Epigenetic Repression of Herpes Simplex Virus Infection by the Nucleosome Remodeler CHD3

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ABSTRACT Upon infection, the genome of herpes simplex virus is rapidly incorporated into nucleosomes displaying histone modifications characteristic of heterochromatin structures. The initiation of infection requires complex viral-cellular interactions that ultimately circumvent this repression by utilizing host cell enzymes to remove repressive histone marks and install those that promote viral gene expression. The reversion of repression and activation of viral gene expression is mediated by the cellular coactivator HCF-1 in association with histone demethylases and methyltransferases. However, the mechanisms and the components that are involved in the initial repression remain unclear. In this study, the chromatin remodeler CHD3 protein is identified as an important component of the initial repression of the herpesvirus genome. CHD3 localizes to early viral foci and suppresses viral gene expression. Depletion of CHD3 results in enhanced viral immediate early gene expression and an increase in the number of transcriptionally active viral genomes in the cell. Importantly, CHD3 can recognize the repressive histone marks that have been detected in the chromatin associated with the viral genome and this remodeler is important for ultimately reducing the levels of accessible viral genomes. A model is presented in which CHD3 repression of viral infection in opposition to the actions of the HCF-1 coactivator complex. This dynamic, at least in part, determines the initiation of viral infection.

IMPORTANCE Chromatin modulation of herpesvirus infection is a dynamic process involving regulatory components that mediate suppression and those that promote viral gene expression and the progression of infection. The mechanisms by which the host cell employs the assembly and modulation of chromatin as an antiviral defense strategy against an invading herpesvirus remain unclear. This study defines a critical cellular component that mediates the initial repression of infecting HSV genomes and contributes to understanding the dynamics of this complex interplay between host cell and viral pathogen.
activities required to remove repressive H3K9 methylation and install activating H3K4 methylation marks at IE promoters. Inhibition of the activities of either of the HCF-1-associated demethylases results in enhanced epigenetic suppression of the viral genome and a block to the progression of infection (16, 17, 32).

It is clear that the recruitment of HCF-1 chromatin modulation activities is critical to the initiation of viral IE expression and the progression of infection. However, the components and mechanisms involved in the dynamic chromatin regulation remain unknown, including those that mediate the stages of nucleosome assembly, modification, and remodeling that are the basis for the initial cell-mediated suppression of the viral genome.

Here, members of the chromodomain helicase DNA-binding (CHD) nucleosome remodeler family were assessed for their potential role in mediating HSV early chromatin dynamics. This family is characterized by the presence of two tandem chromodomains (chromatin organizing domains) and an SNF2-related helicase/ATPase domain (33–35). While specific functions or targets of many of the members are unknown, some have been linked to chromatin remodeling, leading to either transcriptional activation or repression.

Of the family members, CHD3 but not the highly related CHD4 nucleosome remodeler was found to be specifically involved in initial suppression of HSV-1. Depletion of CHD3 resulted in the consistent increase in viral ICP27 expression. The expression of ICP27 in cells transfected with individual CHD3 or CHD4 siRNAs paralleled that in cells transfected with the respective siRNA pools. No impact of either CHD3 or CHD4 depletion was seen on the expression of the cellular control GAPDH mRNAs determined by quantitative reverse transcription-PCR (qRT-PCR). Of the CHD family, depletion of CHD3 resulted in the consistent increase in viral ICP27 expression without any significant impact on the cellular control GAPDH (Fig. 2B; see also Fig. S1A in the supplemental material).

The role of CHD3 in repression of viral gene expression was confirmed by depletion of CHD3 or the highly related CHD4 using siRNA pools and two independent individual siRNAs (Fig. 2C to F; see also Fig. S1B to D in the supplemental material). Depletion of CHD3 but not CHD4 resulted in enhanced viral IE (ICP0, ICP4, ICP22, ICP27; 1.5- to 2.4-fold) and E (UL29, UL30, UL52; 2.0- to 3.5-fold) expression. The expression of ICP27 in cells transfected with individual CHD3 or CHD4 siRNAs paralleled that in cells transfected with the respective siRNA pools. No impact of either CHD3 or CHD4 depletion was seen on the expression of the cellular control TATA binding protein (TBP).

CHD3 mediates repression of a large population of HSV genomes upon infection. Enhanced expression of viral IE genes upon depletion of CHD3 suggests that this CHD family member may function in the initial chromatin-mediated repression of the viral genome. As shown in Fig. 3A, enhanced viral IE gene expression in CHD3-depleted cells can be readily detected at the earliest time postinfection (30 min) compared to control or CHD4- or CHD6-depleted cells. Significant impacts were seen on the cellular control gene (TBP gene; see Fig. S2 in the supplemental material).
Thus, CHD3-mediated suppression of viral gene expression must occur rapidly, prior to any significant expression of IE genes. Additionally, the data suggest that CHD3 would be found proximal to early viral foci. This was confirmed by confocal imaging of cells infected with HSV-1 for 1.5 h and stained for CHD3 and the IE protein ICP4, a marker for early viral foci. As shown in Fig. 3B, CHD3 localizes adjacent/juxtaposed to early punctate (Fig. 3B, top) and more developed ICP4 foci (Fig. 3B, bottom). This localization pattern is more clearly evident in the three-dimensional (3-D) volume reconstruction of an infected cell nucleus (Fig. 3C).

As an additional approach to visualize the association of CHD3 with early foci, cells were infected with HSV-1 at a low PFU (0.001) for 24 h. This allows for the completion of one round of the viral lytic cycle and detection of nascent viral foci at the nuclear periphery of the adjacent cell (21). As shown in Fig. 4A, CHD3 was highly localized proximal to the early viral foci.

The impact of CHD3 on viral IE gene expression and the association with early viral foci suggest that CHD3 is an important component of the initial repression of the viral genomes. Thus, CHD3 could be responsible for suppression of a population of the viral genomes that enter a cell. To investigate this, cells were transfected with CHD3, CHD4, or control siRNAs and infected with HSV-1 for 2 h. The cells were stained for ICP4 viral foci, and the numbers of small, medium, and large foci were counted. Strikingly, depletion of CHD3 but not CHD4 resulted in an increase primarily in the number of small and medium-sized viral foci per cell (Fig. 4B). The substantial increase in the number of small viral foci in CHD3-depleted cells further indicates that this protein is a key component involved in repression of a large percentage (52%) of the infecting viral genomes.

CHD3 depletion compensates for inhibition of the HCF-1-associated histone demethylase LSD1. Reversal of the initial
chromatin-mediated repression of the viral genome is dependent upon the recruitment of the transcriptional coactivator HCF-1 to the IE promoter domains. This coactivator couples two required histone demethylases that function cooperatively to remove the repressive-heterochromatic H3K9-trimethylation mark. Inhibition of the activity of LSD1 results in enhanced epigenetic repression of the viral genome with increased levels of nucleosomes and repressive histone marks. However, it remains unclear how these marks are recognized and translated into chromatin-based suppression of the viral genome.

Strikingly, the CHD3 chromodomains bind both H3K27-trimethyl and H3K9-trimethyl repressive histone marks (36–38). Therefore, the protein is a candidate for an effector that recognizes repressive histone marks associated with the viral genome and promotes the formation of heterochromatic structures by association with corepressors (HDAC1/2, SETDB1) (39–45). To investigate the impact of CHD3 on the "chromatin structure" of the HSV genome during early infection, the accessibility of the viral genome was measured in formaldehyde-assisted isolation of regulatory element (FAIRE) assays (46–48) (Fig. 6; see also Fig. S4 in the supplemental material). As anticipated, inhibition of LSD1 by TCP treatment significantly reduced the level of soluble viral genomes with a parallel increase in the level found in the FAIRE-insoluble fraction (Fig. 6A; see also Fig. S4B to D). In contrast, depletion of CHD3 resulted in an increase in the level of soluble viral genomes with a parallel decrease in the level in the insoluble fraction (Fig. 6C). It should be noted that alterations in FAIRE solubility do not necessarily translate directly to alterations in transcriptional levels, which depends upon multiple parameters. This is illustrated by the increased FAIRE solubility of the actively transcribed cellular GAPDH loci in the absence of CHD3 without a
Additionally, the SNF2H remodeler and the CLOCK acetyltransferase along with those that install activating H3K4 methylation. Addi-
tions to remove the repressive histone H3K9 methylation complex to the viral IE gene promoters that contains the required expression is countered by the recruitment of a coactivator (HCF-1) postinfection. Initially, nucleosomes that bear heterochromatic gene expression.

Recruit or modulate the epigenetic machinery to promote viral opposing elements (e.g., viral or cellular transcription factors) can assembly of a heterochromatic-type chromatin state that limits genetic machinery that initially suppresses infection through the

HSV infections were done in HEPES-buffered Dulbecco’s modified Eagle’s medium (DMEM) containing 1% fetal bovine serum (FBS) for 1 h at 4°C. Following adsorption, infected cells were washed with phosphate-buffered saline (PBS) and incubated in DMEM containing 10% FBS.

Cells and viral infection.

MATERIALS AND METHODS

Cells and viral infection. MRC-5 and HeLa cell lines were maintained according to standard procedures. TERT-immortalized human foreskin fibroblast (HFF) cells were a gift from T. Shenk (Princeton University). HSV-1 strain 17 was a gift from N. Fraser (University of Pennsylvania). HSV infections were done in HEPES-buffered Dulbecco’s modified Eagle’s medium (DMEM) containing 1% fetal bovine serum (FBS) for 1 h at 4°C. Following adsorption, infected cells were washed with phosphate-buffered saline (PBS) and incubated in DMEM containing 10% FBS.

Antibodies, primers, and siRNAs. Antibodies, primer sequences, and siRNAs utilized in these studies are listed in Table S1 in the supplemental material.

LSD1 inhibition. Cells were pretreated with tranylcypromine (TCP; Sigma P8511) or DMSO control for 3 to 4 h prior to infection and maintained throughout the infection as specified in the figure legends.
qRT-PCR and qPCR. cDNA was synthesized from 800 ng of total RNA (NucleoSpin RNAII; Macherey-Nagel) using a Maxima first-strand cDNA synthesis kit (Thermo Scientific) according to the manufacturer’s recommendations. cDNA and DNA were quantified by qPCR using SYBR green master mix (Roche) and a Mastercycler ep realplex (Eppendorf; realplex 2.2 software).

Western blots. Western blots utilized antibodies listed in Table S1 and were quantitated using a Kodak 4000MM image station.

**Immunofluorescence microscopy.** Immunofluorescent staining was done according to standard protocols. Where indicated, cells were treated with CSDK extraction buffer (0.5% Triton X-100, 10 mM PIPES [pH 6.8], 300 mM sucrose, 100 mM NaCl, 3 mM MgCl2, 2.0 mM NaF, 2.0 mM Na2VO4, 10 mM β-glycerophosphate, Complete protease inhibitor) prior to fixation. Cells were visualized using a Leica SP5 confocal microscope with LASAF software (version 2.6.0). Images were assembled from sequential Z-sections using Imaris software (version 7.1.1; Bitplane AG).

**FAIRE assays.** FAIRE assays were done as described with minor modifications (46, 48). Cells were treated with 4% paraformaldehyde, snap-frozen, and subsequently thawed in LB1 buffer (50 mM HEPES [pH 7.5], 150 mM NaCl, 1 mM EDTA, 10% glycerol, 0.5% NP-40, 0.25% Triton X-100). Cells were pelleted at 1,500 g at 4°C, resuspended in LB2 buffer (10 mM Tris-HCl [pH 7.5], 200 mM NaCl, 1 mM EDTA), and incubated for 10 min. Nuclei were pelleted at 1,500 g at 4°C, resuspended in LB3 (10 mM Tris-HCl [pH 7.5], 150 mM NaCl, 1 mM EDTA, 0.25% Sarkosyl, 0.1% sodium deoxycholate, Complete protease inhibitor) and sonicated (Branson Sonifier 450 D, 19% amplitude, 7 cycles of 40 s) until chromatin fragments were in the 200–800-bp size range. Insoluble chromatin was pelleted by centrifugation at 13,000 rpm for 10 min at 4°C and resuspended in LB3 containing RNase A and proteinase K. The insoluble fraction DNA and the nucleosome-depleted DNA (FAIRE) were purified by sequential phenol-chloroform extractions and precipitated with ethanol. Cross-linking was reversed by incubation in 250 mM NaCl for 12 h at 65°C and purified using a CHiP DNA Clean & Concentrator kit (Zymo Research).

**Statistical analyses.** Statistical analyses were done using Prism 6.0 (GraphPad Software, Inc.) and included 2-tailed t-tests (P < 0.05) (sRNA analyses) and analysis of variance (ANOVA) with Dunnett’s post hoc multiple comparisons test (viral foci).

**SUPPLEMENTAL MATERIAL**

Supplemental material for this article may be found at http://mbio.asm.org/lookup/suppl/doi:10.1128/mBio.01027-13/-/DCSupplemental.

**Figure S1, PDF file, 0.3 MB.**

**Figure S2, PDF file, 0.1 MB.**

**Figure S3, PDF file, 0.1 MB.**

**Figure S4, PDF file, 0.7 MB.**

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