



# Complexity of interferon- $\gamma$ interactions with HSV-1

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The intricacies involving the role of interferon-gamma (IFN- $\gamma$ ) in herpesvirus infection and persistence are complex. Herpes simplex virus type 1 (HSV-1) uses a variety of receptors to enter cells and is transported to and from the host cell nucleus over the microtubule railroad via retrograde and anterograde transport. IFN- $\gamma$  exerts dual but conflicting effects on microtubule organization. IFN- $\gamma$  stimulates production of suppressors of cytokine signaling 1 and 3 (SOCS1 and SOCS3), which are involved in microtubule stability and are negative regulators of IFN- $\gamma$  signaling when overexpressed. IFN- $\gamma$  also interferes with the correct assembly of microtubules causing them to undergo severe bundling, contributing to its anti-viral effect. Factors leading to the decision for a replicative virus lytic cycle or latency in the trigeminal ganglion (TG) occur on histone 3 (H3), involve IFN- $\gamma$  produced by natural killer cells and non-cytolytic CD8<sup>+</sup>T cells, SOCS1, SOCS3, and M2 anti-inflammatory microglia/macrophages maintained by inhibitory interleukin 10 (IL-10). Both M2 microglia and CD4<sup>+</sup>CD25<sup>+</sup>Foxp3<sup>+</sup> Treg cells produce IL-10. Histone deacetylases (HDACs) are epigenetic regulators maintaining chromatin in an inactive state necessary for transcription of IFN- $\gamma$ -activated genes and their anti-viral effect. Following inhibition of HDACs by stressors such as ultraviolet light, SOCS1 and SOCS3 are acetylated, and chromatin is relaxed and available for virus replication. SOCS1 prevents expression of MHC class 1 molecules on neuronal cells and SOCS3 attenuates cytokine-induced inflammation in the area. A model is presented to unify the effects of IFN- $\gamma$ , SOCS1, SOCS3, and HSV-1 on H3 and chromatin structure in virus latency or reactivation. HSV-1 latency in the TG is viewed as an active ongoing process involving maintenance of microglia in an M2 anti-inflammatory state by IL-10. IL-10 is produced in an autocrine manner by the M2 microglia/macrophages and by virus-specific CD4<sup>+</sup>Foxp3<sup>+</sup> Treg cells interacting with virus-specific non-cytolytic CD8<sup>+</sup> T cells.

**Keywords:** HSV-1, suppressors of cytokine signaling 1 and 3, Tregs, trigeminal ganglion, interferon-gamma

## INTRODUCTION

Progression and recrudescence of herpes simplex virus type 1 (HSV-1) infection are intimately involved with IFN- $\gamma$ . The interactions of HSV-1 and IFN- $\gamma$  with the host cell cytoskeletal network and the nuclear epigenetic changes involving histone-3 (H3) are examined in lytic and latent infection.

IFN- $\gamma$  has been studied primarily as an immunomodulatory molecule in macrophages, dendritic cells, and lymphoid cells (1, 2). The majority of investigations concerning the effects of IFN- $\gamma$  on the pathogenesis of HSV-1 involve macrophages and other immune cells (3, 4). Although the effects of IFN- $\gamma$  on non-lymphoid cells are not well established, many non-lymphoid cells in human tissues express receptors for IFN- $\gamma$  (5). The IFN- $\gamma$  receptor (IFNGR) is distinctly expressed by endothelial cells and certain epithelial cells. This review focuses on the effects of IFN- $\gamma$  on the cellular events in the pathogenesis of HSV-1 from initial infection in epithelial cells, especially keratinocytes, to latent infection in trigeminal neurons.

Since initial infection of humans with HSV-1 is usually unnoticed, extrapolation of observations occurring in murine models and tissue cultures will be used to portray these events. This review focuses on:

1. Cellular receptors for IFN- $\gamma$  and for HSV-1 and the cytoskeletal effects of receptor ligation.
2. Epithelial and neuronal cells involved in innate resistance to HSV-1 and the cytoskeletal effects including intracellular involvement of pattern recognition receptors (PRRs).
3. Host cell resistance in latency and recurrent infection.
  - a. Receptor ligation.
  - b. Modulating cytokines in latency and recurrent infection.

## CELLULAR RECEPTORS FOR IFN- $\gamma$ AND HSV-1

A heterodimer consisting of two chains, IFNR1 and IFNR2, constitutes the IFNGR. Binding of IFN- $\gamma$  to IFNGR1 induces the rapid dimerization of each IFNGR1 chain, forming a recognition site for the extracellular domain of each IFNGR2. The intracellular regions of this IFN- $\gamma$ -IFNGR complex bring together inactive JAK1 and JAK2 kinases, which transactivate each other and phosphorylate IFNGR1, forming a paired set of STAT1 docking sites on the ligated receptor. After binding in close proximity with JAK kinases, the STAT1 molecules are phosphorylated at tyrosine 701, which activates the STAT molecules to dissociate from the receptor complex form homodimers and translocate to the nucleus as specific gene activators (6). Alternately, Johnson et al. (7) obtained

evidence that suggests a different scenario in which the IFNGR1 chain is complexed to activated STAT1 homodimer and activates JAKs to bind to a specific sequence in the promoter region of immediate early (IE) IFN- $\gamma$ -inducible genes effecting transcription. The activated JAKs are involved in specific epigenetic events such as phosphorylation of tyrosine 41 on histone H3. In turn, this results in dissociation of histone inhibitor protein  $\alpha$ 1 from histone H3, exposing euchromatin for specific gene activation (7). The Johnson model is more satisfying intellectually in explaining the specificity of the transcription factor for the target gene; protein sequences in the IFNGR1 chain would lead the complex to bind to complementary sequences in a protein associated with the specific target gene.

Herpes simplex virus type 1 initially infects epithelial cells, specifically keratinocytes. Dynamin, a microtubule GTPase mediates herpes virus entry into keratinocytes (8). Entry involves both endocytosis and direct fusion at the plasma membrane, processes mediated by dynamin and dependent on cholesterol (8, 9). The various receptors that are known to be involved in HSV-1 entry are listed in **Table 1**. Virus entry appears to be cell specific. Certain cell lines will permit HSV-1 entry through the low pH endocytic pathway while others exhibit entry through the direct fusion with plasma membrane of the host cell (10).

### RETROGRADE CELLULAR TRANSPORT OF HSV-1

Following attachment of the virus by fusion, viral capsids are transported along microtubules to the nuclear pore where the capsid is uncoated and viral DNA is injected into the nucleus (11) (**Figure 1**). Cytoskeletal rearrangements occur within the infected cell upon binding HSV-1 glycoproteins (12). HSV-1 capsids bind to and traffic along microtubules associated with a dynein–dynactin complex (13). Dynein, a minus end-directed microtubule-dependent motor, binds to the incoming capsids and propels them along microtubules from the cell periphery to the nucleus (14). The VP26 capsid protein appears to be the main candidate for viral binding to the dynein motor of microtubules for retrograde transport to cell nucleus (15). Several tegument proteins (VP1/2 and UL37) remain associated with the capsid, which binds to the nuclear pore complex (NPC). After DNA entry into the nucleus, the capsid with remaining tegument proteins is retained on the cytoplasmic side of the nuclear membrane (16). Virus replication occurs in nucleus (16). Sequential gene expression occurs during replication of HSV-1; the  $\alpha$ , IE genes are involved in organizing the transcriptional elements. The  $\beta$  or early phase genes carry out the replication of the viral genome and the  $\beta\gamma/\gamma$  late phase genes are involved in expression of structural proteins in high abundance (17). Although the IE  $\alpha$  gene regulatory protein ICP27 enhances viral gene expression and is predominately nuclear, it shuttles to the cytoplasm during HSV infection, employing an N-terminal nuclear export signal (NES) (18). ICP27 activates expression of  $\beta$  and  $\gamma$  genes by different mechanisms, it shuts off host protein synthesis; it shuttles between the nucleus and cytoplasm in regulating late protein synthesis (19). HSV-1 major capsid protein VP5 gene (UL19) is expressed with  $\beta\gamma$  gene kinetics (20). VP19C is a structural protein of HSV-1 and is essential for assembly of the capsid. It also contains a NES, which permits it to shuttle from the cytoplasm to nucleus for virus assembly (21).

**Table 1 | HSV-1 glycoproteins involved in virus attachment and entry (10).**

HSV-1 glycoprotein	Function	Components
<b>ATTACHMENT PROTEINS</b>		
gB and/or gC	Initial attachment	Heparan sulfate proteoglycans (HSPG); abundantly expressed on the surface of almost all cell types
<b>HSV-1 ENTRY PROTEINS</b>		
gD	Fusion trigger	HVEM (HveA) Nectin-1/nectin-2 3-O-sulfated heparan sulfate proteoglycan (3-OS HS)
gB	Fusogen	Paired immunoglobulin-like type 2 receptor-a (PILRa) Myelin-associated glycoprotein (MAG) Non-muscle myosin heavy chain IIA (NMHC-IIA)
gH-gL	Fusion regulator	$\alpha\beta$ 3 integrin

*HSV-1 and host cell cytoskeletal reorganization mediated by HSV-1 entry, microtubule transport to nuclear pore, and replication of virus.*

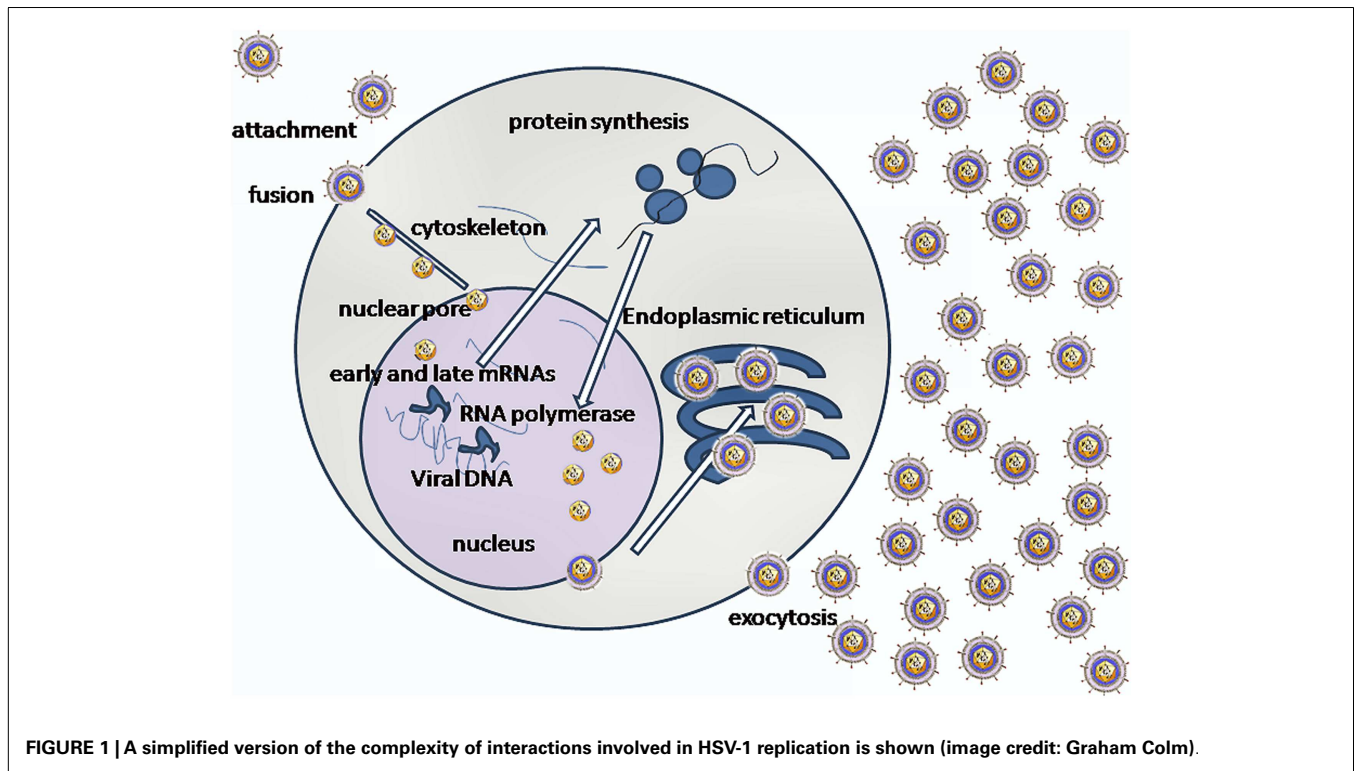
### ANTEROGRADE CELLULAR TRANSPORT OF HSV-1

Non-enveloped capsids recruit kinesin-1 (a positive end microtubule motor) and dynein to undergo transport to their site of envelopment (13). The ability to move bidirectionally appears to depend on cell type and ensures that the capsids come in contact with the appropriate compartment for further development (13). Microtubule-mediated anterograde transport of HSV-1 from the cell nucleus is crucial for the spread and transmission of the virus (22). The majority of HSV-containing structures attached to the microtubules contain the *trans*-Golgi network marker TGN4 (23). This suggests that HSV modifies TGN exocytosis or sorting machinery, which would accelerate the movement of HSV capsids to the cell surface. Their conjecture is supported by the observation that accumulation of HSV particles in cytoplasm is short-lived. In epithelial cells, 10% of enveloped particles are found in the cytoplasm whereas the remaining 90% of these mature particles are on the cell surface (23).

In live imaging of infected rat or chicken dorsal root ganglia, approximately 70% of live viruses undergo axonal transport (24). The enveloped HSV-1 virions were identified in close association with neural secretory markers and trafficked to amyloid precursor protein (APP)-positive vesicles during anterograde egress. To ensure the proper distribution of the cargo (HSV-1 in this case), both positive and negative motors are attached. APP levels were found to be well-correlated with the amount of the components of each motor on the vesicles (25).

### SIGNIFICANCE OF EXOSOMES (MICROVESICLE/L-PARTICLES) IN HSV-1 INFECTION

Electron cryo-tomography was used to visualize HSV-1 interactions with cultured dissociated hippocampus neurons. These infected cells produced and released both infective virions and



non-infectious particles referred to as light (L) particles or exosomes (26, 27). L-particles lack capsids and viral DNA (28–30). Shared assembly and egress pathways were suggested since virions and L-particles formed in close proximity are often associated with clathrin-like coats (26). In contrast to 2D images of 30–100 nm diameter exosomes (27, 31), HSV-1 infected cultures of human foreskin fibroblasts yielded larger 3D images of L-particles; 280 nm diameter size particles were seen intracellularly and 177 nm diameter particles were found extracellularly (26). The complex virus–host interactions at sites of initial HSV-1 infection permit virus persistence in that these microvesicles may interfere with host protective immune responses, e.g., preventing antibody neutralization of infectious virions.

In summary, the cytoskeletal reorganizations involving initial retrograde transit of HSV-1 to the cell nucleus, where viral replication or latency is initiated, to the anterograde transport and export of replicated virus depend on a myriad of viral and cytoskeletal protein interactions. The exosomes exported during lytic infection add an additional layer of complexity to HSV infections.

### HOST CELL CYTOSKELETAL REORGANIZATION MEDIATED BY IFN- $\gamma$

IFN- $\gamma$  exerts effects on a wide range of cellular programs including: upregulation of an anti-viral state, antigen processing and presentation, microbicidal activity, immunomodulation, leukocyte trafficking and apoptosis, and downregulation of cellular proliferation. It orchestrates many of these cellular effects alone or in conjunction with other cytokines or pathogen-associated molecular patterns (PRRs) or bioactive molecules such as lipopolysaccharide (LPS) from gram-negative bacteria (1, 32). The effects of IFN- $\gamma$

on the cell's cytoskeleton are little known. IFN- $\gamma$  induces a higher basal level of F-actin and activation of Rac-1 (a GTPase), which affects cytoskeletal rearrangement resulting in decreased phagocytosis by monocyte-derived macrophages (33). During viral entry, activation of RhoA and Rac-1 results from attachment of Kaposi's sarcoma-associated herpes virus (KSHV or HHV8) glycoprotein B (gB) to integrin  $\alpha 3 \beta 1$ ; this leads to acetylation and stabilization of microtubules (12). It is intriguing to speculate that the activation of Rac-1 by IFN- $\gamma$  may also enhance cytoskeletal reorganization and stabilization of microtubules in HSV-1-infected cells. RhoA and its downstream target Rho kinase are involved in cytoskeletal reorganization in cells infected with other viruses. The Rho family GTPase activity within the host cell triggers microtubule stabilization for viral transport during early infection of African swine fever virus (34).

IFN- $\gamma$  causes an increase in expression of both class I and class II MHC molecules on the cell surface. Trafficking of MHC class II molecules in antigen-presenting cells is dependent on the cytoskeletal network (35) and is dependent on myosin II, an actin-based motorprotein in B lymphocytes (36). In dendritic cells, the microtubule-based proteins, dynein and kinesin, determine retention and transport of MHC class II-containing compartments to the cell surface (37).

Any further effect of IFN- $\gamma$  on the cell cytoskeleton involves indirect association with the effects of this molecule on GTPases involved in cell migration (38). IFN- $\gamma$  inhibits monocyte migration by suppressing actin remodeling of the cytoskeleton and polarization in response to chemokine CCL2, a STA1-dependent process modulating activity of Pyk2, JNK, and the GTPases Rac and Cdc42 (38). Rho kinase (ROCK) is a downstream effector of

Rho GTPase and regulates many crucial cellular processes through its control of actin and microtubules (39). In an adenocarcinoma colonic (T84) cell line, IFN- $\gamma$  treatment activated Rho GTPase that upregulated expression of Rho-associated kinase (ROCK), which then mediated internalization of tight junction proteins from the apical plasma membrane into actin-coated vacuoles; this process was dependent on the ATPase activity of a myosin II motor (40).

Either HSV-1 infection or IFN- $\gamma$  treatment upregulated expression of suppressor of cytokine signaling 1 (SOCS1) in murine keratinocyte cell lines (41). SOCS1 expression was magnified in IFN- $\gamma$ -treated HSV-1 infected keratinocytes, reflecting a profound inhibition of the IFN-mediated anti-viral effect in both the cytoplasm and nucleus of infected keratinocytes. Yokota et al. (42) noted that SOCS3 induction varied among cell lines. They observed that HSV-1 rapidly induced expression of SOCS3 in a human amniotic cell line (FLcells) resulting in efficient viral replication. In human monocytic cell lines (U937 or THP1), HSV-1 did not induce SOCS3 expression; a persistent infection producing low virus yields resulted in those cells (42).

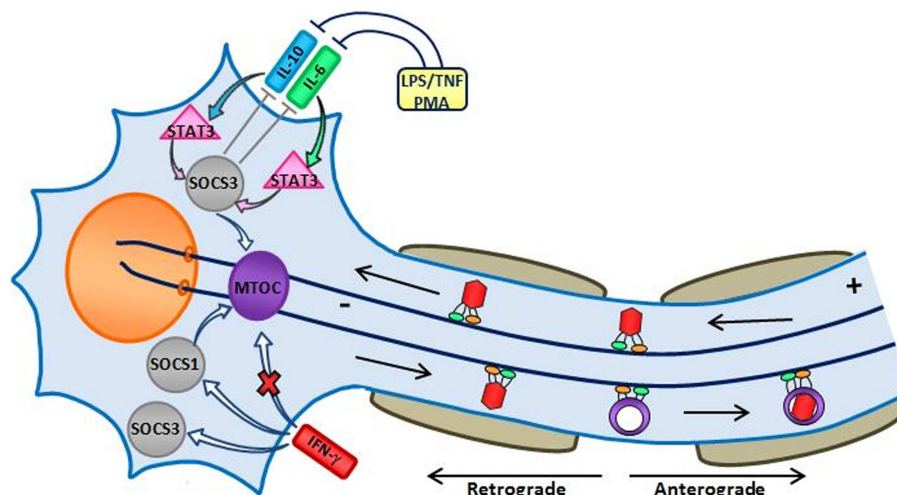
IFN- $\gamma$  promotes expression of SOCS1 at the transcriptional level (43). As shown in **Figure 2**, SOCS1 localizes to the microtubule organizing center (MTOC) (44) as does SOCS3 (45). Both SOCS1 and SOCS3 enhance FAK- and RhoA-activation leading to increased cell adhesion and reduced migration (46).

In summary, IFN- $\gamma$  exerts anti-viral effects, induces expression and trafficking of MHC class II molecules in antigen-presenting cells, effects actin cytoskeletal reorganization involved in phagocytosis and microtubule destabilized bundle formation. In contrast, IFN- $\gamma$  contributes to microtubule stabilization by upregulating expression of SOCS1 and SOCS3.

## HSV-1 LYTIC VERSUS LATENT INFECTION

Lytic HSV-1 infection occurs in epithelial cells. As indicated in **Table 1**, the virus attaches to cell membrane receptors such as heparan sulfate (52), facilitated by viral glycoproteins B (gB) and C (gC) (53). Glycoprotein D (gD) facilitates virus adsorption to the host cell and glycoproteins H and L (gH and gL) are responsible for membrane penetration of the virus into the host cell [reviewed in Ref. (53)]. Furthermore, Dingwell et al. (54) demonstrated that glycoproteins E and I (gE and gI) are responsible for HSV-1 spread from one neuron to another neuron. In lytic infection, virus IE genes ( $\alpha$  genes) are expressed first, followed by expression of early  $\beta$  genes, DNA replication, and expression of late  $\gamma$  genes. The maximum rate of synthesis by  $\alpha$  genes occurs 3–4 h post infection. The  $\beta$  genes are responsible for the highest rate of synthesis 5–7 h post infection. The synthesis of  $\gamma$  genes increases until 12 h post infection. Use of the protein synthesis inhibitor, cycloheximide, confirmed that IE polypeptides expression occurs without prior viral protein synthesis (55). The IE genes consist of ICP0, ICP4, ICP22, ICP27, ICP47, and Us1.5 (56). Wysocka and Herr (57) revealed that IE genes have VP16-response elements (VRE). In latency, a single transcript is generated, which encodes a precursor for four distinct HSV miRNAs, which act to suppress virus replication (58).

In the establishment phase of latency, the virus enters the neuronal cell in which the viral genome remains transcriptionally quiescent. The integrity of the neuron is not compromised, as the cytopathic effect of the productive infection does not occur (59). During establishment of latent infection, gene expression is limited to a gene located within the long repeat elements of the viral genome. Transcription of this gene results in generation of the latency-associated transcripts (LATs) (60). The LAT transcripts (RNAs) have open reading frames; however, the detection



**FIGURE 2 | Hypothetical effect of IFN- $\gamma$  on microtubules of an HSV-1-infected trigeminal neuron (image credit: Trista D. Smith).** Herpes simplex virus type 1 invades nerve endings, which is transmitted by microtubule motor proteins via retrograde transport and its DNA is deposited into the nucleus of the cell (47). IFN- $\gamma$  induces expression of both SOCS1 and SOCS3 (48), but also interferes with the correct assembly of microtubules

causing them to undergo bundling (49). Both SOCS1 and SOCS3 promote the stability of the microtubule network (45, 50). In addition, SOCS3 maintains the integrity of the MTOC by anchoring it to the centrosome (45). Cytokines produced by neighboring cells, e.g., IL-6 and IL-10 by macrophages/microglia, stimulate activation of STAT3; STAT3 stimulates a much stronger induction of SOCS3 in response to IL-10 when compared to IL-6 (51).

of a protein encoded by the LATs has not been observed (58, 61). LAT expression is not an absolute indication of latency establishment (62), as LAT-defective HSV-1 can establish latent infection in mice (28). In contrast, Thompson and Sawtell (63) found that the LAT gene plays a role in establishment of latency, but LAT has no direct role in the HSV-1 reactivation. They found that approximately 30% of the trigeminal ganglion (TG) neurons in mice infected with LAT<sup>+</sup> HSV-1 harbored latent virus, but only 10% of the neurons in mice infected with LAT-null viruses were positive for HSV-1 DNA. LAT expression has no demonstrable effect on neuronal cell survival at 3 and 31 days after infection with defective HSV-1 (thymidine kinase-deleted) mutants (64). LAT expression was not necessary for cell survival during TK-deleted virus infection.

Establishment of latency may result from the inability of IE genes to induce lytic infection. Marshall et al. (65) showed that HSV-1 established latency in mice in the presence of impaired IE gene expression and the latency was not affected by restoration of VP16, ICP0, or ICP4 coding sequences. These observations suggest that the latency is increased when IE gene expression is inadequate to initiate the lytic infection. The presence of HSV-1 DNA in the nucleus of infected neurons is an important factor for HSV-1 to establish latency (56). During latency, the role of VP16 to initiate lytic gene expression may be inhibited by a defect in the VP16 transport from nerve endings to the neuronal cell body, or due to the presence of this protein in reduced amounts in the neurons (66). Two competitive inhibitors for transcription of VP16, namely the octamer-binding protein (Oct-2) (67) and N-Oct3 (68) compete with VP16 for binding to an  $\alpha$  gene promoter. VP16 fails to form a complex with HCF-1 in the Golgi apparatus of sensory neurons. The HCF-1 protein moves to the nucleus upon reactivation of HSV-1 *in vitro* (69). In humans, HSV-1 reactivation can be spontaneous or results from exposure to ultraviolet (UV) irradiation, emotional stress, fever, or immune suppression. Reactivation causes shedding of the virus transported through neuronal axons to the epithelial cells where it can replicate and start a lytic cycle. Hyperthermia efficiently induced HSV-1 reactivation from latency in a few neurons of the TG in infected mice (70). In latency, a single transcript is generated, which encodes a precursor for four distinct HSV miRNAs, which act to suppress virus replication (71).

### IMMUNE RESPONSE TO HSV-1

Initial host responses to viral infection include production of interferons- $\alpha/\beta$  by the first cells infected, IFN- $\gamma$  by human natural killer (NK) cells recognizing the gB and gC of virus-infected targets (72), and proinflammatory cytokines and chemokines by monocytic cells (73). Viruses are recognized by the innate immune system through PRRs such as the Toll-like receptors (TLRs). HSV virions are recognized by the cell membrane TLR2 and intracellular HSV genomic DNA is recognized by the cytoplasmic TLR9. Dendritic cells recognize HSV using both TLR2 and TLR9 (74). Virus-induced IFN- $\alpha$  and IFN- $\gamma$  are products of human peripheral mononuclear leukocytes (PML) exposed to UV and light-inactivated HSV (75). In the innate response to HSV-2, TLR2 and TLR9 restrict viral load in the brain by synergizing to induce an early cytokine (type I IFN, IL-6, IL-12, RANTES) and cellular responses (76, 77). In mice lacking both TLR2 and

TLR9, HSV induces uncontrolled virus replication and lethal encephalitis (77).

### THE ROLE OF EXOSOMES (MICROVESICLES OR L-PARTICLES) IN HSV-1 IMMUNITY

Both B cell and T cell immune responses develop during primary viral infection. However, early viral evasion strategies interfere with complete elimination of virus and permit persistence of HSV-1. During HSV-1 infection, microvesicles/exosomes containing viral tegument proteins and glycoproteins, some of which are early transcription factors, are released. Because these virus-like vesicles lack both the viral capsid and DNA, they cannot produce a replication-infective cycle, but can interfere with immune elimination of virus (29, 30, 78). Also, the viral envelope gB is involved in inhibiting the MHCII molecule antigen-processing pathway by coupling with HLA-DR and shunting the complex through microvesicles/exosomes instead of the cell surface (31). This capture of the gB-HLA-DR complex puts complexes into the cellular microenvironment to induce tolerance in bystander T cells (27, 31).

### IMMUNE EFFECTOR CELLS AND LATENCY

An understanding of the mechanisms that control the HSV-1 latency is elusive. Reactivation from latency is associated with pathological disease due to shedding of the reactivated virus from the sensory ganglia (79). CD8<sup>+</sup> T cells can inactivate HSV-1 without inducing neuronal apoptosis. It was shown that CD8<sup>+</sup> T cell lytic granules, granzyme B, can destroy the HSV-1 IE protein, ICP4, which acts as transactivator of  $\beta$  genes required for viral DNA replication. HSV-1 latency is accompanied by chronic inflammation without neuronal damage (80). Trigeminal ganglia latently infected with HSV-1 are infiltrated with CD3<sup>+</sup> and CD8<sup>+</sup> T cells, CD68-positive macrophages, IFN- $\gamma$ , tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), IP-10, and RANTES. These observations suggest that the presence of the immune cells and elevated levels of cytokines within the latently infected trigeminal ganglia are responsive to the clinical use of immunosuppression drugs and subsequent reactivation of virus in the cranial nerves. Immune cell infiltration in latently infected trigeminal ganglia may occur in response to spontaneous reactivation of some neurons leading to expression of HSV-1 lytic cycle transcripts (81). Because of the absence of detectable virus in latently infected TG, this process was referred to as spontaneous molecular reactivation.

CD8<sup>+</sup> T cells and macrophages/microglia and their cytokine, TNF- $\alpha$ , exert a role in maintaining HSV-1 latency in the trigeminal ganglia. However, NK cells and  $\gamma\delta$  T cells and their production of IFN- $\gamma$  play a role in preventing viral replication during the lytic infection (82). HSV-specific CD8<sup>+</sup> T cells migrate to and are retained in the ophthalmic branch of the TG after intraocular infection (83). In the absence of replicating virus, HSV-1-specific CD8<sup>+</sup> T cells remain active, secreting IFN- $\gamma$  in the latent TG. The activated virus-specific memory CD8<sup>+</sup> T cells, expressed the CD94-NK cell receptor subfamily G2a inhibitory molecule. These cells were not cytotoxic for the Qa-1<sup>b</sup>-expressing neuronal targets, of which there were many in the HSV-1 latent TG. When the Qa-1<sup>b</sup>/CD94-NKG2a interaction was blocked in *ex vivo* experiments, neuronal lysis occurred. Since TGF- $\beta$ 1 can induce expression of

the inhibitory CD94-NKG2a molecules, the source of bioactive TGF- $\beta$ 1 in the latent TG was attributed to CD4<sup>+</sup>Foxp3 Treg cells also present in the latent TG (83). These observations indicate the presence of a regulatory system that protects irreplaceable neurons from immune destruction (83). Qa1 expression, whether on neurons or lymphoid cells present in the TG, is protected; binding of CD94/NKG2a to Qa1 on activated CD4<sup>+</sup> T cells provides protection from NK cell-mediated lysis (84).

### IFN- $\gamma$ AND HSV-1 INDUCE EXPRESSION OF SOCS1

SOCS1 expression in response to IFN- $\gamma$  by sensory neuronal cells, but not by microglia, is responsible for the lack of expression of class I MHC molecules by sensory neurons (85). HSV-1 can evade the immune response by SOCS1 expression (41). HSV-1 is resistant to anti-viral effect of IFN- $\gamma$  in keratinocytes, the major cell replicating virus in recurrent lytic infection. HSV-1-infected keratinocytes exhibit high levels of SOCS1 mRNA and protein expression by preventing STAT1 $\alpha$  activation in response to IFN- $\gamma$  signaling. In this same study, viral ICP0 was involved in activating host cell SOCS1 gene; i.e., both IFN- $\gamma$  and HSV-1 induced expression of SOCS1 in keratinocytes (41).

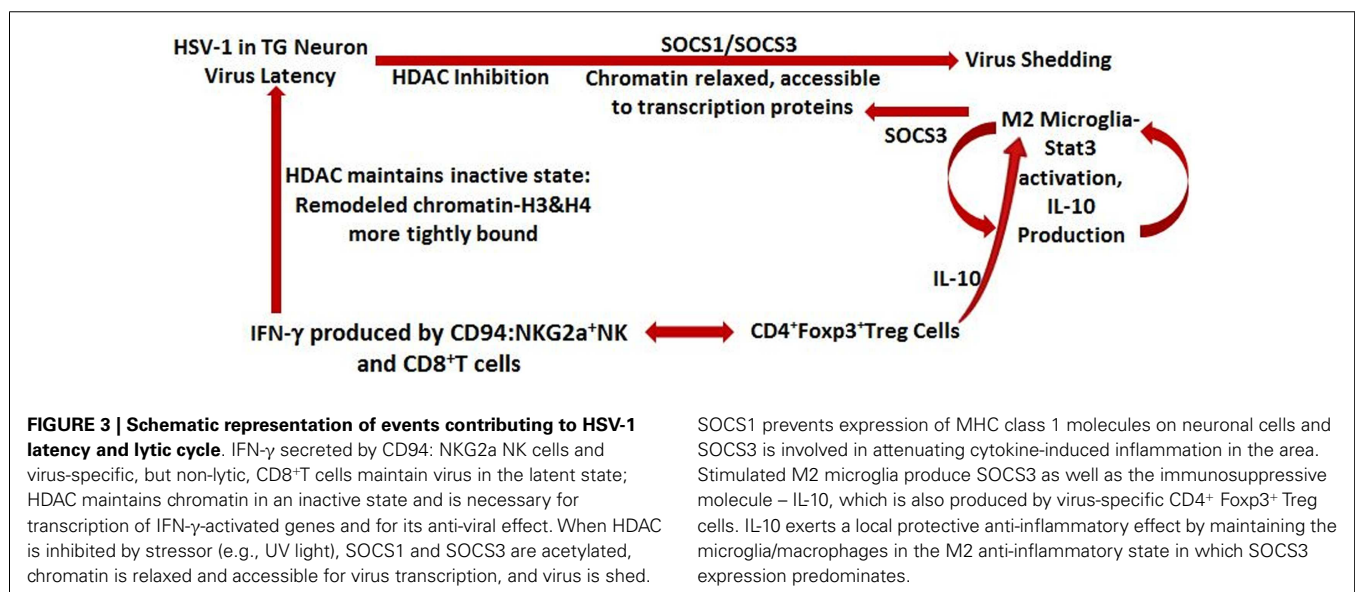
The conundrum involving the association and interactions of histones, HSV-1, IFN- $\gamma$ , and SOCS1/3 in herpesvirus infection and latency is intriguing. Protein acetylation is important in herpesvirus infection as well as in activation of IFN- $\gamma$ -stimulated genes. Histone acetylation determines how tightly the DNA is wound around the histones. In histones H3 and H4, chromatin is relaxed and accessible to the transcriptional proteins and subsequent increase in gene transcription. In areas of hypoacetylation, chromatin is condensed and genes are silenced (86). Histone deacetylases (HDACs) are transcriptional and epigenetic regulators controlling HSV-1 infection (87). Trichostatin A (TSA), an HDAC inhibitor, suppresses JAK2/STAT3 or JAK3/STAT3 signaling by inducing the promoter-associated histone acetylation of SOCS1 and SOCS3 (88). TSA treatment causes a relaxation of the chromatin structure, a process essential for initiation of transcription.

Induction of SOCS1 and SOCS3 expression by TSA is associated with an increase in acetylation of H3 and H4 histone proteins in colorectal cancer cells (88). TSA treatment of HSV-1-quiescently infected neurons induces a productive lytic infection (89). HDAC is essential for the transcriptional activation of IFN- $\gamma$ -stimulated genes and for host anti-viral immune responses; TSA treatment of cell cultures (HepG2, Huh7, and HeLa cells) promoted the proteasomal degradation of IFN regulatory factor 1 (IRF-1) (90). These observations contribute to a deeper understanding of the fact that IFN- $\gamma$  is essential in the TG to maintain virus latency. When IFN- $\gamma$  is neutralized by specific antibody, virus replication occurs in the brain stem of latently infected mice (3).

When SOCS1 level is elevated over that of SOCS3 in macrophages/microglia, an inflammatory M1 phenotype exists secreting inflammatory cytokines (Bigley et al., unpublished observations) and when SOCS3 predominates in these cells, an anti-inflammatory phenotype exists (91). SOCS3 is involved in attenuating the cytokine-induced inflammatory response in macrophages and microglia by production of endogenous IL-10 and STAT3 activation (92). These observations are illustrated in **Figure 3**.

### CONCLUSION

The actin-microtubule cytoskeletal reorganizations that occur in response to HSV-1 infection permit retrograde and anterograde transit of HSV-1 in lytic infection as well as the epigenetic changes that occur in HSV latent and lytic infections. IFN- $\gamma$  suppression of actin remodeling of the cytoskeleton may influence its anti-viral effect. Cytoskeletal reorganizations involved in retrograde transport of HSV-1 to the neuronal cell nucleus, where viral replication or latency is initiated, to the anterograde transport and export of replicated virus depend on a variety of viral and cytoskeletal protein interactions. A unifying model is proposed to explain latency and emergence from latency at histone H3 sites in nuclei of sympathetic neurons as an active ongoing process. Maintenance of latency involves intimate interactions



among immune cells, virus-specific non-lytic CD8<sup>+</sup> cytotoxic T cells and CD4<sup>+</sup>CD25<sup>+</sup>Foxp3<sup>+</sup> Treg cells, and M2 microglia. HSV-1 latency occurs when HDAC maintains chromatin in an inactive state permitting IFN- $\gamma$  produced by NK cells and non-cytolytic CD8<sup>+</sup> T cells to exert its anti-viral effect. The anti-inflammatory state of the M2 microglia/macrophages is maintained by IL-10 produced by the SOCS3-producing M2 microglia/macrophages and by virus-specific CD4<sup>+</sup>Foxp3<sup>+</sup>Treg cells. When HDAC is inhibited, SOCS1 and SOCS3 are acetylated and chromatin is relaxed, permitting virus transcription and replication and anterograde transport and shedding of HSV-1 in a lytic cycle of infection. Modulation of SOCS1–SOCS3 expression is a potential strategy for the treatment of not only viral infections but also inflammatory diseases.

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