Abstract #27 | Poster

Unveiling Follicular Lymphoma's Common Progenitor Cells

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Follicular lymphoma (FL) is the most prevalent low-grade germinal center (GC) derived non-Hodgkin lymphoma. FL poses a significant challenge in oncology, evading cure with current therapeutic options. Through meticulous phylogenetic analysis of successive human FL tumors, evidence has emerged regarding the existence of common progenitor cells (CPCs). These cells serve as the foundation for each subsequent FL relapse, displaying notable resistance to current treatment methods. The targeting of these resistant CPCs is imperative to pave the way for the cure of FL.

To understand the intricate dynamics underlying CPC formation and the evolution of FL, we engineered mouse models that faithfully replicate the early and recurrent gene mutations observed in FL, including BCL2 translocation, CREBBP and KMT2D loss-of-function (LoF) mutations (BCK mice). In comparison to control (Ctrl) counterparts, BCK mice exhibited a remarkable increase in GC B cell and memory B cell (MBC) expansion, reaching up to an 80-fold augmentation. To understand the populations of mutant B cells resistant to chemo-immunotherapy, we subjected mice to a standard human-like treatment regimen of R-CHOP (Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, Prednisone). Administration of the mouse-adapted R-CHOP therapy resulted in the complete depletion of B cells in Ctrl mice. However, in contrast, treatment of BCK mice unveiled the emergence of a resistant B cell population. Notably, while mock-treated BCK mice exhibited an equivalent enrichment of cells with both a GC and MBC phenotype, R-CHOP-treated mice predominantly had cells with an MBC phenotype among the resistant cells. We have employed cutting-edge methodologies, including CITE-seq, to dissect the molecular signatures of these BCK therapy-resistant cells. Furthermore, we have introduced an innovative in vitro platform that harnesses a GC B cell culture system to amplify CPCs, facilitating subsequent high-throughput drug screening.

This approach is poised to identify specific vulnerabilities within the CPC population, paving the way for the development of therapies tailored to overcome FL resistance mechanisms. Through these concerted efforts, we edge closer to the long-awaited goal of discovering a definitive cure for Follicular Lymphoma.