mice, until now.

In this issue of *Blood*, Egle and colleagues (page ___) describe a new model of FL by *Bcl2* overexpression using *VavP* control sequences. About 15% to 25% of mice developed a syndrome resembling au-



toimmune glomerulonephritis that was strain dependent. However, 37% to 50% of mice developed FL by 18 months of age following a florid GC hyperplasia.² Other hematologic tumors also occurred at lower frequencies, including plasma cell tumors, lymphoblastic or large B-cell lymphoma, thymic lymphoma, or histiocytic sarcoma. Interestingly, levels of the *Bcl2* transgene expression were independent of lymphomagenesis; rather, CD4⁺ T-cell help appeared essential for FL.

There are several exciting features in this valuable genetic model of human FL. The key seems to be pan-lymphoid *Bcl2* expression and time, which yield increased numbers of CD4⁺ T cells that support robust GC B-cell expansions. Antigenic stimulation through sIg, with associated somatic hypermutation (SHM), has been described previously in human FL but not mouse FL, which usually lacks SHM and GC-signature Bcl6 protein expression.³ Egle and colleagues show that antigenic selection is ongoing in this model, and the FL cells express the proliferating cell nuclear antigen (PCNA) GC-signature marker, features

similar to human FL. Furthermore, Egle et al suggest that increased CD4⁺ T cells in *VavP-Bcl2*, but not *Eμ-Bcl2*, transgenic mice support the premalignant GC expansion required to generate enough apoptosis-resistant B cells for a secondary transforming mutation. If this hypothesis is correct, why are T-cell expansions not part of human follicular lymphomagenesis? Is there a T-cell help mechanism in human GCs that is so powerful that it obviates the need for excess CD4⁺ T cells beyond those usually present? And what are the additional genetic/epigenetic mistakes that complement *Bcl2* overexpression to cause mouse FL? Do they have similar counterparts in human FL? This model, and one other that causes a spectrum of GC-based B-cell malignancies by overexpression of the *TCL1* oncogene in both B and T cells,⁴ provide systems for determining some of the most difficult mechanisms in early GC B-cell transformation.

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