Virology 479-480 (2015) 555–561

Contents lists available at ScienceDirect

Virology

journal homepage: www.elsevier.com/locate/yviro

Review

# Dynamic modulation of HSV chromatin drives initiation of infection and provides targets for epigenetic therapies

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ARTICLE INFO

*Article history:*
Received 26 November 2014
Returned to author for revisions
25 January 2015
Accepted 30 January 2015
Available online 18 February 2015

*Keywords:*
Herpes simplex virus
Chromatin
Demethylase
LSD1
JMJD2
HCF-1
Latency

ABSTRACT

Upon infection, the genomes of herpesviruses undergo a striking transition from a non-nucleosomal structure to a chromatin structure. The rapid assembly and modulation of nucleosomes during the initial stage of infection results in an overlay of complex regulation that requires interactions of a plethora of chromatin modulation components.

For herpes simplex virus, the initial chromatin dynamic is dependent on viral and host cell transcription factors and coactivators that mediate the balance between heterochromatic suppression of the viral genome and the euchromatin transition that allows and promotes the expression of viral immediate early genes.

Strikingly similar to lytic infection, in sensory neurons this dynamic transition between heterochromatin and euchromatin governs the establishment, maintenance, and reactivation from the latent state. Chromatin dynamics in both the lytic infection and latency-reactivation cycles provides opportunities to shift the balance using small molecule epigenetic modulators to suppress viral infection, shedding, and reactivation from latency.

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Upon infection of a cell, the genomes of herpesviruses undergo a striking transition from a non-nucleosomal state in the viral capsid to a chromatin state that resembles the host cell's genome. While previously considered to be inconsequential for viral lytic infection, it has become clear that the assembly, modification, and remodeling of viral chromatin plays a critical regulatory role in determining the progression of infection.

## Fates of infecting viral genomes

Post entry, the viral capsid is transported to the nuclear pore where the genome is released from its compacted state into the cell nucleus. At this point, the fate of the genome may be highly dependent upon

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http://dx.doi.org/10.1016/j.virol.2015.01.026
0042-6822/Published by Elsevier Inc.

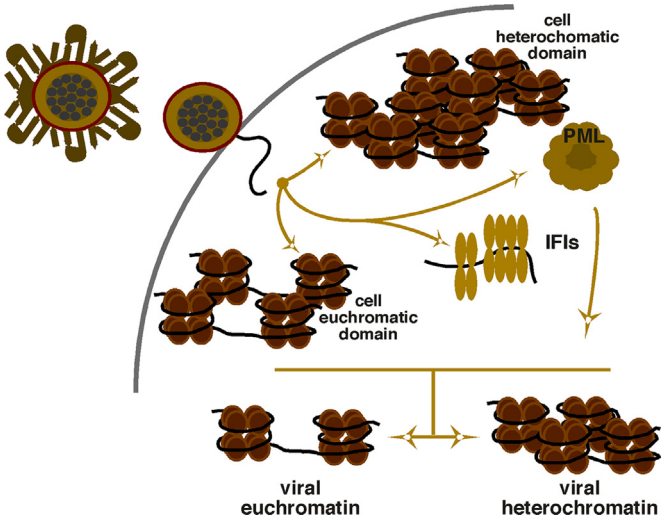


**Fig. 1.** Fates of infecting HSV genomes. Complex cell–viral interactions determine the fate of an individual non-chromatinized genome as it is released into the nucleus. The localization of the infecting genome to subnuclear domains enriched in factors promoting heterochromatin or euchromatin may be an important determinant of the state of the chromatin assembled on the viral genome. In addition, sequestering by PML bodies or suppression by assembled IFIs (interferon-induced factors) may promote subsequent nucleosome assembly into repressive heterochromatic structures. The initial state of the viral chromatin appears to be dynamic and ultimately modulated by chromatin machinery.

the subnuclear localization or microenvironment that is enriched in either repressive cofactors or transcriptional activators and coactivators (Silva et al., 2008). This review will focus on components that are directly involved in the initial modulation of the viral chromatin state. However, it is important to point out that multiple interactions of the host cell and virus play roles in determining the balance between heterochromatic suppression and euchromatic activation of the population of infecting viral genomes (Fig. 1).

Two classes of histone chaperone complexes are involved in replication-independent deposition of nucleosomes containing histone H3.3. The heterochromatin associated Daxx (death domain-associated protein) and the SWI/SNF chromatin remodeler ATRX (alpha thalassemia/mental retardation syndrome X-linked) appear to be involved in nucleosome assembly that ultimately progresses to a heterochromatic state (Drane et al., 2010; Everett, 2013; Ishov et al., 2004; Lukashchuk and Everett, 2010). While it has not been directly demonstrated that this chaperone/remodeler complex promotes heterochromatic assembly on the HSV genome, Daxx/ATRX is involved in the initial repression of the infecting viral genome (Lukashchuk and Everett, 2010). In contrast, the chaperones HIRA (histone cell cycle regulator) and ASF1a (anti-silencing factor) are implicated in H3.3 assembly that ultimately promotes viral gene expression (Oh et al., 2012; Placek et al., 2009). The localization of the infecting genome to sites enriched for either of these chaperone complexes and the associated chromatin modulation components may determine the initial chromatin state.

In addition to subnuclear microenvironments, the association or juxtaposition of viral genomes with PML (promyelocytic leukemia) nuclear bodies plays a role in the initial response to the viral genome (Everett, 2013). Interestingly, there is a diverse population of PML bodies (Sahin et al., 2014) including those proximal to pericentric regions that are enriched in the repressive cofactors Daxx and ATRX (Chang et al., 2013; Ishov et al., 2004). These bodies maintain the heterochromatic structures of the region's repeats and may function similarly to repress a population of infecting genomes.

Antiviral responses, such as the recognition of non-chromatinized viral DNA by IFIs (interferon inducible proteins, i.e. IFI16) can prevent the binding of transcriptional activators to the viral genome by the formation of oligomer structures. This process has been linked to the ultimate heterochromatic suppression of the HSV genome (Johnson et al., 2014; Orzalli et al., 2013) although the mechanism(s) by which IFIs are coupled to chromatin modulation are unclear and may be an indirect consequence of inhibiting the association of transcriptional activators (e.g. Sp1) with the genome (Caposio et al., 2007; Gariano et al., 2012).

## Multiple states of HSV chromatin

Two important observations were made that illustrated the complex patterns of HSV chromatin upon initial infection. While previous studies had suggested that the levels of nucleosomes associated with the viral genome were low or inconsequential, it was subsequently demonstrated that the genome was in fact associated with canonically spaced nucleosomes (Lacasse and Schang, 2010, 2012). These studies revealed that rapid remodeling of viral associated nucleosomes, likely based upon high-level acetylation of histones, resulted in technical underrepresentation in ChIP assays or when using standard micrococcal nuclease protection protocols. In contrast to this “euchromatic” state, genomes associated with heterochromatic chromatin structures were also observed upon initial infection (Liang et al., 2009; Narayanan et al., 2007; Silva et al., 2008). The levels of repressive heterochromatic histone marks associated with the viral genome were readily detected at the initial stage of infection but were rapidly reduced concomitant with the expression of viral IE genes (Liang et al., 2009).

Thus, two opposing states of viral chromatin were found in the population of lytically infected cells. These observations suggested that the fate of a given infecting genome is likely determined by multiple opposing factors and that the initial state of the viral chromatin is relatively dynamic.

## Activators and coactivators controlling HSV IE gene expression

To a large extent, the productive infection is dependent on the successful activation of viral immediate early (IE) gene transcription. HSV IE gene promoter regulatory regions are designed to respond to multiple transcription factors and transcriptional coactivators that function cooperatively to drive high-level expression in a rapid manner (Fig. 2) (Knipe et al., 2013; Kristie et al., 2010; Vogel and Kristie, 2013). During lytic infection, the viral encoded IE activator VP16 is released from the tegument structure of the infecting virus and is recruited to viral IE enhancer elements by interaction with

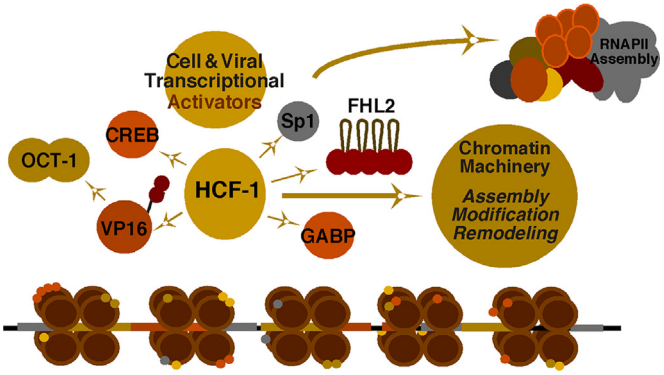


**Fig. 2.** Viral and cellular factors mediating HSV IE gene expression. Multiple classes of cellular DNA-binding transcription factors cooperate with the viral IE activator VP16 to drive high-level expression of viral IE genes. HCF-1 is a central component required for mediating transcriptional potential of these factors by coupling interactions with cellular chromatin modulation machinery.