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. 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 \( \text{BCL2} \) 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 \( \text{E}^{\mu}\text{-Pim-1} \) transgenic mice. White pulp expansions of sIgM+/H11001+/B220+/H11001+/CD19+/H11001 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 \( \text{Bcl2} \) gene overexpression and do not display a typical follicular pattern. Despite several attempts, a \( \text{BCL2} \)-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 \( \text{Bcl2} \) overexpression using \( \text{VavP} \) control sequences. About 15% to 25% of mice developed a syndrome resembling autoimmune glomerulonephritis that was strain dependent. However, 37% to 50% of mice developed FL by 18 months of age following a florid GC hyperplasia. 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 \( \text{Bcl2} \) 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 \( \text{Bcl2} \) 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. 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 \( \text{VavP-Bcl2} \), but not \( \text{E}^{\mu}-\text{Bcl2} \), 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 \( \text{Bcl2} \) 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 \( \text{TCL1} \) oncogene in both B and T cells, provide systems for determining some of the most difficult mechanisms in early GC B-cell transformation.

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