Impaired germinal center confinement and plasma cell differentiation by MYC activation is critical for Burkitt lymphomagenesis

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Abstract

Interference with plasma cell (PC) differentiation is considered a hallmark of activated B-cell (ABC) diffuse large B-cell lymphoma (DLBCL), in contrast to other germinal center (GC) B-cell lymphomas. ABC-DLBCLs have enforced NF-κB activity, which normally triggers B-to-PC differentiation. However, this is prevented by *BLIMP1*-loss or by enforced BCL6 expression, which represses *BLIMP1*.

Here, we hypothesized that interference with PC differentiation is an unappreciated general hallmark of GC-derived lymphomagenesis. The prototypical GC-derived Burkitt Lymphoma (BL) is devoid of NF-κB activity but displays increased PI3K signaling; primarily thought to enhance cancer cell survival. However, like NF-κB, PI3K can trigger B-to-PC differentiation. BLs also display MYC overexpression, increasing cell proliferation, and BCL6 expression as part of the GC program. It is unknown if BCL6 suffices to curb a PI3K-driven PC differentiation pressure or instead MYC is required.

MYC forms with MIZ1 a transcriptional repressor complex in GC B-cells at the positive selection stage, where B-to-PC differentiation is initiated. We also found that MYC and MIZ1 are ubiquitously expressed in primary BLs. We generated mice overexpressing PI3K in GC B-cells together with MYC or a MYC mutant (vd) that cannot interact with MIZ1. Compared to MYCvd, MYC restricted pre-PC/PC formation, impaired GC confinement and exacerbated B-cell dissemination in blood; phenotypes reminiscent of BL mutations impairing S1PR2 signaling. Single cell RNAseq revealed differential enrichment for B-cell receptor signaling, acting cytoskeleton and Rho pathways; known regulators of PC differentiation and cell motility. In the long-term, MYCwt synergized with PI3K for BL development, whereas MYC_{VD} developed PC hyperplasia, and was unable to form BL.

Thus, an unappreciated PI3K-driven PC differentiation pressure exists and MYC-MIZ1 complexes counteract this effect, ensuring BL development. Knowledge on the regulation and targets of MYC-MIZ1 complexes may uncover truly novel therapeutic opportunities for BL and other GC B-cell lymphomas.