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Herpes Simplex Viruses and Induction of Interferon Responses

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Abstract: Herpes simplex viruses (HSV) are human pathogens responsible for a variety of diseases, including localized mucocutaneous lesions, encephalitis, and disseminated diseases. HSV infection leads to rapid induction of innate immune responses. A critical part of this host response is the type I IFN system including the induction of type I IFNs, IFN-mediated signaling and amplification of IFN response. This provides the host with immediate countermeasure during acute infection to limit initial viral replication and to facilitate an appropriate adaptive immune response. However, HSV has devised multiple strategies to evade and interfere with innate immunity. This review will focus on the induction of type I IFN response by HSV during acute infection and current knowledge of mechanisms by which HSV interferes with this induction process.

Key words: Herpes simplex virus(HSV); Innate immunity; Interferon

INTRODUCTION

Herpes simplex viruses (HSV), belonging to the family of *Herpesviridae*, are large DNA viruses that encode more than 80 gene products (87). A prominent feature of HSV is their ability to establish latent or lytic infection, in which viral replication is regulated in a temporal cascade fashion. During HSV infection, the viruses interfere with innate immunity, particularly the type I interferon (IFN) system (22, 42, 99). Type I IFN responses are initiated by pattern recognition receptors (PRRs) that detect invariant molecular structures shared by pathogens of various origins (pathogen-associated molecular patterns, PAMPs).

Toll-like Receptors (TLRs) are a group of PRRs residing on the cell plasma and/or endosomal membranes. Among them, TLR 3, 7, 8 and 9 recognize distinct types of virally-derived nucleic acids and activate signaling cascades that result in the induction of type I IFNs (22, 42, 99, 105). Their expression patterns and magnitudes vary among tissues, with preferential expressions in immune cells. Of note, these TLRs are expressed, albeit differentially, in the epithelial cells from HSV-targeted oral, ocular and genital mucosa (31) as well as in the central nervous system (CNS) resident cells (3, 44). TLR7 and TLR8 recognize single-stranded RNA (ssRNA) (17, 29), whereas TLR9 senses unmethylated deoxycytidylate-phosphate-deoxyguanylate (CpG) DNA(30). TLR7/8/9 induction of type I IFNs are mediated by an adaptor protein called myeloid differentiation primary response protein 88 (MyD88). Interacting with the Toll/

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interleukin-1 receptor (TIR) domain of TLRs, MyD88 then recruits other adaptor proteins such as interleukin-1 receptor–associated kinases 1 and 4 (IRAK1 and IRAK4), and the tumor necrosis factor receptor-associated factor 6 (TRAF6), leading to the activation of IRF7, canonical IκB kinase (IKK) α/β/γ complex and the MAPK cascade (57). IKKs result in activation of NF-κB while MAPK cascade activates the activating protein 1 (AP-1) (42, 61, 115). Consequently, activated IRF7, coordinated with activated transcription factors NF-κB and AP-1, results in the transcription of both IFN-α/β genes (57) as well as inflammatory cytokines (42). In contrast to TLR7/8/9, TLR3 is activated by double-stranded RNA (dsRNA) produced during viral replication (1). The induction of type I IFNs by TLR3 is mediated through TIR domain–containing adaptor inducing IFN-β (TRIF) (75, 110). TRIF either interacts with two noncanonical IKKs, TANK-binding kinase 1 (TBK1) and IKKε (also known as IKK-i (96)) which activate IRF3, or recruits the TRAF6–TAK1–TAB2 complex which activates NF-κB and AP-1 (38, 71, 93). Consequently, these transcription factors coordinate the transcriptional regulation of the IFN-β and IFN-α 4 gene specifically (107). Activated IRF3 is also able to induce a subset of IFN-stimulated genes (ISGs), in the absence of IFN production (5, 25, 66, 113), which contributes to antiviral responses.

TLR-independent induction of type I IFNs is mediated by cytoplasmic PRRs including retinoic acid-inducible gene I (RIG-I)/melanoma differentiation-associated gene 5 (MDA5) and DNA-dependent activator of IFN-regulatory factors (DAI). RIG-I/MDA5 sense dsRNA during viral replication and transcription in infected cells (24, 114). Specifically, RIG-I recognizes uncapped 5'-triphosphate ssRNA (33, 82), whereas MDA5 is the primary responder to polyinosine-polycytidylic acid (poly (I:C)), a synthetic dsRNA analogue (24, 40). RIG-I/MDA5 associates with an adaptor protein, IFN-promoter stimulator 1 (IPS-1; also known as MAVS, VISA or CARDIF) (41, 62, 94, 109) which resides on the mitochondrial outer membrane and interacts with TRAF3 (26, 73). TRAF3 recruits and activates TBK1/IKKε (26), leading to activation of IRF3 and IRF7 (21, 95) and thus induction of type I IFNs. A recent study shows that RIG-I/IPS-1 is also involved in dsDNA-induced type I IFN response (15). DAI is activated by binding to either B-form or Z-form DNA from a variety of sources, leading to type I IFN gene expression through the activation of IRF3 and, probably, IRF7 (104). The signal transduction from DAI to IRFs seems to be mediated by direct interaction between DAI and the TBK1/IRF complex (104, 106). This pathway thereby provides a way for mounting type I IFN responses against DNA viruses.

It is notable that secreted type I IFNs then initiate a positive feedback loop (91) by binding to type I IFN receptors on the surface of neighboring cells in a paracrine and autocrine manner and trigger the Janus kinase-signal transducer and activator of transcription (Jak-STAT) pathway, leading to the expression of an array of ISGs. These ISGs, together with various cytokines and chemokines secreted by the infected cells, exhibit anti-viral, anti-proliferative and immunomodulatory functions (22, 83, 99). Emerging evidence suggests that HSV interacts with the innate immune system in a complex way. Although HSV triggers type I IFN responses, the large coding capacity of HSV enables it to express multiple viral products to interfere with these responses and thus to establish a

successful infection. This review will focus on the induction and interference of innate immunity in terms of type I IFNs by HSV.

INDUCTION OF TYPE I IFN RESPONSES BY HSV

The induction of IFN-α/β by HSV during early infection has been reported in mouse models early in the 1980's and mouse resistance to generalized infection was for both HSV-1 and -2 attributed to a genetically determined difference in the capacity for IFN-α/β production, which was shown to segregate with the X-chromosome (80, 116). Studies with gene knock-out mice and cells have demonstrated the essential roles of IRF3 in the induction of IFN-β/α4 and IRF7 in the activation of IFNα-non4 subtypes by viruses in fibroblasts and epithelial cells (4, 91, 92). Later, it was reported that infection of human fibroblasts with both HSV-1 and human cytomegalovirus (HCMV) activated IRF3 and induced type I IFNs (84). HSV-1 induction of IFN-α/β was also observed in infected human corneal epithelial cells (HCECs) (49), a clinically and physiologically relevant cell type. In addition, infection of murine peritoneal cells by HSV-2 induces a rapid production of IFN-α/β within 4 h of infection (55). It has been shown that HSV entry alone was sufficient to induce innate antiviral responses in human fibroblasts (16, 66). Consistent with this, UV-inactivated HSV-1 that is competent for entry but not for replication is able to induce IFN-α production in peripheral blood mononuclear cells (PBMCs) (89). This induction process also requires IRF3 (16, 72). However, the receptor and precise mechanism for the induction of innate antiviral response by HSV virus entry is still unclear, although phosphoinositide 3-kinase (PI3 kinase) family members have been implicated to play a role during this event (72). The envelope glycoproteins of HSV-1, particularly glycoprotein D (gD), has been shown to induce IFN-α production in PBMCs (2, 51) through a mechanism involving unknown intracellular signaling and engagement of chemokine receptors CCR3 and CXCR4 (2). The mechanism by which these chemokine receptors mediate HSV induction of type I IFNs remains unclear. In light of this, HSV gD is shown to be a strong inducer of IFN-α/β in PBMC-derived dendritic cells and mannose receptors on target cells are indicated to be involved (89). In contrast to the stimulating role of gD in PBMCs, HSV-1 induction of IFN-α/β in macrophages does not rely on gD, suggesting that other components of HSV may function as the inducer (56).

A recent study demonstrated that HSV activation of TLR2 contributes to lethal encephalitis (50). TLR2 is an extracellular PRR sensing microbial lipopeptides and mainly induces inflammatory cytokine production in a MyD88-mediated NF-κB-dependent manner (105). The fact that HSV-1 caused a higher mortality in wild type mice than in $TLR2^{-/-}$ mice revealed a detrimental effect of TLR2-mediated cytokine overproduction (50). Intriguingly, a recent study, in which a cell line expressing four HSV-1 entry glycoproteins (gB, gD, and the heterodimer gHgL) was used to stimulate monocyte-derived DCs, demonstrated that the collective induction of type I IFNs in DCs by HSV-1 glycoprotein complex was TLR2-independent (86). This thus supports a model of two parallel pathways in DCs, one mediated by TLR2 recognition of an unidentified agonist (s) from HSV-1 and the other one mediated by undefined receptor (s) on DC

surface recognizing the HSV-1 glycoprotein complex. HSV genomic DNA is normally unmethylated and very GC-rich, thereby containing abundant CpG motifs (88, 118) which is the ligand for TLR9(30). Genomic HSV-2 DNA has been shown to trigger TLR9 and mediate activation through a MyD88-dependent endocytic pathway leading to type I IFN production in plasmacytoid dendritic cells (pDCs) (54). These are a restricted subset of DCs that are equipped with high levels of TLR7/9 and specialize in secreting copious type I IFNs, particularly IFN-α, after stimulation with viral nucleic acids (42). The strict requirement for TLR9 in IFN-α secretion induced by HSV-2 was further confirmed *in vivo* (54). In line with this, a study using KOS HSV-1 recombinant virus showed that HSV induction of type I IFNs in pDCs was indeed mediated by the TLR9/MyD88 pathway *in vitro* (46). In support of the aforementioned studies using laboratory strains of HSV, clinically isolated TLR2-activating HSV-1 and HSV-2 subspecies have been shown to induce the production of inflammatory cytokines and type I IFNs by a sequential recognition mechanism of TLR2 → TLR9 in conventional DCs (cDCs) (90). However, the requirement of TLR9 for HSV induction of type I IFNs seems cell type-specific. Mice lacking either MyD88 or TLR9 are still capable of controlling HSV-1 replication *in vivo* after local infection, indicating that TLR9- and MyD88-independent pathways in cells can compensate for this host defect (46). Indeed, TLR9-independent type I IFN response to HSV infection has been reported to exist in pDCs, cDCs, macrophages and fibroblasts (32, 46, 56, 85), suggesting that TLR9 only partially contributes to type I IFN response to HSV in cell types other than pDCs.

Recent studies suggest that the double-stranded structure of DNA possesses immunomodulatory effects by TLR-independent pathways when introduced into the cytosol (34). Introduction of B-from dsDNA into the cytosol induces TLR/MyD88/TRIF-independent, TBK/IKKε- and IRF3-mediated production of type I IFNs, especially IFN-β, and their inducible genes in both immune and non-immune cells (15, 35, 36, 74, 97, 100, 104). These studies suggest that the double-stranded HSV genomic DNA is recognized by cytoplasmic receptors, resulting in type I IFN production. However, the mechanisms of DNA virus recognition are not well understood to date. Thus far only one cytoplasmic DNA sensor, named DAI, has been discovered and shown to contribute to HSV-1-mediated type I IFN gene induction (104). Interestingly, mouse embryonic fibroblasts (MEFs) deficient in IPS-1, are unable to produce type I IFNs in response to HSV (85), indicating the possible involvement of dsRNA sensors RIG-I/MDA5. In line with this, Cheng *et al.* (15) showed that HSV has the potential to trigger dsDNA signaling pathways in a RIG-I/IPS-1-dependent manner leading to IFN-β production in human hepatoma cells. Nevertheless, the notion that IPS-1 and RIG-I are required for cytosolic dsDNA-triggered type I IFN production is contradictory to previous findings (48, 77, 102). Current knowledge suggests that type I IFN expression activated by either cytosolic dsDNA or HSV-1 particle (containing genomic DNA) entry share the same pathway downstream of DAI and RIG-I/IPS-1 that is mediated by TBK1/IKKε and IRF3. The role of RIG-I/IPS-1 in HSV induction of type I IFNs still awaits further investigation.

Recently, a genetic etiology for herpes simplex virus-1 encephalitis (HSE) in two children with autosomal recessive deficiency in the intracellular protein UNC-93B was identified (7), shedding light on the possible link between TLR3 and HSV-1 pathogenesis. Human UNC-93B, which has orthologues in several distantly related species, is an endoplasmic reticulum protein with 12 membrane-spanning domains controlling TLR3, TLR7, TLR8 (TLR8 is absent in mice) and TLR9 response by physically interacting with these TLRs (117). When challenged with either TLR3 agonist or HSV-1, skin-derived fibroblasts from the UNC-93B-deficient HSE patients cannot produce IFN-β and IFN-λ, nor are they able to mount immune responses to TLR7/8/9 agonists (7). It has been also reported that patients deficient in IRAK4, an adaptor involved in all TLR-mediated signaling except for TLR3 and TLR4, a LPS sensor (81), are not susceptible to most viral infections, indicating that the type I IFN response through TLR7, 8, and 9 is dispensable for protective immunity to most microbes (47, 112). Particularly, IRAK-4 deficient patients whose TLR3 signaling is still intact are not susceptible to HSE. Given that UNC-93B deficient patients whose TLR3-mediated pathway is impaired are susceptible to HSE (7), these data implicate that TLR3 may play an important role in HSE resistance. In addition, two unrelated patients with HSE have been identified carrying the same heterozygous dominant negative mutation in a TLR3 allele (20). Fibroblasts derived from the patients displayed a significantly diminished responsiveness to TLR3 agonist and HSV-1 challenge in terms of abnormally weak type I IFN production and markedly increased susceptibility to HSV-1 infection. Furthermore, stimulated with several viruses, these TLR3 heterozygous fibroblasts produced type I IFNs in response to most infections, except HSV-1 and vesicular stomatitis virus (VSV), consistent with the natural resistance of these patients to most viruses other than HSV-1. Thus, this establishes the essential role of TLR3 and the importance of TLR3-UNC93B-signaling pathway for primary immunity to HSV-1 in CNS, although human TLR3 appears to be redundant in host defenses to most other microbes. Nonetheless, the question remains how HSV-1, a DNA virus, triggers dsRNA sensor TLR3. This may be answered by the fact that HSV-1 generates dsRNA intermediates via symmetrical transcription (37, 108).

INTERFERENCE WITH THE INDUCTION OF TYPE I IFNs BY HSV

Facing the intricate yet delicate host immune system consisting of innate and adaptive immunity, many viruses have developed multiple cunning strategies to evade host immune attacks at different stages. HSV is one of the most successful human pathogens, interfering with the antiviral responses using versatile strategies. For instance, $\gamma_1$34.5, one critical virulence factor of HSV-1, is able to counteract the antiviral response initiated by double-stranded RNA-activated protein kinase (PKR) (13, 28), a type I IFN inducible cellular enzyme which dictates translational arrest and apoptosis by phosphorylating the α-subunit of the eukaryotic translation initiation factor 2 (eIF2α) upon dsRNA recognition (23). HSV-1 infection also causes the disappearance of Jak1 and Stat2 molecules partially by virion host shutoff (*vhs*) protein (11), an HSV encoded mRNA-specific RNase (98), leading to inhibition of Jak/Stat-mediated IFN signaling and subsequent robust antiviral response.

It has been shown that virus entry of HSV triggers the rapid activation of IRF3 leading to innate immune responses including production of IFN-β and a subset of ISGs (16, 66, 70, 72, 84). However, restriction or inhibition of these immediate early responses after HSV viral replication has also been observed (16, 66, 70), suggesting that HSV-1 encodes viral products that inhibit the early IFN response mediated by IRF3. Infected cell protein 0 (ICP0), an immediate-early protein of HSV-1, is the first viral component whose antagonistic function has been described. HSV-1 bearing deletion in the ICP0 gene was found hypersensitive to IFN while IFN only marginally reduced the replication of wild-type (wt) HSV-1 (65). Expression of ICP0 was then shown to suppress the induction of ISGs during early HSV infection (19). Further investigation revealed that the ICP0 RING finger domain inhibits IRF3- and IRF7-mediated activation of ISGs and this inhibition process involves the proteasome, although no proteasomal degradation of known IRF3 signaling components can be observed (53). A study with immunofluorescence staining techniques revealed that ICP0 sequesters activated IRF-3 and CBP/p300, critical transcriptional coactivators for efficient IRF3-mediated transcription of IFN-β and certain ISGs (107, 111, 113), to nuclear structures away from the host chromatin at early times post HSV-1 infection, thus resulting in reduced transcription of IFN-β/ISGs and an inhibition of the host response (60). However, the presence of ICP0 promoted proteasome-dependent degradation of activated IRF3 (60), which is paradoxical to Mossman's report (53). The discrepancy between these studies might be due not only to the sensitivity of the techniques used but also to different focuses - one studied the nuclear portion of IRF3 (activated form) (60) while the other evaluated the entire endogenous level of IRF3 (53).

Although ICP0 has been shown to play a pivotal role in antagonizing innate immune responses, studies using an ICP0 mutant virus suggest that multiple viral products/mechanisms may exist to block HSV-induced IRF3-mediated IFN production(59, 60). In fact, the critical virulence factor $\gamma_1$34.5 has been linked to IFN resistance of HSV several years ago. One study using mice lacking IFN signaling due to the knockout of IFN-α/β receptor (IFN-α/β/R$^{-/-}$) showed that the replication of γ134.5-null virus in normal mice was strongly inhibited while its replication in IFN-α/βR$^{-/-}$ mice was restored to almost wild type level, and a $\gamma_1$34.5 rescue marker can largely suppress the phenotype of the $\gamma_1$34.5-null virus (52). Dissection of $\gamma_1$34.5 protein also supports the notion that it renders HSV resistant to IFN response (10, 12), which seems to be correlated with $\gamma_1$34.5's anti-PKR function, a well characterized feature of the $\gamma_1$34.5 protein (13, 28). In contrast, a $\gamma_1$34.5 second-site suppressor mutant, which harbors a null $\gamma_1$34.5 gene and a second-site deletion causing early expression of the late gene U_S11 (27, 64), suppresses the phenotype of the $\gamma_1$34.5-null mutant by inhibiting PKR activity *in vitro* (8, 9) but remains as severely attenuated as the $\gamma_1$34.5-null mutant *in vivo* (63). This implicates additional functions of the $\gamma_1$34.5 protein other than anti-PKR to antagonize host responses. In accordance with this, counteracting PKR by $\gamma_1$34.5 was found insufficient for overcoming host responses and for efficient viral replication (14). Microarray analysis in mouse embryonic fibroblasts (MEFs) showed that

antiviral genes, including IFN-β and a subset of ISGs, in $\gamma_1$34.5-null virus-infected cells were differentially regulated compared to those in wt HSV-1-infected cells during the early phase of infection (78). This result implies that $\gamma_1$34.5 may modulate type I IFN induction either directly or indirectly.

Other HSV viral components such as immediate-early protein ICP27 and mRNA-specific RNase *vhs* also appear to be able to interfere with virus induction of type I IFNs/ISGs. It has been reported that ICP27-deficient virus elicits a much higher production of IFN-α/β and inflammatory cytokines in monocyte-derived macrophages and DCs, and activates both NF-κB and IRF3 more potently than wt HSV-1 (58). Other studies reveal that ICP27 also functions in both the suppression of NF-κB activity by stabilizing IκB, the inhibitor of NF-κB (43), and the interruption of IFN signaling pathways downstream of IFN induction by down-regulating the phosphorylation of STAT1, a component of the Jak-Stat pathway (39). However, whether ICP27 exerts a direct or indirect impact on type I IFN production and what the precise mechanism (s) is are still open questions awaiting further investigation. Although *vhs* protein renders HSV resistant to IFN response (69, 76, 101), the inhibitory effect of *vhs* on IFN response is controversial (53, 103). A study using IFN-α/β receptor knockout mice suggests that HSV-2 *vhs* down-regulates type I IFN-mediated responses *in vivo* (68). But whether *vhs* interferes with the induction of type I IFNs directly is not clarified. A clue was provided by the finding that MEFs infected with *vhs*-null HSV-2 produced >50-fold more IFN-α/β than cells infected with wt HSV-2 and *vhs* rescue virus (18). The precise mechanism by which the presence of *vhs* suppresses type I IFN production remains to be defined. Nonetheless, with potent RNase activity, *vhs* may limit the amount of mRNAs encoding type I IFNs and ISGs, thereby inhibiting their synthesis. A study using an HSV-2 point mutant that synthesizes full-length *vhs* protein lacking RNase activity lends support to this idea (45). It is also reported that cells infected with *vhs* defective HSV display higher levels of viral RNA (79), which leads to another hypothesis that the loss of *vhs* allows accumulation of double-stranded viral RNA, a potent PAMP which can trigger cellular dsRNA sensor TLR3/RIG-I/MDA5 and finally induce a high production of type I IFNs and ISGs.

CONCLUDING REMARKS

Innate immunity constitutes the first line of host defenses against invading pathogens. The arsenal of type I IFN responses represents the critical part of innate immunity. Several TLRs and cytosolic sensors recognizing virus-associated molecular patterns have been discovered and their molecular signaling pathways leading to the production of type I IFNs and ISGs have been illustrated, while the list of PRRs, their agonists as well as cellular mediators is still growing. HSV infections can induce the production of type I IFNs, ISGs and inflammatory cytokines, especially during early phases of acute infection, via multiple mechanisms in a cell type-specific manner. Several components of HSV such as envelope glycoproteins, genomic DNAs and replication dsRNA intermediates are all indicated to be inducers of type I IFNs. Concordantly, cellular receptors TLR2, TLR9/DAI and TLR3/RIG-I/MAD5 that sense lipoproteins,

DNAs and dsRNAs have all been reported to be involved in HSV-induced innate responses, although molecular mechanisms remain elusive. Since these PRRs are expressed, albeit differentially, by almost all cell types, the induction of type I IFNs by HSV infection predictably involves multiple pathways simultaneously. However, in order to establish infection, HSV has developed multiple strategies to counteract these host responses, making it one of the most successful human pathogens. HSV encodes several proteins such as ICP0, ICP27 and *vhs*, which may function cooperatively against the induction of type I IFNs. In addition, HSV interferes with IFN signaling, IFN-inducible product (including ISGs, PKR etc.) -mediated responses and adaptive immunity (6, 67), which is not discussed in this review. Therefore, the battle between HSV and the host immune system is a complex, dynamic process, the outcome of which will determine pathogenesis. Further understanding of this process will aid us to find effective solutions for prevention and cure of diseases caused by HSV.

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