EPSTEIN-BARR VIRUS INFECTION OF RESTING B CELLS REQUIRES ACTIVATION OF MULTIPLE SIGNALING PATHWAYS THAT CONVERGE ONTO THE STRESS PROTEIN ZFP36L1

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The Epstein-Barr virus efficiently infects primary B cells and the transformation process that follows infection has been extensively characterized [1]. However, little is known about the very early events that take place after virus binding. To better characterize these early steps of infection, we performed label-free mass spectrometry on B cells exposed to a series of mutants which allowed us to block infection at different stages: virus binding, fusion with the target cell and virus entry, genome transfer, and latent viral gene expression.

Exposure of primary B cells to a fusion-deficient virus led to the activation of intracytoplasmic tyrosine kinases and of STAT3, accompanied by a modest secretion of two pro-inflammatory cytokines, IL-6 and TNFα. Cellular entry of DNA-free virus-like particles (VLP), which mimic the release of tegument proteins during wild-type infection without viral DNA transfer to the nucleus, showed activation of the p38-MK2 pathway and of the stress response protein ZFP36L1, a known regulator of pro-inflammatory transcripts containing AU-rich sequences in their 3´UTR [2]–[4]. Consequently, VLP infection was not accompanied by additional cytokine release compared to fusion-deficient virus infection.

Infection with a virus that is able to infect cells and inject its DNA into the host' nucleus but cannot initiate latency was not sufficient to further boost the activation of the p38-MK2-ZFP36L1 axis and substantially increase IL-6 and TNFα secretion. In contrast, infection with a wild type virus doubled cytokine release and was dependent on the establishment of latency. We found that activation of STAT3 and p38-MK2 was necessary to efficiently insert the viral DNA into the nucleus and initiate virus transcription. Finally, by using a library of viral mutants, we could show that activation of the above described signaling pathways is mediated by several envelope and tegument proteins. Our study identifies a molecular pathway whose activation leads to virus infection and dampening of the immune response against the virus. It also shows the complexity of the interactions between the virus and its host upon virus entry and opens opportunities to efficiently prevent infection.

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