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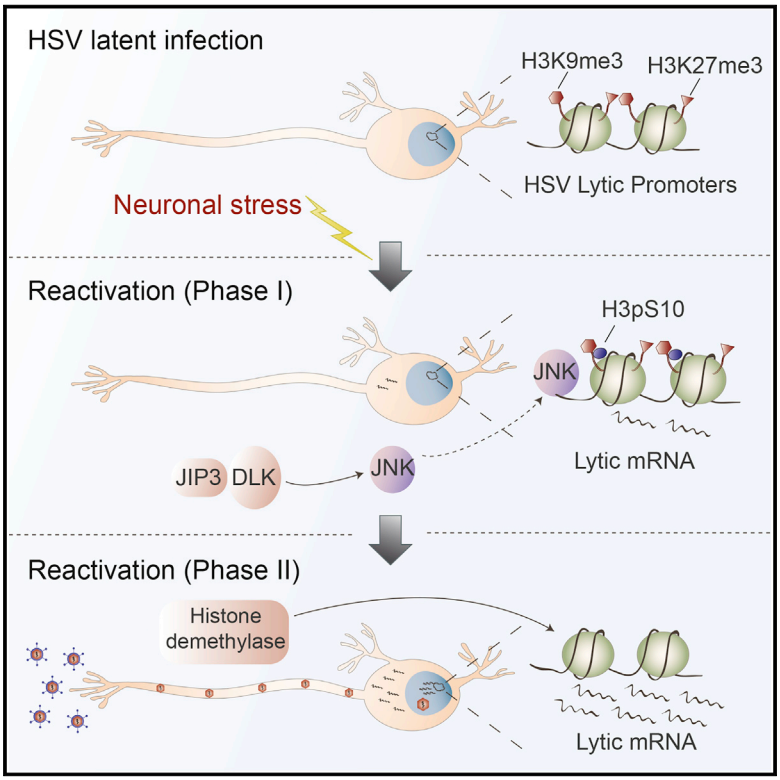
Neuronal Stress Pathway Mediating a Histone Methyl/Phospho Switch Is Required for Herpes Simplex Virus Reactivation

Graphical Abstract



Highlights

- Neuronal-specific JNK stress pathway is critical for HSV reactivation from latency
- JNK is required for the first phase of HSV lytic gene expression in reactivation
- First phase of lytic gene expression is independent of histone demethylase activity
- JNK signaling results in a histone methyl/phospho switch on HSV lytic gene promoters

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In Brief

Stress stimulates HSV reactivation from latent infection through unknown mechanisms. Cliffe et al. show that a neuronal stress pathway involving cJun N-terminal kinase (JNK) activation is crucial for HSV reactivation. JNK signaling induces histone phosphorylation on repressed viral promoters, therefore linking cell stress with initial stimulation of viral gene expression.

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Neuronal Stress Pathway Mediating a Histone Methyl/Phospho Switch Is Required for Herpes Simplex Virus Reactivation

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SUMMARY

Herpes simplex virus (HSV) reactivation from latent neuronal infection requires stimulation of lytic gene expression from promoters associated with repressive heterochromatin. Various neuronal stresses trigger reactivation, but how these stimuli activate silenced promoters remains unknown. We show that a neuronal pathway involving activation of c-Jun N-terminal kinase (JNK), common to many stress responses, is essential for initial HSV gene expression during reactivation. This JNK activation in neurons is mediated by dual leucine zipper kinase (DLK) and JNK-interacting protein 3 (JIP3), which direct JNK toward stress responses instead of other cellular functions. Surprisingly, JNK-mediated viral gene induction occurs independently of histone demethylases that remove repressive lysine modifications. Rather, JNK signaling results in a histone methyl/phospho switch on HSV lytic promoters, a mechanism permitting gene expression in the presence of repressive lysine methylation. JNK is present on viral promoters during reactivation, thereby linking a neuronal-specific stress pathway and HSV reactivation from latency.

INTRODUCTION

Herpes simplex virus (HSV) persists for the lifetime of the host in the form of a latent infection in peripheral neurons (Knipe and Cliffe, 2008; Roizman et al., 2013). Periodically, HSV must re-enter the lytic phase of replication in order to produce progeny virus for dissemination, a process known as reactivation. However, during latent infection, the viral lytic genes are extensively downregulated and their promoters assembled into repressive heterochromatin (Cliffe et al., 2009; Kwiatkowski et al., 2009; Wang et al., 2005). Therefore, reactivation requires viral lytic gene expression to be induced from silenced promoters in the absence of viral proteins.

The earliest events in HSV reactivation are poorly understood, but recent work suggests that while similarities exist, there are several differences in the mechanisms of HSV gene expression during reactivation versus de novo lytic infection (Roizman et al., 2013). During lytic replication, over 70 viral gene products are expressed in a cascade-dependent fashion. Recruitment of the cellular transcriptional machinery is dependent on both cellular and viral (HSV immediate-early activator, VP16) transcriptional transactivators to promote expression of the immediate-early (IE) mRNAs. Viral early (E) gene expression occurs following the synthesis of the IE proteins, and finally late (L) gene expression is dependent upon viral DNA replication (Roizman et al., 2013). In contrast, during the early stages of reactivation the initial wave of lytic gene expression is not necessarily dependent upon VP16 expression (Kim et al., 2012). In addition, E and L gene expression can occur in the absence of viral protein synthesis (Du et al., 2011; Kim et al., 2012; Thompson et al., 2009), and L gene expression is not dependent on viral DNA replication (Kim et al., 2012). This initial phase of viral gene expression appears to represent an event that is distinct from full reactivation (i.e., the production of infectious virus), and has been termed phase I or animation (Kim et al., 2012; Penkert and Kalejta, 2011). During phase I, the observation that all three classes of viral genes are induced in the absence of viral protein synthesis suggests that host cell proteins initiate this process.

Although cellular proteins, including histone demethylases, have been found to be required for HSV reactivation (Hill et al., 2014; Liang et al., 2009, 2012, 2013; Messer et al., 2015), as yet no direct link has been identified between a reactivation stimulus and the earliest induction of lytic gene expression. Reactivation of HSV can be trigged by different forms of neuronal stress including nerve growth factor (NGF) deprivation through