Combinatorial Transcription of Herpes Simplex Virus and Varicella Zoster Virus Immediate Early Genes Is Strictly Determined by the Cellular Coactivator HCF-1*

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The mammalian transcriptional coactivator host cell factor-1 (HCF-1) functions in concert with Oct-1 and VP16 to assemble the herpes simplex virus (HSV) immediate early (IE) transcription enhancer core complexes that mediate the high level transcription of these genes upon infection. Although this transcriptional model has been well characterized in vitro, the requirements and significance of the components have not been addressed. Oct-1 was previously determined to be critical but not essential for HSV IE gene expression. In contrast, RNA interference-mediated depletion of HCF-1 resulted in abrogation of HSV IE gene expression. The HSV IE gene enhancer domain is a model of combinatorial transcription and consists of the core enhancer and multiple binding sites for factors such as Sp1 and GA-binding protein. It was striking that HCF-1 was strictly required for VP16-mediated transcriptional induction via the core enhancer as well as for basal level transcription mediated by GA-binding protein and Sp1. HCF-1 was also found to be essential for the induction of varicella zoster virus IE gene expression by ORF10, the VZV ortholog of the HSV IE transactivator VP16, and the autostimulatory IE62 protein. The critical dependence upon HCF-1 demonstrates that this cellular component is a key factor for control of HSV and VZV IE gene expression by functioning as the common element for distinct factors cooperating at the IE gene enhancers. The requirements for this protein supports the model whereby the regulated transport of HCF-1 from the cytoplasm to the nucleus in sensory neurons may control IE gene expression and reactivation of these viruses from the latent state.

The immediate early genes of herpes simplex virus are models for inducible combinatorial transcription, in which the regulated expression of these genes is mediated by enhancer-promoter assemblies. These domains consist of reiterated core enhancer elements (TAATGARAT; EC) that are targeted by the viral IE induction factor VP16 in conjunction with the cellular POU domain protein Oct-1 and the transcriptional coactivator HCF-1 (1–3). In vitro, the assembly and specificities of this core regulatory complex depend upon the recognition of the EC element by Oct-1. VP16 provides two levels of specificity by selective recognition of the homeodomain surface of Oct-1 and by cooperative recognition of the core element (4–7). The third component, HCF-1, is required to stabilize the enhancer assembly and functions as a transcriptional coactivator to mediate the activation potential of VP16 (8–10).

In addition to the EC elements, flanking sites for cellular transcription factors such as GABP and Sp1 play significant roles in determining the high-level expression of the IE genes (11–13). However, the regulatory potential of these factors is dependent upon the enhancer core, suggesting that interactions or activities of the core components are required for their synergistic stimulation of the IE gene transcription. Based upon the in vitro assembly model, it would be expected that Oct-1 would be an essential component of the viral regulatory circuit. However the expression of the viral IE genes is induced in a VP16-dependent manner during infection of Oct-1-deficient cells, suggesting that this component is important but that alternative mechanisms exist (14). Because HCF-1 interacts with GABP and Sp1 as well as VP16, it remained possible that this component was the common primary determinant of the IE gene transcription (8, 15–17). HCF-1 is a unique cellular complex consisting of polypeptides derived from a 230-kDa precursor protein by site-specific proteolytic processing (10, 18–20). The protein was originally identified as being required for the formation of the stable IE EC complex. Later, it was shown to be the target for cellular transcription factors GABP (15), Sp1 (16), KROX20, E2F4 (21), LZI2 (22), Zhangfei (23), chromatin modification proteins (Set1/Ab2 HMT) (24), and coactivators (PGC) (25), and to function as a transcription coactivator. HCF-1 has also been implicated in the control of multiple stages of cell cycle progression that may be a reflection of the protein's transcriptional functions (26–29). In support of this, array studies have implicated HCF-1 in the expression of critical cellular proteins involved in general transcription, mRNA splicing, DNA replication-repair, and signal transduction (30).

The requirement and significance of HCF-1 for IE gene expression was addressed by selective RNA interference-dependent depletion. It was striking that the depletion of HCF-1 abrogated HSV IE gene expression mediated by Oct-1–VP16, GABP, and Sp1. The stringent requirement for HCF-1 in the face of multiple regulatory factors indicates that these genes exemplify a layer of regulation in which the coactivator is the
critical component. More strikingly, whereas HCF-1 functions as the mediator for such general factors as GABP and Sp1, this activity is specific for the combinatorial context of the IE genes.

In a manner analogous to HSV, the IE62 gene of the related α herpesvirus VZV also contains reiterated inducible enhancer core complexes that assemble containing HCF-1, Oct-1, and ORF10 (VZV ortholog of VP16) (31). In addition, however, the VZV IE62 gene product also contributes to the induction of its own expression and to the expression of the majority of VZV genes. As for HSV, depletion of HCF-1 demonstrated that the protein was required for the VZV ORF10 and IE62 activation of the VZV IE62 promoter, indicating that HCF-1 determines a critical common stage in human α herpesvirus IE gene transcription.

These results have general implications for the HSV IE gene transcriptional model and the initiation of the viral lytic replication cycle. In this context, the availability of HCF-1 in a given cell would represent a critical determinant in the initiation of lytic cycle. More significantly, HCF-1 is specifically sequestered in the cytoplasm of sensory neurons, the site of HSV and VZV latency. The data presented here support the model whereby the cytoplasmic localization of HCF-1 would promote the establishment of viral latency and the regulated transport of this coactivator to the nucleus would represent a critical stage in the induction of the IE viral genes during the reactivation stage (32).

EXPERIMENTAL PROCEDURES

Cell Culture and Virus—HeLa, BSC-1, and Vero cells were maintained according to standard procedures. HSV-1(F) stocks were produced and titrated in Vero cells. VZV (Webster) was obtained from the American Type Culture Collection.

Silencer Constructs and Transfections—pU6-si-HCF-1 contained the si-HCF-1 sequence GGGACATTCCCATCATTACG in pBS-U6-si (gift of Y. Shi, Harvard University) (33). pU6-si-sc1 and pU6-si-sc2 contained the control scrambled siRNA sequences GGGTACATCCTGTATACAGAC and GGGATCATTACTGACCAC, respectively. pU6-si-HCF-1 contained the si-HCF-1 sequence CCGTGCATGCTAATGATATTCCTTTGGGTAC and pU6-si-Sc2 contained the scrambled siRNA sequences GGTACATCCTGTAATGAGATGCCAT, GGGTACATCCTGTAATGAGATGCCAT, and pU6-si-Sc1 contained the scrambled siRNA sequences GGGTACATCCTGTAATGAGATGCCAT. The cells were transfected with pCMV-VP16 and pCMV-VP16-NLS. The cells were cotransfected with the si-HCF-1 construct and GFP (Fig. 1A) in which cells expressing GFP were progressively depleted for HCF-1 over 72 h.

Depletion of HCF-1 Abrogates HSV-1 IE Gene Expression—The dependence of HSV IE expression on HCF-1 was addressed by transfection of cells with constructs expressing the si-HCF-1 or the control construct. 72 h after transfection, the cells were infected or mock-infected with 0.1 or 1.0 pfu/cell for 5 h. As shown in Fig. 2A, an 80% depletion of HCF-1 resulted in reduced expression of the IE proteins ICP4 and ICP0 to less than 10% of the expression in control transfected cells (0.1 pfu/cell). Likewise, infection of HCF-1-depleted cells at 0.1 pfu/cell resulted in a significant reduction in HSV viral yields (−2 log) at 18 h after infection (data not shown). The results suggested that the expression of the viral IE genes was critically dependent upon the levels of HCF-1.

At higher multiplicities of infection (1.0 pfu), however, the expression of the IE proteins and the viral yields were only slightly reduced in the infected culture. It is likely that this reflects the infection of the total cell population, in which only a percentage of cells was significantly depleted for HCF-1. In addition, high levels of viral template and encapsidated VP16 may compete for residual HCF-1 in partially depleted cells. Therefore,

Viral Titers and Plaque Assays—Viral yields from infection of HCF-1 depleted and control HeLa cells were determined according to standard procedures. VZV plaque assays were done by infection of control and HCF-1 depleted BSC-1 cells (2.5 × 104) with 80 tissue culture infectious dose 50% end point (a measure of the viral titer) and incubation in Earle’s modified Eagle’s media with 1% fetal bovine serum. After 6 days, the plaques were counted, and the plaque sizes were determined using a Leica microscope with a Zeiss Axiosvert camera and ImagePro 4.5 software (Media Cybernetics, Silver Spring, MD).

RESULTS

RNA Interference-mediated Depletion of HCF-1—In vitro studies have suggested that the expression of the HSV-1 IE genes is dependent upon the synergistic interaction of multiple factors and the assembly of multiprotein enhancer core complexes. Using Oct-1-deficient cells, it was determined previously that this component was critical but not essential for viral IE gene expression, suggesting that multiple-alternative regulatory pathways exist (14). However, in vitro protein interactions have suggested that the coactivator HCF-1 might represent an essential component that is common to these various mechanisms.

Because HCF-1 is a ubiquitously expressed mammalian cell protein, the requirements for this coactivator component in the regulation of HSV IE genes was investigated by specifically depleting the protein in cells using RNA interference methods. As shown in Fig. 1A, constructs expressing HCF-1-specific silencer RNAs or control scrambled RNAs from the U6 promoter were transfected into cells, and the levels of HCF-1 were monitored by Western blot. The levels of HCF-1 were specifically reduced in cells transfected with the si-HCF-1 over the course of 48 h after transfection. In contrast, the control scrambled siRNAs had no effect on the HCF-1 levels. The specific reduction in HCF-1 expression was clearly evident in cells cotransfected with the si-HCF-1 construct and GFP (Fig. 1B) in which cells expressing GFP were progressively depleted for HCF-1 over 72 h.

The dependence of HSV IE expression on HCF-1 was addressed by transfection of cells with constructs expressing the si-HCF-1 or the control construct. 72 h after transfection, the cells were infected or mock-infected with 0.1 or 1.0 pfu/cell for 5 h. As shown in Fig. 2A, an 80% depletion of HCF-1 resulted in reduced expression of the IE proteins ICP4 and ICP0 to less than 10% of the expression in control transfected cells (0.1 pfu/cell). Likewise, infection of HCF-1-depleted cells at 0.1 pfu/cell resulted in a significant reduction in HSV viral yields (−2 log) at 18 h after infection (data not shown). The results suggested that the expression of the viral IE genes was critically dependent upon the levels of HCF-1.
cells were transfected with si-HCF-1 or control constructs and infected with HSV-1 at 10 pfu/cell. The levels of HCF-1 and the expression of the viral IE ICP4 were monitored by immunofluorescence (Fig. 2B). It was striking that cells that were significantly depleted for HCF-1 (>90%) also exhibited a lack of HSV IE gene expression, demonstrating that HCF-1-depleted cells supported no significant viral IE gene expression.

**HCF-1 Is Required for VP16-, GABP-, and Sp1-mediated Transcription**—The induction of HSV IE gene transcription is dependent upon VP16, the virally encoded transactivator that is packaged in the virion and released into the cell upon infection (2). It is also dependent upon multiple cellular transcription factors, such as Oct-1, Sp1, and GABP (Fig. 3A). The abrogation of IE gene expression in HCF-1-depleted cells suggested that this coactivator component was critical for mediating expression via the multiple transcription factors involved. This requirement was directly assessed using luciferase reporter constructs. HCF-1-depleted and control cells were cotransfected with a luciferase reporter construct containing the HSV ICP4 promoter-regulatory domain (−330 to +33, ICP4RD) and increasing amounts of a construct expressing the VP16 transactivator. VP16 induces the transcription of the viral IE genes via both the viral EC complex containing Oct-1, VP16, and HCF-1 and via the ets factor GABP. As shown in Fig. 3B, increasing amounts of VP16 increasingly stimulated the expression of the ICP4 regulatory domain-reporter in control cells (160-fold). However, this induction was compromised in HCF-1-depleted cells (50% reduction).

It should be noted that the magnitude of the effect of HCF-1 depletion in this context was dependent upon the percent of cells expressing the reporter gene that had been initially depleted for HCF-1 (60%). Therefore, this reduction represents a near ablation of VP16-mediated stimulation in the depleted cells.

As noted above, the induction of the viral genes is dependent upon multiple transcription factors and response elements. Therefore, the contribution of these individual elements and their dependence upon HCF-1 was assessed using reporter constructs containing a minimal promoter (TK −49 to +33) and EC, GABP, or Sp1 binding elements (Fig. 3C). In cells transfected with the control silencer construct, VP16 induced the expression of the EC (12-fold), GABP (4.5-fold), and GABP-EC (34-fold) element reporters. It was striking that in HCF-1-depleted
cells, VP16 induction of these reporters was nearly completely abrogated (reduced by 90, 67, and 87%, respectively).

It has been suggested previously that the nuclear import of VP is mediated by HCF-1 (37). Therefore, it remained possible that the HCF-1 dependence of the VP16 mediated induction of the IE genes reflected a failure of nuclear transport in HCF-1-depleted cells. However, in HCF-1-depleted cells, the induction mediated by both WT VP16 and VP16 containing a donor nuclear localization signal was both equally reduced. In addition, quantitative immunofluorescent assessment of VP16 and VP16-NLS localization demonstrated that these proteins were equally represented in the nucleus in both control and HCF-1-depleted cells (average of nuclear mean fluorescence: control, 0.29; HCF-1-depleted, 0.30) (data not shown).

HCF-1 was required for VP16-mediated induction via the EC and GABP elements. The effect of HCF-1 depletion on the basal level expression mediated by each element as well as the specificity of this dependence for the HSV IE genes is shown in Fig. 3D. Increasing amounts of reporter constructs containing the indicated promoter-regulatory domains (ICP4-RD, CMV-IE, and RSV-LTR (100, 200, 300, 500 ng)) or constructed promoters (TATA, GABP, EC, SP1 (50, 100, 150, 250 ng)) at 48 h after transfection with pU6-si-HCF-1 (Si) or pU6-si (C). The basal expression level for each construct was normalized to the activity of the control GL3-promoter construct and represented as the percentage of the promoter expression in HCF-1-depleted cells relative to that in the control cells. In these experiments, the transfection efficiency was 60% and the extent of HCF-1 depletion in transfected cells was 80% in transfected cells.

The requirement for HCF-1 to mediate GABP and Sp1 determined basal level expression of the HSV IE genes was assessed by transfecting increasing amounts of the control min-
HCF-1 Control of HSV and VZV IE Gene Expression

**DISCUSSION**

The transcriptional regulation of the IE genes of HSV has been a model for combinatorial regulation by multiprotein assemblies. *In vitro* studies have defined the components and specificities involved in the protein-DNA and protein-protein interactions. The results have significant implications for both the lytic replication cycles as well as the establishment and reactivation of these viruses from the latent state.

**FIG. 4. Regulation of VZV IE-62 gene expression in HCF-1-depleted cells.** A, the structure of the VZV IE2 regulatory-promoter domain is schematically illustrated depicting the VZV EC and binding sites for Oct-1 (Oct), GABP, and c-AMP response (CRE). HSV VP16 and the VZV ORF10 homolog are shown, indicating the conserved regions (Core) and the VP16 transactivation domain (TA). B, HeLa cells were transfected with pU6-si-HCF-1 or with pU6-si. 48 h later, the cells were cotransfected with the VZV EC reporter (50 ng) and increasing concentrations of pCMV-ORF10 (0, 100, 200, 500 ng). The expression levels of the reporter were normalized to that of the TATA control reporter construct. C, HeLa cells were cotransfected with 50 ng of the IE62–45 reporter or the TATA control reporter and increasing amounts of pCMV-IE62 (0, 100, 200, 500 ng) 48 h after transfection with pU6-si-HCF-1 or pU6-si. D, cells were transfected with increasing amounts of the TATA control or the IE62–45 reporter (50, 100, 200, 300, 500 ng) 48 h after pU6-si-HCF-1 or pU6-si transfection. The basal expression level for each construct is represented as the percentage of the promoter expression in HCF-1-depleted cells relative to that in the control cells.

**HCF-1 Control of HSV and VZV IE Gene Expression—**HCF-1 was clearly critical for the expression of the HSV IE genes but was dispensable for the activation of the CMV IE and RSV LTR. However, the second α herpesvirus, VZV, encodes a transactivator, ORF10, that is highly related to VP16 (31) and is similarly packaged in the VZV virion. In addition, the VZV IE62 regulatory domain consists of a number of transcription elements including enhancer core elements that mediate the assembly of an Oct-1/ORF10/HCF-1 complex (31) (Fig. 4A). VZV differs from HSV, however, in that the IE62 protein acts as a transactivator that mediates the assembly of an Oct-1/ORF10/HCF-1 complex (36, 38) that is copackaged in the VZV virion (39). Therefore, to determine the potential role of HCF-1 in the ORF10 and IE62 regulation of the VZV IE gene, reporter constructs containing the VZV EC element and the VZV IE62 responsive promoter were transfected into control and HCF-1-depleted cells. As expected from the demonstrated assembly of Oct-1/ORF10/HCF-1 on the VZV TC element, HCF-1 was required to mediate ORF10 activation of the VZV EC reporter construct (Fig. 4B). However, HCF-1 was also required for VZV IE62 induction of both the base TATA promoter and the natural IE62 promoter (Fig. 4C). The specificity of this requirement was evident in the lack of HCF-1 effect upon the basal level expression of both constructs (Fig. 4D).

The requirement for HCF-1 for both ORF10- and IE62-mediated expression of the VZV IE gene suggested that HCF-1 would be essential for VZV lytic replication. This was demonstrated by a significant reduction in VZV plaque size in HCF-1-depleted cells. Cultures of BSC cells were transfected with the control or HCF-1 silencer constructs and subsequently infected with 80 TCID VZV. Because HCF-1 is required for cell cycle progression (26–29) and because VZV replication may depend upon cell cycle, experimental conditions were adjusted to ensure that the cellular HCF-1 levels were depleted by only 50%. Under these conditions, cells continue to undergo mitosis at a normal rate (data not shown). At 6 days after infection, the cultures were stained, and the plaque numbers and sizes were quantitatively determined and compared with those in nontransfected control cells (Fig. 5). As shown, despite the depletion of only 50% of the endogenous cellular HCF-1, the average size of VZV plaques in these cultures were less than 15% of the average control plaque size. The results further emphasize that the coactivator HCF-1 functions as a critical common determinant for the expression of both HSV and VZV IE genes, even though these viral promoters are regulated via complex combinatorial transcription factor interactions. The results have significant implications for both the lytic replication cycles as well as the establishment and reactivation of these viruses from the latent state.
interactions that govern the induced high-level transcription of these genes. Oct-1, GABP, and Sp1 might suggest that the protein is required to modulate the specific arrangement of a more complex critical regulatory assembly. On the other hand, HCF-1 may mediate interactions or activities that are required to circumvent common rate-limiting stages in the IE gene transcriptional activation, such as modulation of chromatin structure or mediation of required interactions with general factor components.

Similar to the requirement for HCF-1 in the regulated expression of HSV IE genes, HCF-1 was also determined to be critical for the VZV ORF10- and IE62-mediated induction of the VZV IE62 promoter. The requirement for HCF-1 in ORF10 induction of the VZV IE62 gene is consistent with in vitro studies that previously demonstrated VZV enhancer core complex assembly with Oct-1/ORF10/HCF-1 (31). However, VZV IE expression is also positively autoregulated by IE62, presumably via increasing the affinity of the TATA-binding protein (TBP) for the nonconsensus IE62 TATA element (40, 41). Induction of the minimal VZV IE promoter by IE62 in an HCF-1-dependent manner suggests that HCF-1 may cooperatively facilitate this activity. On the other hand, IE62 may have multiple functions in transcriptional induction and the HCF-1 dependence reflects an alternate mechanism.

Irrespective of the biochemical mechanisms involved in HCF-1-mediated transcription, it is clear that this component is essential for both HSV and VZV lytic replication cycles as defined by its requirement for viral IE gene expression. More significantly, the concerted regulation of the viral IE genes by HCF-1 has implications for the viral latency establishment and reactivation processes in sensory neurons. Although the details and molecular mechanisms involved in latency and reactivation remain unclear, it is likely that blocks to IE gene expression would promote the establishment of latency, whereas re- sumption of IE expression would be key to the reactivation process. It is noteworthy that HCF-1 is specifically sequestered in the cytoplasm of sensory neurons and is rapidly transported to the nucleus in response to stimuli that result in viral reactivation (32). The strict dependence of IE gene transcription upon this coactivator supports the model whereby the sequestering of HCF-1 would promote the establishment of latency. Furthermore, given that HCF-1 functions as an IE-specific coactivator for factors such as GABP and Sp1, the induced transport of HCF-1 to the nucleus could promote transcriptional activation of the HSV IE genes, leading to the initiation of viral reactivation in the absence of the transactivator VP16. In a similar manner, transport of HCF-1 could mediate the activation of VZV genes in concert with expressed VZV regulatory proteins during reactivation (42).

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FIG. 5. Replication of VZV in HCF-1-depleted cells. BSC-1 cells transfected with pH1–4-si-HCF-1 (si) or the control vector p-H1-si (C) were infected with VZV. Six days after infection, the plaques were counted, and the average sizes were determined. The amount of remaining HCF-1 in pH1–4-si-HCF-1 transfected BSC-1 cells over a 5-day period is shown at the bottom.
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