proceedings

Abstract

Reactivation of Herpes Simplex Virus (HSV) from Latency in Response to Neuronal Hyperexcitability †

Sean Cuddy [1], Austin Schinlever [2], Sara Dochnal [2], Jon Suzich [2], Mina Farah [2], Chris Boutell [3] and Anna Ruth Cliffe [2,*]

[1] Neuroscience Graduate Program, University of Virginia, Charlottesville, VA 22903, USA; src4da@virginia.edu
[2] Department of Microbiology, Immunology and Cancer Biology, University of Virginia, Charlottesville, VA 22903, USA; ars3jy@virginia.edu (A.S.); sd9fb@virginia.edu (S.D.); jbs4de@virginia.edu (J.S.); mf4rf@virginia.edu (M.F.)
[3] MRC-University of Glasgow Centre for Virus Research, Garscube Campus, Glasgow G61 1QH, Scotland, UK; chris.boutell@glasgow.ac.uk
* Correspondence: ac2nm@virginia.edu
† Presented at Viruses 2020—Novel Concepts in Virology, Barcelona, Spain, 5–7 February 2020.

Published: 19 June 2020

Abstract: Herpes Simplex Virus (HSV) establishes a latent infection in neurons, in which viral transcription is restricted and viral promoters are associated with heterochromatin. In response to certain stimuli, the virus reactivates to permit transmission. The exact physiological triggers of reactivation, the cell signaling pathways involved, and how signals act on heterochromatin-associated lytic promoters, are not understood. Previously, we identified a role for a neural stress pathway involving DLK and JNK activity in HSV reactivation, triggered by nerve growth factor (NGF) deprivation. Reactivation was associated with a JNK-dependent histone phospho/methyl switch on lytic gene promoters. Because the same histone phospho/methyl switch occurs in cortical neurons following hyperexcitability (triggered by forskolin), we examined whether HSV reactivation was linked to hyperexcitability, and the contribution of JNK activity and histone phosphorylation. Using our primary neuronal model of HSV reactivation, we found that forskolin triggered DLK/JNK-dependent reactivation via a pathway that was distinct from NGF deprivation. The initial burst of HSV lytic gene expression in response to forskolin occurred independently of histone demethylase activity, and was accompanied by a histone phospho/methyl switch. To determine whether forskolin-mediated reactivation was linked to neuronal activity, we investigated the contribution of ion channel activity. Inhibition of voltage-gated potassium and sodium channels, or hyperpolarization-activated cyclic nucleotide-gated channels, prevented forskolin-mediated reactivation. In addition, hyperexcitability, resulting from the removal of a tetrodotoxin block, triggered HSV reactivation in a DLK/JNK-dependent manner. We next investigated whether physiological triggers induce HSV reactivation via hyperexcitability. IL-1 induced DNA damage associated with hyperexcitability in adult neurons. IL-1 also triggered DLK/JNK-dependent HSV reactivation, which was dependent on ion channel activity. Therefore, these data indicate that neuronal hyperexcitability in response to physiological stimuli, such as inflammation, trigger HSV reactivation, and mark out the activation of DLK/JNK and a histone phospho/methyl switch as key events in the hyperexcitability-mediated reactivation.

Keywords: Herpes simplex virus reactivation; IL-1; histone phosphorylation