SIRT2 INHIBITION SUPPRESSES LYTIC AND LATENT EBV INFECTION

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Sirtuins are evolutionarily conserved deacylases that modulate the growth of both DNA and RNA viruses [1]. Evrys Bio recently identified SIRT2 inhibitors that display broad-spectrum antiviral activity including on herpesviruses such as cytomegalovirus. Given the dearth of EBV antiviral therapeutics, we sought to determine the effect of sirtuin modulation on lytic and latent models of EBV infection. In two distinct EBV lytic reactivation models (Akata BL anti-Ig and P3HR1 BL Z-HT expression), we observed a dose dependent inhibition of viral gene expression and particle production by the SIRT2 inhibitors FLS-359 and FLSX-008, but not a structurally related molecule with no anti-SIRT2 activity, FLSX-009. Given the role of SIRT2 in B-cell lymphomagenesis, we also sought to investigate SIRT2 modulation in EBV latent infection models. Primary B-cell infection with EBV generates lymphoblastoid cell lines (LCLs) as an established model of lymphoma initiation in the immune suppressed. We found that LCL growth was suppressed in a dose-dependent manner by SIRT2 inhibitors and BrdU assays supported a role for G1/S growth arrest with minimal induction of apoptosis. Furthermore, primary B-cell proliferation induced by EBV and TLR9 activation through CpG was inhibited by SIRT2 inhibition as well. We performed bulk RNAseq analysis of both lytic (Akata) and latent (LCL) models of EBV infection treated with the SIRT2 inhibitors and found suppressive effects on cell cycle markers with an increase in metabolic stress and amino acid starvation transcriptional programs. Taken together, SIRT2 inhibition shows promise as a novel hist-directed therapeutic option to inhibit EBV.

[1] Koyuncu E, Budayeva HG, Miteva Y V, et al., 2014, *MBio*., 5(6), 02249-14.