EPSTEIN-BARR VIRUS: FROM KISSES TO CANCER, AN INGENIOUS IMMUNE EVADER

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EBNA2 is a well-known driver of B-cell transformation. It is a key transcription factor able to induce viral and host gene expression, leading to cell proliferation and evasion from anti-tumor immune surveillance. We have previously shown that EBNA2 induced the immune-checkpoint (IC) Programmed Death Ligand 1 (PD-L1) expression by downregulating miR-34a [1-3]. In this study, we have investigated if EBNA2 may have any effect on the expression of another IC, the T cell co-stimulator ligand (ICOSLG) in B-cell lymphoma cells. Flow cytometry analysis showed that ICOSLG expression was decreased in the presence of EBNA2 in DLBCL and BL cell lines. *In silico* analysis indicated the presence of a miR-24 binding site in the 3'UTR of ICOSLG[4]. First, we confirmed increased miR-24 expression in EBNA2 transfected B-cell lymphoma cells by real time qPCR. Assays with a lentiviral luciferase reporter system carrying the 3'UTR ICOSLG sequence validated the miR-24 binding to this sequence. Expression of ICOSLG as well as of c-myc (another miR-24 target) was reconstituted as a result of miR-24 inhibition. Immunostaining of EBV/EBNA2 positive B-cell lymphoma biopsies support our in vitro data.
Our results show how on the one hand, the virus uses EBNA2 to influence miR-24 in DLBCL and BLs to subvert immune recognition by reducing ICOSLG and on the other, increase proliferation by decreasing the pro-apoptotic c-myc with the same miRNA. We propose that inhibition of miR-24a could be important for a miRNA-based therapy in B-cell lymphoma to simultaneously release anti-tumor immunity and pro-apoptotic signals.

References

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