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Immunosurveillance of premalignant germinal center B cells

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Germinal centers (GCs) are intrinsically mutagenic sites of B-cell diversification and the origin of most B-cell lymphomas. However, whether they are subject to active immune surveillance has remained unknown. This question is central to follicular lymphoma pathogenesis and is exemplified by in situ follicular neoplasia (ISFN), a premalignant GC lesion that only rarely progresses to overt malignancy. ISFN therefore provides a unique human setting in which to test whether emerging lymphoma-prone GC B-cells are normally restrained by immune surveillance.
We found that human ISFN biopsies show enrichment of $CD8^+$ T-cells, consistent with endogenous immune control. Because ISFN is characterized by BCL2 translocation and frequent CREBBP mutations, key early genetic features of follicular lymphoma, we generated mice in which GC B-cells harbor BCL2 overexpression together with *Crebbp* deficiency. Longitudinal analysis in these mice showed that premalignant GC B-cells carrying these lesions are selectively eliminated by $CD8^+$ T-cells, establishing that GCs are not immune-privileged but instead are subject to active immune surveillance.

We next asked how this protective barrier is overcome during progression to overt lymphoma. Introduction of *Kmt2d* loss, a lesion enriched in established follicular lymphoma, abolished $CD8^+$ T-cell-mediated clearance and allowed premalignant GC B-cells to persist. Single-cell transcriptomic analysis of $PD\text{-}1^+CD8^+$ T-cells identified a mechanism of immune escape in which progressive oncogenic evolution induces TGFβ signaling in $CD8^+$ T-cells, impairing their differentiation into effector cells.

Together, these findings identify $CD8^+$ T-cell GC surveillance as a previously unrecognized barrier lymphomagenesis and show that follicular lymphoma evolution requires stepwise genetic escape from this constraint.