

Epstein-Barr virus orchestrate the Tumor Microenvironment of Burkitt Lymphoma

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Abstract

The tumor microenvironment (TME) plays a central role in B-cell lymphomas, and it is highly variable with regards to immune-suppressive and/or anti-inflammatory cells. Several evidence enhances the idea that EBV influence TME by evolving multiple effective countermeasures to evade immune system and the consequent activation of antiviral cascades. The contribution of immune effector and immune suppressor components of the TME in Burkitt Lymphoma (BL) remains poorly understood.

The aim of the present work was to thoroughly characterize the immune landscape of subtypes of BL. We studied 33 BL cases: 7 BL EBV-positive with granulomatous reaction, 8 BL EBV-positive, 8 BL EBV-, 10 BL with 11q aberration.

We performed the gene expression profiling (GEP) of 770 immune-related genes using the Nanostring nCounter PanCancer Immune Profiling Panel on FFPE samples.

Based on principal component analysis (PCA), BL subtypes clustered into 3 groups: BL EBV-positive with granulomatous reaction cases (**cluster 1**), BL EBV-positive cases (**cluster 2**), BL with 11q aberration cases and BL EBV-negative cases (**cluster 3**). Interestingly, GEP of BL samples revealed a high degree of heterogeneity showing differently expression in functional categories such as immune-response, proliferation, cell cycle and apoptosis.

Combining GEP and multi-parametric immunohistochemistry (IHC), we can appreciate the up-regulation of genes inducing M2 polarization in BL EBV-positive than BL EBV-negative, giving rise to a tolerogenic response. Additionally, overexpression of immun checkpoints (ICPs) PD-L1 and CTLA4 can induce T cell exhaustion and immune escape in EBV-associated lymphomas. Interestingly, cases with granulomatous reaction showed a down-regulation of genes involved in immunescape, and this is in line with favorable outcome and spontaneous regression in such cases. Finally, our preliminary results may provide insights on TME within the different subtypes of BL and they will be confirmed in a large cohort of samples.