Dynamic Roles of Epstein-Barr Virus Reactivation: Identifying Novel Mechanisms of EBV-Positive Lymphoma Progression and Treatment

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Epstein-Barr virus (EBV) is a prevalent herpesvirus which is strongly implicated in the development of numerous cancers. Central to tumor progression, hypoxia has also been demonstrated to play a significant role in the EBV life cycle by inducing a switch from latent to lytic replication. Using an in vitro hypoxia model, the present study showed that HIF-1α-induced EBV lytic reactivation led to a significant increase in VEGF-A expression compared to EBV– lymphoma cells. This supports a novel role for lytic infection in promoting vascular instability and tumor growth. Targeting the virus using the antiviral drug acyclovir (ACV) may offer an alternative therapeutic strategy for EBV+ cancers. While data presented here indicate ACV is ineffective in context of low-level viral reactivation, high-level induction of lytic gene expression using sodium butyrate (SB) and phorbol 12-myristate 13-acetate (PMA) was achieved in EBV+ lymphoma cells, rendering them susceptible to ACV. However, lytic reactivation also appeared to increase the metastatic potential of lymphoma cells as seen by the up-regulation of LMP1, an EBV oncogene, and VEGF-A, a potent inducer of vascular permeability. Introduction of the phenolic compound resveratrol inhibited LMP1 and VEGF-A expression, demonstrating its potential to reduce the risk of complications associated with lytic EBV infections. Taken together, these findings support novel roles for EBV reactivation in lymphoma progression and suggest therapeutically targeting this form of infection may offer an effective alternative to chemotherapy in the treatment of EBV+ disorders.

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