# SYNCYTIN-1 PROMOTES EPSTEIN-BARR VIRUS LYTIC REPLICATION THROUGH PI3K/AKT SIGNALING

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The human endogenous retroviral element *ERVW1* encodes the ancestral viral envelope protein Syncytin-1 that now serves a canonical role in the human placenta. While generally repressed after embryonic development, Syncytin-1 is de-repressed in some cancers or auto-inflammatory conditions, most notably multiple sclerosis. Syncytin-1 can also be upregulated by exogenous viral infections, such as with EBV or SARS-CoV-2. With EBV underlying a number of lymphomas and cancers, and recent studies linking EBV infection to long COVID and multiple sclerosis, we find that Syncytin-1 gene expression is higher in $EBV^+$ lymphoblastoid and Burkitt lymphoma cells undergoing EBV lytic activation. Knockdown of Syncytin-1 leads to a defect in viral lytic gene expression, protein expression, and virus production, while overexpression of Syncytin-1 results in enhanced lytic readouts. Investigating the mechanism of these pro-lytic effects reveals an association of Syncytin-1 levels with the activation of the phosphatidylinositol 3 kinase (PI3K)/protein kinase B (AKT) pathway, and knockdown of Syncytin-1 leads to a decrease in phosphorylated PI3K/Akt effector proteins. Further, Syncytin-1 cannot enhance the activation of the lytic cascade in the absence of the PI3K/Akt signaling pathway. While Syncytin-1 overexpression alone is unable to trigger the EBV lytic cycle, we find that Syncytin-1 and the PI3K/Akt pathway promote the enrichment of activating transcription factors at the viral promoter of *BZLF1* encoding the EBV latent-to-lytic switch ZEBRA. Our findings thus reveal a novel function for Syncytin-1 that promotes EBV lytic activation via a known cellular signaling pathway. With the potential to enhance EBV lytic activation and transmission, viral dysregulation of and dependency on Syncytin-1 is likely to influence the development of EBV-associated malignancies, long COVID, and multiple sclerosis.