Abstract #28 | Poster

Immunosurveillance of Precancerous Germinal Center B Cells

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Most Non-Hodgkin Lymphomas (NHLs) originate from germinal center (GC) or post-GCB cells. While the immune system actively targets precancerous cells in epithelial-derived cancers, it is uncertain if the same applies to precancerous GCB cells. Knowledge on Follicular Lymphoma (FL), the most common low-grade NHL derived from GCB cells, prompted us to develop novel mouse models to mimic the precancerous state. In FL, BCL2 translocation and CREBBP loss-of-function (LoF) mutations are characteristic of a precancerous state. These mutations can be detected years before FL diagnosis, hinting at potential immune involvement in preventing FL.

Our research affirms the effectiveness of the mouse models in replicating the FL precancerous state. Mice with BCL2 overexpression (OE) alone or together with CREBBP LoF showed increased GCB cell expansion, up to 6-fold compared to control. This expansion involved reduced GCB cell death rather than increased proliferation, consistent with FL slow-growing nature. Mice harboring mutant GCB cells also exhibited a significant increase in memory B cells, up to 20-fold when compared to control. As the GC reaction progressed, the impact of CREBBP LoF emerged, profoundly altering GCB cell phenotypes, and triggering a remarkable surge in cell expansion, escalating up to 80-fold compared to mice with BCL2 OE alone or control. However, this hyperplasia was swiftly followed by a decline, indicative of immunosurveillance targeting precancerous GCB cells. Prior to the reduction of GCB cells with BCL2 OE and CREBBP LoF, we observed a notable expansion of PD1+ CD8+ T cells expressing granzyme A and perforin. These activated CD8+ T cells also expressed CXCR5, facilitating their infiltrating into the B cell follicle to specifically eliminate GCB cells with BCL2 OE and CREBBP LoF. Preemptive depletion of CD8+ T cell effectively prevented the loss of precancerous GCB cells.

The examination of the GC reaction over time provided new perspectives into the immunosurveillance of precancerous GCB cells and FL development. The data supports the concept that precancerous GCB cells must overcome robust anti-tumor immunity for Lymphoma to ensue. This knowledge offers potential explanation for the infrequent and extended duration of the transition from precancerous GCB cells to full-blown FL. These models provide a foundation to explore mechanisms underlying immune evasion by precancerous GCB cells.