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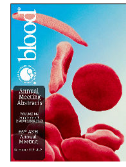

The 65th ASH Annual Meeting Abstracts

POSTER ABSTRACTS

603.LYMPHOID ONCOGENESIS: BASIC

T-Cell Signaling Mediates the Epigenetic Priming of Germinal Center B-Cell Plasticity and Stem Functionality

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Chemo-immunotherapy can prolong life expectancy of patients with Diffuse Large B-cell Lymphomas (DLBCL). However, the emergence of donor-derived lymphoma cases after stem cell transplantation and the relapse of a third of DLBCL patients, strongly suggests the existence of persisting lymphoma repopulating cells (LRC) with stem-like functionality. This apparently controversial concept arises from the fact that DLBCLs originate from mature rather than progenitor cells. Identifying the biological and epigenetic features of these elusive LRC, and how they arise from normal germinal center (GC) B cells, is therefore critical and remains underexplored.
Although fully mature, GC B cells naturally manifest remarkable phenotypic plasticity as compared to other cell types. We hypothesized that this plasticity reflects stem-like programming and functionality. Along these lines, we found that GC B cells are uniquely enriched for pluripotent stem cell transcriptional signatures, and increased chromatin accessibility at stem cell enhancers. We reasoned that the capacity to undergo induced Pluripotent Stem Cells (iPSC) reprogramming could serve as a surrogate assay for stem-like plasticity. Therefore, we investigated the potential of GC B cells to form iPSCs using a doxycycline-dependent mouse strain that enables the inducible expression of Yamanaka transcription factors (TF) in any given cell. Strikingly, GC B cells isolated from our mice manifested a 10-fold ($p<0.0001$) increase in iPSC reprogramming as compared to other mature B cells.
GC B cells are a heterogenous mix of functionally distinct subpopulations. Using single cell RNA-seq and iPSC assays in sorted cells, we noted that the rare population (˜3%) of GC B cells selected by T-cell help manifested the stem-like transcriptional profile and iPSC reprogramming phenotype. Moreover, blocking T-cell help during the GC reaction *in vivo* using CD40 blockade abrogated iPSC forming capacity. Lymphoma-associated *EZH2* ^{Y641F} mutations impair GC B-cell interactions with T $_{FH}$ cells due to aberrant repression of immune synapse genes. Accordingly, *EZH2* ^{Y641F} GC B cells manifested loss of the iPSC phenotype. T-cell help induces MYC in GC B cells. However, induction of MYC in mature naïve B cells did not confer them with iPSC potential indicating that other mechanisms must be at play.
Lymphoma-associated *Btg1* ^{Q36H}mutations confer fitness in GC B cells by enhancing their response to T-cell help. Reciprocal to *EZH2* ^{Y641F}, *Btg1* ^{Q36H}mutant GC B cells manifested further significant increase in iPSC formation. Performing multi-ome (simultaneous single-cell RNAseq and ATACseq) studies in GC B cells revealed massive gain in chromatin accessibility of *bona fide* stem cell super-enhancers in GC B cells that received T-cell help. There was also a reduced accessibility at genes that maintain B-cell lineage (e.g. Pax5) and GC phenotypes (e.g. Foxo1).
Finally, lymphoma-associated Histone 1 mutations induce upregulation of stem cell programs in GCs and could enhance iPSC reprogramming in fibroblasts. We therefore hypothesized that H1 deficiency would overcome the GC dependency

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on T-cells for their plasticity phenotype. Indeed, increased iPSC formation occurred across all GC subpopulations in $H1_{C/E}^{-/-}$ (HIST1C/HIST1E knockout) mice. We speculate that restricting plasticity to B cells under selection by T cells, limits the potential for GC B cells to acquire high levels of plasticity, hence reducing the potential for these cells to initiate lymphomas. Consistent with this notion, we found that DLBCL patients enriched for these stem cell signatures manifested inferior clinical outcomes.

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