Biochimica et Biophysica Acta 1799 (2010) 257–265

Contents lists available at ScienceDirect

Biochimica et Biophysica Acta

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

Review

Control of α-herpesvirus IE gene expression by HCF-1 coupled chromatin modification activities

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ARTICLE INFO

Article history:
Received 12 March 2009
Received in revised form 15 July 2009
Accepted 1 August 2009
Available online 12 August 2009

Keywords:
HCF-1
Herpesvirus
Coactivator
Set1
LSD1

ABSTRACT

The immediate early genes of the α-herpesviruses HSV and VZV are transcriptionally regulated by viral and cellular factors in a complex combinatorial manner. Despite this complexity and the apparent redundancy of activators, the expression of the viral IE genes is critically dependent upon the cellular transcriptional coactivator HCF-1. Although the role of HCF-1 had remained elusive, recent studies have demonstrated that the protein is a component of multiple chromatin modification complexes including the Set1/MLL1 histone H3K4 methyltransferases. Studies using model viral promoter–reporter systems as well as analyses of components recruited to the viral genome during the initiation of infection have elucidated the significance of HCF-1 chromatin modification complexes in contributing to the final state of modified histones assembled on the viral IE promoters. Strikingly, the absence of HCF-1 results in the accumulation of nucleosomes bearing repressive marks on the viral IE promoters and silencing of viral gene expression.

Published by Elsevier B.V.

Infection by the α-herpesviruses (HSV, herpes simplex virus and VZV, varicella zoster virus) follows a tightly regulated viral gene transcription program that begins with the expression of the viral immediate early (IE) genes and ultimately results in the production of viral progeny and cell lysis. Following a primary infection, these viruses also establish latency in neurons of the host sensory ganglia. Periodic interruption of the latent state can result in recurrent lytic infection, presumably initiated via induced transcription of the viral IE genes. Thus, transcriptional control of the viral IE genes is both a critical regulatory point in the initiation of lytic infection as well as initiation of viral reactivation from latency. Additionally, these genes are transcribed by the host cell RNAPII machinery and have proven to be excellent model systems for the investigation of cellular transcriptional control mechanisms.

1. Regulatory domains of the α-herpesvirus immediate early genes

Control of α-herpesvirus immediate early gene expression is complex. The enhancer–promoter domains of these genes contain binding sites for members of a number of distinct families of transcription factors. This complexity allows for multiple cooperative regulatory pathways and provides the ability to respond to different cell environments and signals. This multi-path regulation may also reflect the mechanisms involved in the reactivation of these viruses from the latent state.

A characteristic IE gene, shown in Fig. 1, consists of a basal promoter and an upstream regulatory domain that contains a reiterated enhancer core element (EC; ATGCTAATGARATTCTTT). The EC element nucleates the formation of a multi-protein enhanceosome complex that is the primary mediator of IE gene expression and consists of the cellular POU-homeodomain protein Oct-1, the viral IE activator (VP16 for HSV and ORF10 for VZV), and the cellular transcriptional coactivator HCF-1 *rev. in* [1,2].

The assembly of the enhanceosome is dependent upon the recognition of the noncanonical octamer (ATGCTAAT) in the EC element by the Oct-1 bipartite POU-Homeo domain [3–5]. The viral IE activators, which are packaged in the tegument structure of these viruses and released into the cell upon infection, provide specificity by recognition of both the 3′ sequences of the EC element (GARATTCTTT) and the exposed surface of the Oct-1 homeodomain [3,6–9]. In addition, these IE activators also bind and recruit the cellular coactivator HCF-1 into the EC complex, resulting in a stable enhanceosome assembly [10–12].

In addition to the enhanceosome complex, additional cellular transcription factors such as GABP and Sp1 bind to sites flanking the EC element and contribute to the induced level of IE gene transcription [13–15]. Strikingly, factors like GABP can also provide alternative means of stimulating IE gene expression even in the absence of the enhanceosome nucleating factor Oct-1 [16].

Abbreviations: HCF-1, Host Cell Factor-1; HSV, herpes simplex virus; VZV, varicella zoster virus; HMT, histone methyltransferase; HDM, histone demethylase; MLL1, mixed-lineage leukemia; LSD1, lysine-specific demethylase 1; H3K4, histone H3-lysine 4; H3K9, histone H3-lysine 9

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1874-9399/$ – see front matter. Published by Elsevier B.V.
doi:10.1016/j.bbagrm.2009.08.003

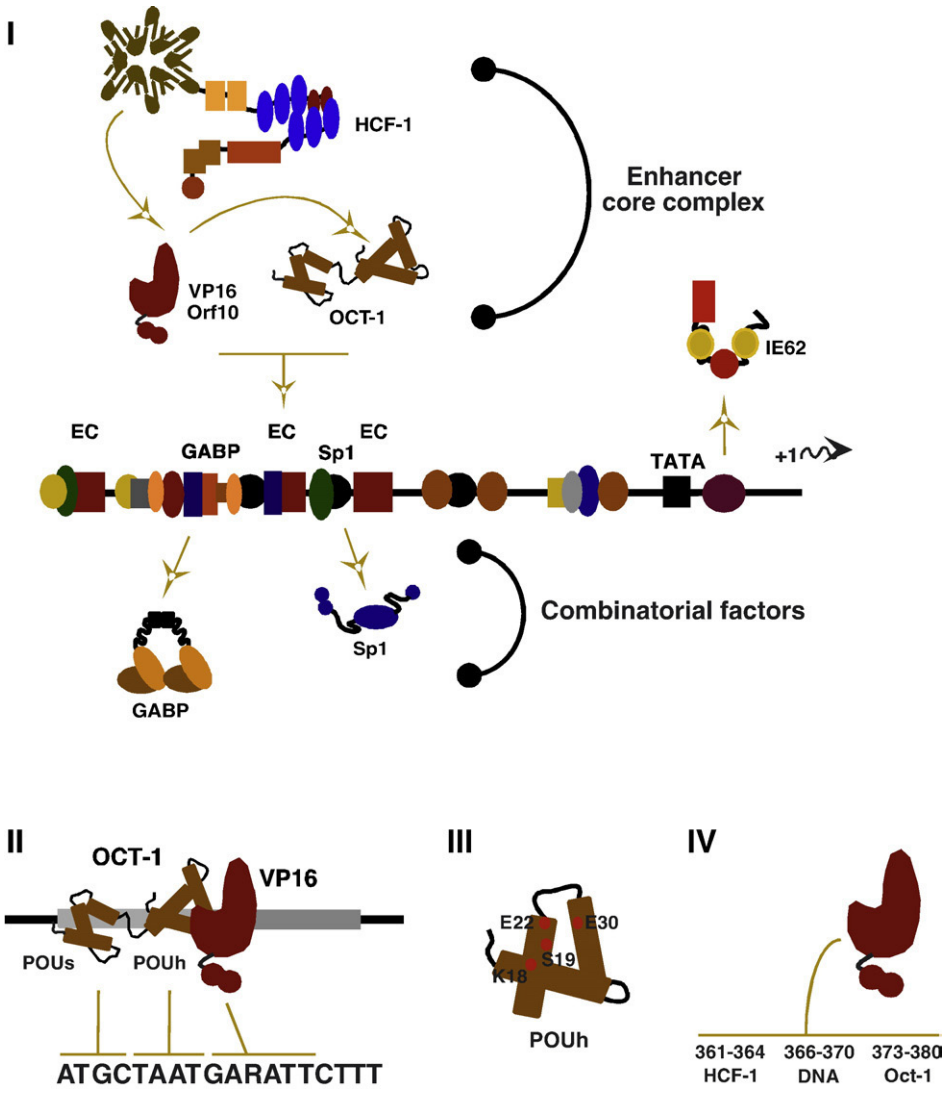

Fig. 1. Components regulating the expression of the α-herpesvirus IE genes. (I) The IE genes of HSV and VZV enhancer–promoter domains are complex and contain binding sites for multiple factors functioning synergistically or cooperatively. Viral IE activators (VP16 for HSV; ORF10 for VZV) interact with Oct-1 and HCF-1 to form the stable enhanceosome complex. A second VZV IE activator IE62 stimulates expression via its own recognition elements. Cellular factors such as GABP and Sp1 amplify the enhancer core (EC, TAATGARAT) mediated expression of the IE genes but may also function independent of the EC complex to stimulate IE gene expression. (II) Oct-1 recognizes the EC element via a bipartite DNA binding domain consisting of POU-specific (s) and POU-homeo (h) domains. (III) The viral activator, VP16, recognizes the surface of the Oct-1 POU-homeo domain via specific residues in helix 1 and 2 and provides specificity by recognition of the 3′ sequences of the EC element. (IV) Clustered residues in the carboxy-terminal region of VP16 mediate interactions with HCF-1, DNA, and Oct-1.

2. Combinatorial regulation of IE genes is determined at the level of the coactivator HCF-1

Much of what has been learned about HCF-1 to date is derived from investigation of its interactions with both viral and cellular transcription components. HCF-1 was originally identified and purified as a protein required for the stable assembly of the viral IE EC complex [11]. However, the protein is now recognized as an essential cellular coactivator with global impact on gene transcription and cell cycle progression via interactions with multiple cellular transcription factors, coactivators, and chromatin modification components.

HCF-1 interacts with components that mediate both basal level and viral induced expression of the α-herpesvirus IE genes [17]. These transcriptional activators bind various HCF-1 domains, suggesting that the protein orchestrates a coordinated regulatory process that results in the high level expression of the IE genes upon initial infection (Fig. 2). The viral IE activators (VP16 and ORF10) bind the amino-terminal kelch domain [18–20] (Fig. 2). Many of the factors that bind this domain, including the viral IE activators, contain a small interaction motif (D/EXHY; referred to as the HBM, HCF binding motif) [18,21,22]. However, despite this common motif, mutations in the HCF-1 kelch domain indicate that there are distinct binding determinants for different factors and that multiple HBM proteins may interact with the same HCF-1 molecule [23,24]. In addition to the viral IE activators, the CREB/ATF family member CREB3/Luman also binds the kelch domain and can induce a representative viral IE gene in an HCF-1 dependent manner [18,25,26]. Conversely, Zhangfei, a second bZIP protein that binds this domain can inhibit HCF-1 dependent activation of the HSV IE genes [27,28] and has been hypothesized to play a role in suppression of lytic infection.

The mid-amino-terminal (MN) domain of HCF-1 interacts with GA-binding protein (GABP/NRF2) [29], Sp1 [30], and IE62, a second VZV IE activator that is associated with HCF-1 via Sp1 [31]. Sp1 plays a significant role in the basal level expression of the IE genes [13] while GABP plays a co-stimulatory role in the presence of the viral IE activator [15,17]. As noted above, GABP can also promote the regulated induction of the IE genes even in the absence of the viral