Title: Defining the role of Epstein-Barr virus (EBV) in diffuse large B-cell lymphoma (DLBCL) pathogenesis

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Scientific Abstract:

Background: Diffuse large B-cell lymphoma (DLBCL) is the most common aggressive lymphoma. DLBCL is not a single disease, but a group of histologically similar yet genetically distinct cancers with unique prognostic and therapeutic features. The recently defined genetic landscape of DLBCL includes at least seven subtypes, but does not consider Epstein-Barr virus (EBV) status, despite up to 14% of DLBCL being EBV-positive and EBV's known role in B cell lymphomagenesis. We performed a reanalysis of published DLBCL genetic data to molecularly define EBV-positive DLBCL, and characterized its cell line models.

Methods: Published whole exome (WES) and RNA sequencing data were analyzed in silico to identify EBV-positive (EBV+) DLBCL tumors. Differential analyses of the mutation and transcriptomic profiles of the viral and cellular genes of EBV+ and EBV-negative tumors were performed. WES, RNAseq, and immunoblotting were performed on EBV+ DLBCL cell lines Farage, BCKN1, IBL1, and Val to assess the extent to which they accurately reflect profiles from EBV+ DLBCL tumors.

Results: We identified 20 EBV+ DLBCLs in the NCI cohort (n=481). EBV+ DLBCL is significantly enriched within the BN2 subtype (p=0.0051, Barnard's test) and comprised ~1/3 of EBV+ DLBCLs. The remaining ~2/3 are distinct from currently defined subtypes. Several differentially mutated genes within the BN2 tumors were found to correlate with EBV status. These include subtype-defining genes, genes involved in B cell receptor signaling and cell cycle regulation, and those known to be downstream of EBV. This finding supports our hypothesis that EBV oncogenes can functionally compensate for specific cellular mutations in DLBCL. Preliminary transcriptomic analyses found EBV+ DLBCL to have increased inflammatory and immune signatures, and JAK/STAT and NF-kB signaling. By RNAseq and immunoblot we determined the cell lines Farage, BCKN1, and IBL1 to have EBV Latency III, while Val has Latency II. All lines are infected with EBV Type 1 strain, except IBL1 which harbors EBV Type 2. Genes mutated in BCKN1, IBL1, and Val are consistent with 'Unclassified' subtype, whereas Farage is ST2 subtype.

Conclusion: EBV+ DLBCL, like DLBCL itself, is not a single disease. A subset of EBV+ DLBCL is enriched within, and likely have a shared pathogenesis with, BN2 DLBCL. The remaining EBV+, 'Unclassified' DLBCL may constitute a novel subtype(s). EBV status correlates with distinct mutation and gene expression profiles, including subtype-defining features. Thus, integrating EBV status into the classification of DLBCL is likely to better inform tumor subtyping and molecular studies, and resolve the specific role(s) of EBV in DLBCL. Characterization of EBV+ DLBCL cell lines revealed limited correspondence with EBV+ tumors, underscoring the need for additional cell line models to support in vitro studies of EBV+ DLBCL.

Written Lay Abstract:

Lymphoma is a cancer that starts in our immune system. Aggressive lymphoma grows and spreads quickly. Diffuse large B-cell lymphoma (DLBCL) is the most common type of aggressive lymphoma. DLBCL is a group of cancers that have different genetic origins and need to be treated differently. Researchers know there are at least seven different types of DLBCL, but there are likely more. When someone is infected with a virus called Epstein-Barr virus (EBV), healthy B-cells can change and lead to cancer. In this study, researchers wanted to see if EBV should be a factor used to define types of DLBCL, which could help doctors find the specific cancer treatment a patient needs.

The researchers in this study used genetic data from 481 tumors from people with DLBCL. They found 20 of these DLBCL cancers were caused by EBV. About one third (1/3) of these DLBCL cancers caused by EBV can be grouped under the existing type called BN2. The researchers found that two thirds (2/3) of the 20 EBV-caused tumors were different from existing types of DLBCL. Because of the specific genetics of these types found, patients may benefit from different cancer treatments than those that are used to treat DLBCL of all types.

The fact that two thirds of the DLBCL cancers caused by EBV cannot be easily defined by a current DLBCL type means that it could be helpful to include EBV infection in defining types of DLBCL. These findings tell us that researchers need new ways to study DLBCL cancers caused by EBV, with the hope of understanding what treatments would be best for these patients.

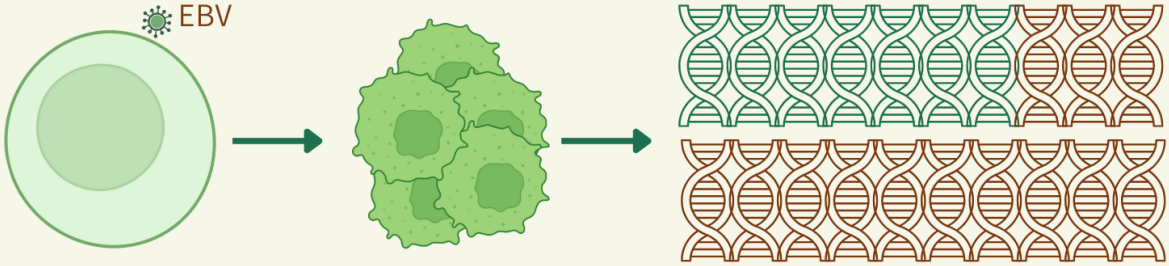
Visual Lay Abstract:

Epstein-Barr Virus and Lymphoma

Diffuse large B-cell lymphoma (DLBCL) is the most common type of aggressive lymphoma, a cancer of the immune system.

Different genetic types of DLBCL can be treated differently.

Epstein-Barr Virus (EBV) is very common, and usually does not harm us. However, in rare cases it can lead to cancer. Researchers want to know how EBV affects DLBCL is typed and treated.



Healthy B-Cell

EBV changes B-cell and leads to cancer, such as DLBCL

⅔ of the 20 different DLBCL gene types found in this study did not match current genetic definitions

Epstein-Barr Virus infection can change genetic type of DLBCL.

To better understand and treat DLBCL,
we should consider Epstein-Barr Virus infection.

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