Immunoglobulin class-associated BCR silencing in high-grade germinal center B cell lymphomas

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Abstract

B cell receptor (BCR) critically contributes to the growth of multiple types of B cell-Non-Hodgkin lymphomas (B-NHL), representing a preferred target of therapy. BCR importance for high-grade B cell lymphomas (HGBL) remains enigmatic. Screening for immunoglobulin (Ig) expression in germinal center (GC)-derived HGBL identified 30 out of 51 cases (59%) with undetectable Ig heavy (H) chain (IgH^{UND}) protein in Double-hit (DH) lymphomas (DHL) with MYC/BCL2 (MB2) rearrangements and Triple-hit lymphomas (THL). Among MB2 DHL/THL, Ig-positive cases consistently expressed IgM/D BCRs, whereas the IgH^{UND} counterparts systematically completed IgG/E/A isotype switching. IgH^{UND} HGBL malignant cells transcribed potentially productive IgH variable (V) gene rearrangements with mutational traits indicating weakened preservation of Ig structural integrity. Most IgH^{UND} DHL/THL presented transcriptomic and mutational profiles enforcing the GC dark zone (DZ) B cell program operating within an underrepresented immune contexture. IgH^{+} MB2 DHL/THL presented a GCB light-zone-like (LZ) transcriptional profile featuring an immune-rich microenvironment permeated by immunosuppressive signals. Single cell studies indicated lowest BCR expression in IgH-switched DZ GCB cells. Altogether, the data support a scenario whereby acquisition of BCL2 and MYC rearrangements drives the transformation of distinct GC B cells subsets differing in IgH class expression, with impact on BCR levels. In particular, whereas switched immunoglobulins are associated with outgrowth of MYC/BCL2 lymphomas from DZ B cells undergoing BCR downmodulation, IgM expression promotes MB2-driven transformation of LZ-like B cells arrested prior to DZ re-entry, or exit from the GC reaction. The conservation in IgH^{UND} MB2 DHL/THL of productive Ig V-gene rearrangements with signs of weakened selection for BCR integrity identifies a mechanism of lymphoma dependence on isotype-switched IgH chains, which operates in the absence of measurable BCR. Our data have clinical implications, demanding routine assessment of IgH status determination for optimal selection of GCB-derived lymphoma patients suitable for antibody-based therapies targeting BCR components.