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Host factors associated with either VP16 or VP16-induced complex differentially affect HSV-1 lytic infection

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Abstract

Herpes simplex virus type 1 (HSV-1) is an important human pathogen with neurotropism. Following lytic infection in mucosal or skin epithelium, life-long latency is established mainly in sensory neurons, which can periodically reactivate by stress, leading to recurrent disease and virus transmission. During the virus's productive infection, the tegument protein VP16, a component of HSV-1 virion, is physically associated with two cellular factors, host cell factor-1 (HCF-1), and POU domain protein Oct-1, to construct the VP16-induced complex, which is essential to stimulate immediate early (IE)-gene transcription as well as initiate the lytic programme. Apart from HCF-1 and Oct-1, VP16 also associates with a series of other host factors, making a VP16-induced regulatory switch to either activate or inactivate virus gene transcription. In addition, VP16 has effects on distinct signalling pathways via binding to various host molecules that are essentially related to innate immune responses, RNA polymerases, molecular chaperones, and virus infection-induced host shutoff. VP16 also functionally compensates for given host factors, such as PPAR-γ and ß-catenin. In this review, we provide an overview of the updated insights on the interplay between VP16 and the host factors that coordinate virus infection.

KEYWORDS
HSV-1, IE, latency, VP16, VP16-induced complex

1 | INTRODUCTION

Herpes simplex virus-1 (HSV-1) is an enveloped DNA virus belonging to Herpesviridae family.[1] As an important human pathogen, it is responsible for cold sores, with symptoms of painful blisters, ulcers or sores at the site of infection, including the skin and mucosa.[2–4] HSV-1 infection in tonsils and the adjacent lymph nodes may cause tonsillitis.[5,6] In rare cases, HSV-1 infection leads to more severe complications, such as keratitis and encephalitis, which may progress to blindness and death, respectively.[7,8] Of note, HSV-1 infection is the leading cause of infectious blindness in the USA.[9] Approximately 3709 million individuals (aged 0–49 years) or ~67% of the world populations are infected by HSV-1, with highest prevalence in Africa, South-East Asia and Western Pacific, according to a worldwide estimation in 2012.[10]

HSV-1 gene expression is divided into three distinct phases during the lytic infection: immediate early (IE), early (E), and late (L).[11–13] IE proteins play critical roles in regulating the expression of both E and L genes during infection.[14] Following lytic infection in the epithelium, HSV-1 enters peripheral sensory neurons, such as trigeminal ganglia, as well as the central nervous systems (CNS), where life-long latency is established, marked by the silencing of lytic gene transcription and concomitant expression of the latency-associated transcripts (LAT).[15–19] LAT is a noncoding RNA of multifunction involved in the regulation of latency, as well as reactivation from latency in response to external stimuli.[15,16,20–22] During latency, the chromatized viral genome persists as a multi-copy episome with nucleosome structure in the nucleus.[23,24] Chromatin assembly and distinct histones modifications orchestrate the transcriptional status of either lytic genes or LAT.[25]

The transcriptional activator VP16 is involved in the regulation of both lytic infection and latency-reactivation in neurons.[26–28] VP16 promoters contain unique neuro-specific sequences that are essential for latency-reactivation in neurons because they can be activated by neuron-associated factor(s) independent of both IE products, such as ICP0 and ICP4, and viral DNA replication.[29,30] So far, the neuron-associated factors have not been extensively addressed, while the host factors affecting HSV-1 lytic infection via association with either VP16 or VP16-induced complex has been extensively characterised. A panel of cellular factors including HCF-1, Oct-1, RNA polymerase II, TBPs, TAFs, HSP90, Lamin A/C, β-catenin as well as chromatin modification enzymes such as LSD1 and JMJD2, have been identified as interactors with VP16 directly or indirectly to regulate viral infection through different mechanisms. In addition, these interactions are potentially co-regulated by viral proteins, such as ICP22, ICP0, and vhs.[31–34] Here the detailed mechanism focussing on the roles of these interplays in lytic infection are summarised and discussed.

2 | VP16 INITIATES IE TRANSCRIPTION VIA VP16-HCF-1-OCT1 COMPLEX

Various kinds of cell cultures, such as epithelial cells, endothelial cells, fibroblasts, and neuronal cells support HSV-1 productive infection.[35–37] The viral gene expression is coordinated by both viral and cellular transcriptional machinery.[38] For example, the viral tegument protein VP16, an L protein, is required to stimulate the expression of IE genes.[39] Upon infection, the viral tegument VP16 released into host cells binds to host cell factor-1 (HCF-1), and enters nucleus, where they associate with POU domain protein Oct-1, as well as VP16-responsive *cis*-regulatory elements containing a TAATGARAT (R is a purine) sequences found in the promoters of HSV-1 IE genes.[40–46] The triplex VP16-HCF-1-Oct, also termed as VP16-induced complex, is essential to initiate the lytic infection via induction of IE-gene transcription.[47] Following this dogma, de novo IE proteins stimulate the transcription of other viral genes such as E genes encoding the DNA synthetic machinery. Both IE- and E-gene products are either directly or indirectly involved in the activation of L gene transcription.[12] For example, ICP0, an IE protein, binds to the cellular protein RanBP10 to form a complex stimulating VP16 expression.[48] Therefore, the L protein VP16 and IE protein ICP0 form a positive feedback loop to stimulate de novo expression of individual proteins, providing a paradigm of inter-stimulation between L and IE proteins.

It has been reported that HCF-1 stabilises the association between VP16 and its essential co-activator Oct-1 in the HCF-1-Oct-1-VP16 complex.[49] A single serine to alanine substitution at position 375 in VP16 will disrupt the association with Oct-1.[50] Mutation of HCF-1 P134S leads to disruption of VP16-induced complex, as well as inhibition of VP16-dependent transcription.[42,44] These data further underscore the importance of the formation of VP16-induced complex for VP16 to keep its biological functions. Recently, a report showed that optineurin (OPTN), a conserved autophagy receptor, selectively targeted VP16 to degradation by autophagy in neurons,[51] providing a novel mechanism of cellular response to restrict HSV-1 replication via degradation of VP16. Of course, the OPTN-mediated degradation of VP16 may involve the VP16-induced complex. Whether similar events also occurred during virus latency or latency-reactivation cycles are interesting questions that will no doubt be determined in future studies.

HSV-1 VP16 protein is approximately 65 kDa in size containing 490 amino acids.[52] As a transcriptional activator, VP16 contains a transcriptional activation-related domain located within the carboxy-terminal (approximately the last 81 amino acids),[52,53] and a central conserved core characterised by alignment of VP16 protein from the five herpesviruses including HSV-1, VZV (varicella zoster virus), GHV-1 (gallus herpesvirus 1), EHV-1 (equine herpesvirus 1) and BoHV-1 (bovine herpesvirus type 1).[49] The conserved core is important for directing the assembly of the VP16-induced complex as well as subsequent binding to and activation of the IE promoters.[49] By using proteomic analysis, a series of VP16-associated proteins have been identified in HSV-1-infected cell cultures (at 3 hpi), such as MED1, MED4, MED6, MED10, MED12, MED13, MED14, MED15, MED16, MED17, MED18, MED20, MED22, MED23, MED24, MED25,MED26, MED27, MED30, MED31, CCNC, O-glycosyl transferase (OGT), two vesicle-associated proteins (VAPA and VAPB), three 14-3-3 proteins (YWHAB, YWHAQ, and YWHAZ), and a heterogeneous ribonucleoprotein, hnRNP3A.[43] Of note, a report

published by an independent lab shows that OGT associates with HCF-1,[54] which is in agreement with the finding that OGT associates with VP16. However, the effects of these identified molecules on either VP16 or VP16-induced complex remain to be elucidated.

Based on the crystal structure of VP16, the conserved core region forms a seat-like structure, where the amino acid sequences required for recognition of specific DNA-sequence and virion assembly are in high order. However, the amino acid sequences in association with HCF and Oct-1 are disordered.[55] These characters essentially support the conformational changes of VP16 during assembly of VP16-induced complex, which ensure the specific recognition of target DNA sequence (TAATGARAT) stringently, and concomitantly maintain the flexibility of its biological activity.[47] This literature described above indicate that VP16 associates with various host factors, which may partially modify the structure of either VP16 or VP16-induced complex, a mechanism to regulate VP16 transcriptional activity, which is important for the virus's productive infection.

3 | VP16 REGULATES IE TRANSCRIPTION VIA INTERACTIONS WITH RNA POLYMERASE II-ASSOCIATED FACTORS

Transcription in eukaryotes is conducted mainly by three RNA polymerases (Pol) including RNA polymerase I (Pol I), Pol II and Pol III.[56] Pol II, is a complex protein molecule containing 12 subunits (RPB1-12) in human. It catalyses synthesis of the precursors of mRNA and most of small nuclear RNA (snRNA), as well as microRNA.[57,58] In eukaryotes, Pol II-mediated transcription cycles can be divided into four distinct stages: recruitment, initiation, elongation, and termination.[59] During HSV-1 infection, the Pol II transcription system is hijacked and adapted, where it recruits Pol II to the viral genome and alters both loading and positioning of Pol II on the host genes, which are in favour of virus gene transcription,[60] while expression of host proteins are concomitantly affected.

VP16 can enhance pol II-mediated gene transcription via association with specific host factors, such as the transcription factor II D (TFIID), a multiprotein complex containing TATA binding protein (TBP) and at least eight TBP-associated factors (TAFs).[61,62] For example, it has been reported that the transactivation domain (TAD) of VP16 binds to dTAFII40, a subunit of TFIID.[50] In addition to TFIID, literature has indicated that VP16 also interacts with general transcription factors, such as TFIIB,[63] and TFIIH subunit p62.[64,65] Together with these associated transcription factors, VP16 stimulate the assembly of Pol II preinitiation complex,[66,67] which is essential to initiate transcription (Figure 1a). Whether VP16 also interacts with subunits of the other TFII is an interesting question that deserves further studies in the future.

In addition to the transcription factor II, VP16 also affects Pol II holoenzyme via association with components of the mediator complex, such as the mediator coactivator subunit ARC92/ACID1.[68,69] VP16 is not the only viral protein that has influence on the function
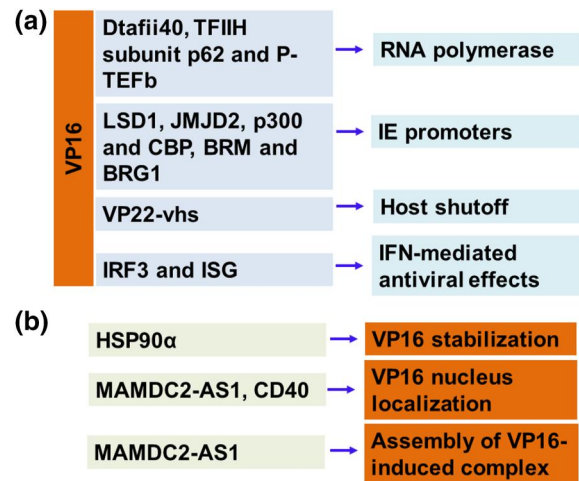

FIGURE 1 The known host factors affecting HSV-1 infection by interacting with VP16 with distinct mechanisms. (a) VP16-associated factors regulate HSV-1 productive infection via having effects on the activity of RNA polymerase and IE promoters, host shutoff, and IFN-mediated antiviral signalings (b) The host factors that regulate HSV-1 productive infection via affecting stabilisation and localization of VP16, as well as assembly of VP16-induced complex

of Pol II. Other identified viral proteins include ICP27, ICP8, and ICP22- all of which have been shown to regulate viral transcription through association with either Pol II or Pol II holoenzyme. For example, both ICP27 and ICP8 are associated with the Pol II holoenzyme,[70] and ICP22 mediates the association between the FACT complex (comprised of SSRP1 and Spt16) and the transcription elongation factors SPT5 and SPT6 with viral genomes,[71] which are important for E and L gene transcription. Taken together, these studies show that the association of VP16 along with the other viral proteins including ICP27, ICP8, and ICP22, with components of either Pol II or activator of Pol II is essential for viral transcription.

It should be noted that a large number of activators or coactivators are physically associated with individual subunits of Pol II and have been shown to illicit biological activity of Pol II. So it is possible that there are components of Pol II or Pol II-associated factors that have not yet been identified that are either associated with or recruited by VP16 and are essential for viral transcription. To date, it remains unclear what the interactions between VP16 and components of Pol I and III are or whether they are important for the virus infection.

The viral protein VP22 contains an internal VP16 interaction domain that mediates association with the TAD of VP16.[72–74] This association leads to relocalization of VP16 to the cytoplasm in infected cells,[75] a possible mechanism to regulate VP16 biological functions. Surprisingly, it has been reported that ICP22 has inhibitory effects on IE transcription by decreasing the phosphorylation of Pol II, and blocking the transcription elongation processes.[76,77] The positive transcription elongation factor b (P-TEFb) regulates PolII-mediated gene transcription in eukaryotes. It has been reported that P-TEFb binds to both ICP22 and VP16, forming a complex,

where ICP22 blocks the recruitment of P-TEFb to the IE promoters while VP16 reverses the blocking effects.[77] Obviously, VP16 acts in concert with ICP22 to recruit p-TEFb to the IE promoters, which has contradictory effects on the transcription elongation associated factors in IE promotors (Figure 1a). Since the lytic gene transcription is shut down during latency but are activated during latency-reactivation, where VP16 play an important role during these processes,[30] we speculate that the interplays between VP16 and components of Pol II are concomitantly changed, an important question remain to be addressed in the future.

4 | VP16 EPIGENETICALLY REGULATES IE PROMOTERS TO MAKING THEM ACCESSIBLE TO POL II

There is an intrinsic epigenetic mechanism to silence the invading DNA for eukaryotic cells. Following HSV-1 lytic infection, the incoming naked viral genome is rapidly compacted into repressive heterochromatin by association with heterochromatic histones, such as histone 3 (H3) lysine 9-trimethylation (H3K9me3), and H3K27me3.[78–80] Consequently, both Pol II and the associated transcription factors cannot fully access to the promoters of lytic genes within heterochromatin, which lead to epigenetic silencing. However, the heterochromatin is unstable that can be progressively converted into transcription active euchromatin, as demonstrated by dynamically changing markers of heterochromatin into euchromatin, which consequently facilitates transcription of lytic genes.[81]

It has been reported that both VP16 and ICP0 are implicated in the conversion of viral genome from heterochromatin to euchromatin with distinct mechanisms.[31,82] ICP0 is able to sequentially remove H3K9me3 and H3K27me3, a possible reason to reverse the host epigenetic silencing machinery.[38] VP16 can recruit chromatin modification enzymes, including the histone demethylases LSD1 and the family of JMJD2 proteins to the heterochromatin, which ultimately leads to demethylation of various histones.[83–85] In addition, a panel of chromatin-modifying coactivators, such as histone acetyltransferases including CBP/p300, ATP-dependent chromatin-remodelling complex SWI/SNF including BRM and BRG1 (BRM-related gene-1),[86,87] as well as TBPs (TATA-binding proteins), are recruited to IE gene promoters by VP16, a mechanism to regulate IE expression.[66] Collectively, VP16 plays critical roles in epigenetic activation of IE promoters via recruitment of both chromatin modification enzymes and chromatin-modifying coactivators (Figure 1a).

5 | VP16 AND VHS ASSOCIATION REGULATES VIRUS REPLICATION AND HOST SHUTOFF

The virion host shutoff (vhs) protein encoded by HSV-1 gene UL41, is an mRNA-specific endonuclease that is able to trigger rapid host shutoff via disruption of preexisting polyribosomes, and degradation of host mRNA on.[88–90] In addition, vhs also induces nuclear retention

of cellular mRNA, a possible mechanism of HSV-1-induced host shutoff.[91] Though vhs is functionally associated with host shutoff, it is also essential to facilitate the expression of specific viral proteins.[92,93] For example, along with virus regulatory protein ICP27, vhs enhances the translation of virus true-late mRNAs, with cell type-dependent manners.[32,94,95] In addition, VP22, VP16 and vhs forms a trimeric complex to disrupt the RNase activity of vhs,[96] a possible mechanism to inhibit vhs-mediated host shutoff. Of note, translation of vhs requires VP22 but not the VP22-VP16 complex, even though the complex is in favour of cytoplasmic localization of vhs mRNA.[97] Interestingly, it has been reported that the VP22-VP16 complex enhances the rescue of vhs-induced nuclear retention of late transcripts.[91] These novel findings confer VP16-VP22 a novel biological function to regulate HSV-1-induced host shutoff (Figure 1a).

Like VP16, vhs is also incorporated into the virions and becomes a viral tegument protein.[44,92,98] Vhs can bind to VP16 via the residues 238–344, which is not located at the TAD of VP16.[98,99] Once inside the host cells, VP16 and vhs works collaboratively to facilitate virus replication through distinct approaches. VP16 activates transcription of IE genes, while vhs induces host shutoff to generate an environment suit for virus replication.[99] In addition, vhs may promote the incorporation of VP16 into virions via association with VP16, making it unable to recognise and subsequently associate with TAATGARAT consensus sequence in IE promoters.[98] So, vhs may affect virus IE transcription via interaction with VP16 through distinct mechanisms. In summary, vhs facilitates IE transcription at early stages while it inhibits IE expression by blocking association of VP16 to IE promoters, and promoting incorporation of VP16 into virions at late stages. Since vhs could bind to VP16, whether it dynamically associates with VP16-induced complex and thereby is enriched on the viral IE promoters to regulate HSV-1 lytic infection, latency, as well as latency-reactivation cycles is an interesting question.

6 | VP16 AFFECTS THE INNATE IMMUNE RESPONSE-RELATED SIGNAL PATHWAYS

Ribonucleic acid (RNA) helicases, such as retinoic acid-inducible gene I (RIG-I) and melanoma differentiation-associated gene 5 (MDA-5), are able to recognise RNA of invading pathogens leading to the production of type I interferons (IFNs).[100] It has been established that the MDA5/MAVS-dependent pathway also is responsible for surveillance of invading HSV-1 in human primary macrophages.[101] Upon recognition, RIG-I interacts with MAVS leading to stimulation of type I IFN production via phosphorylation and activation of both IRF-3 and IRF-7 through IKKε and TBK1.[102] The secreted IFNs through either autocrine or paracrine can bind to the cognitive receptors, and activate JAK/STAT pathway. This leads to formation of the IFN-stimulated gene factor 3 (ISGF3) transcription complex, which drives the expression of antiviral genes, such as protein kinase R (PKR), and Mx GTPases (103).

To survive in an infected host, HSV-1 has evolved strategies to subvert the host immune responses. For example, ICP0 disrupts IRF-3 signalling to decrease IFN-β production.[104] Mechanistically, ICP0

recruits activated IRF-3 and CBP/p300 coactivator to nuclear structures leading to the inactivation and degradation of IRF-3, which ultimately reduces transcription of IFN-β.[105] Like ICP0, VP16 is involved in the inhibition of IFN-β production through association with IRF-3 and inhibition of IRF-3 phosphorylation, which blocks the formation of IRF-3-CBP-DNA complex in the context of virus infection.[103] Moreover, literature has indicated that VP16 blocks the downstream signalling pathways of IFN-stimulated genes (ISGs) stimulated by IFN-β,[103] therefore VP16 not only inhibits production of IFNs but also disable of ISGs.

In addition to regulating lipid metabolism, peroxisomes have been found to be involved in immune defenses due to the fact that peroxisomal MAVS stimulate production of ISGs independent of type I IFNs.[106-108] Interestingly, it has been reported that during HSV-1 productive infection, VP16 blocks peroxisomal MAVS-mediated production of ISGs to evade the cellular defenses.[109,110] Taken these reports together, VP16 plays a role in blocking production of both IFNs and ISGs (Figure 1a).

7 | VP16 INTERACTS WITH CELLULAR MOLECULAR CHAPERONES TO FACILITATE VIRUS REPLICATION

Heat-shock protein 90 (HSP90), a cellular molecular chaperone, plays critical roles in HSV-1 infection. HSP90 specific inhibitors, such as AT533, significantly decrease HSV-1 replication.[111] HSP90 contains four major isoforms including HSP90α, HSP90β, tumour necrosis factor receptor-associated protein 1, and glucose-regulated protein 94 (GRP94).[112] It has been reported that HSP90α associates with VP16, and stabilises VP16 expression by inhibition of macroautophagy-mediated protein degradation, which facilitates the transactivation of HSV-1 IE genes.[113] Recently, it has been reported that HSV-1 productive infection increases the abundance of a cellular lncRNA, MAMDC2 antisense 1 (MAMDC2-AS1), which binds to HSP90α to facilitate the nuclear transport of VP16,[114] providing new evidence that the cellular lncRNA is involved in the regulation of VP16 function via in collaboration with HSP90α (Figure 1b). However, whether HSP90/MAMDC2-AS1 associates with VP16 in the VP16-HCF-1-Oct1 complex is unknown at this time.

8 | LAMIN A/C PROMOTES NUCLEAR ACCUMULATION OF VP16

Lamin A/C are components of Lamina, which is a mesh-like layer of intermediate filaments attached to the inner membrane of the nuclear envelope.[115] Lamina facilitates the shuttle of molecules into and out of the nucleus. Nuclear localization of VP16 is essential to initiate IE transcription, which is important for HSV-1 productive infection. Now, several host factors have been revealed to promote VP16 nucleus localization through distinct mechanisms. For example, the host factor HCF-1 binds to VP16, and stabilises the VP16-HCF-1-Oct-1

triplex and promotes nuclear accumulation of VP16.[116,117] Nuclear lamina provides a site for assembly of the VP16-HCF-1-Oct-1 complex, and subsequent association with IE promoters.[118,119] Lamin A/C facilitates VP16 nucleus localization by promoting the formation of the VP16-induced complex. In addition, Lamin A/C-rich microdomains are associated with euchromatin and active genes,[120] which are indispensable for the formation of virus replication centres, and the initiation of IE and E gene transcription.[121] These data suggest that laminA/C is involved in the regulation of VP16 nuclear localization and VP16-mediated transcription of viral genes.

9 | HSV-1 VP16 INTERACTS WITH THE MINERALOCORTICOID RECEPTOR NR3C2 FOR VIRUS REPLICATION

The mineralocorticoid receptor (MR), also referred to as the aldosterone receptor, is an intracellular steroid hormone receptor, belonging to the nuclear receptor superfamily of proteins.[122-124] MR is widely expressed in diverse cell types, including neurons and epithelial cells.[122] Recently, it has been reported that MR, NR3C2 (nuclear receptor subfamily 3 group C member 2), possess anti-viral activity against HSV-1 replication in cell cultures,[125] and HSV-1 infection increases MR expression depending on VP16 protein expression because MR, VP16, and Oct-1 forms a complex which binds to MR promoter to stimulate MR transcription.[125] It is reasonable that during the productive infection, de novo VP16 may partially increase MR expression, a potential cellular feedback to limit virus replication. These reports provide evidence that VP16 also regulates transcription of cellular genes.

It has been reported that CD40 L exhibits antiviral properties against HSV-1 replication in vivo.[126] Further studies indicate that the activation of CD40 by the cognitive ligand CD40 L delays of the nucleus translocation of VP16, a possible mechanism to inhibit HSV-1 replication.[127] Peroxisome proliferator-activated receptor-γ (PPAR-γ) is a ligand-activated nuclear receptor that regulates the transcription of various genes. PPAR-γ plays an essential role in adipogenesis and glucose homoeostasis.[128] Studies have indicated that the activation of CD40 by CD40 L leads to increased transcription of PPAR-γ gene in macrophages,[129] and the TAD of VP16 is able to stimulate the PPAR-γ signalling pathway.[130] Of note, it has been reported that inhibition of MR leads to increased protein levels of PPAR-γ,[131] which supports the findings that MR has antiviral effects.[125] Taken these studies together, it is highly possible that VP16 is initiating crosstalk between MR and CD40/PPAR-γ.

10 | VP16 TRANSACTIVATION DOMAINS (TAD) HAVE THE CAPACITY TO STIMULATE VARIOUS CELLULAR FACTORS

The TAD of VP16 has been widely used to characterise transcriptional activators in eukaryotes.[66] The TAD of VP16 can be fused to a

DNA-binding domain (DBD) of another protein in order to increase expression of a desired target gene. For example, a mutant PPAR-γ (VP-PPAR-γ) protein, constructed by genetic fusing the VP16 TAD to wild-type PPAR-γ, is constitutively active. Overexpressed VP-PPAR-γ results in ligand-independent activation of PPAR-γ and subsequent induction of the PPAR-γ target genes,[130] suggesting that the fusion of the VP16 TAD to wild-type PPAR-γ confers VP-PPAR-γ the capacity to induce sustained expression of PPAR-γ target genes.

The transcription factor C/EBPα (CCAAT enhancer binding protein α) acts in concert with GABP (GA-binding protein) to regulate the promoter of myeloid-specific FCAR (Fc receptor for IgA).[132] Shimokawa et. al generated a chimaeric protein with the truncated DNA binding domain (DBD) of C/EBPα fused to the TAD of HSV-1 VP16. In concert with GABP, the fused protein was able to increase the transcriptional activity of FCAR promoter of up to 35-fold,[133] providing evidence that VP16 TAD has a strong capacity to stimulate the gene transcription of the heterogeneous target genes. Therefore, it is a promising strategy to genetically fuse the TAD of VP16 to a given transcriptional regulators, in order to generate a hybrid active molecule, keeping sustained activation of the target genes.

However, TAD of VP16 does not always enhance the biological functions of the fused protein. For example, it has been shown that the C terminus of β-catenin can be functionally replaced by the VP16 TAD because a plasmid containing β-catenin gene with C-terminus substituted by HSV-1 VP16 TAD demonstrated transcriptional activity similar to that of intact β-catenin.[134] Taken these reports together, TAD of VP16 alters the activity of a fused transcriptional factor via the target protein-dependent manners. Interestingly, VP16 protein is able to increase β-catenin dependent transcription and β-catenin steady state protein levels.[11] Whether VP16 protein can increase the protein levels of PPAR-γ and C/EBPα, and activate PPAR-γ- and C/EBPα-dependent transcription remains to be investigated.

11 | CONCLUSIONS AND DISCUSSIONS

HSV-1 undergoes lytic infection, latency and latency-reactivate cycles, with VP16 extensively involved in these processes. VP16 plays important roles in the regulation of HSV-1 infection or pathogenesis. Even though a large number of host factors have been identified in the virus lytic infection, these indicated that still there are undiscovered factors which are essential to understand the virus pathogenesis. Moreover, VP16 is critical for the onset of both lytic infection and latency-reactivation. Whether these identified host factors are involved in the onset of latency-reactivation is an interesting question that needs to be addressed in the future. Considering the importance of VP16 on the virus infection both in vivo and in vitro, further characterisation of the host factors that interacts with VP16 will benefit our understanding of the virus pathogenesis.

AUTHOR CONTRIBUTIONS

Xiuyan Ding and Liqian Zhu: Conceptualisation and original draft preparation. Donna M. Neumann and Liqian Zhu: Literature analysis, reviewing, and editing. Donna M. Neumann: Final English editing.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that supports the findings of this study are available from the corresponding author upon reasonable request.

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