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Oncolytic herpes simplex virus interactions with the host immune system

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Abstract

Oncolytic viruses (OVs), like oncolytic herpes simplex virus (oHSV), are genetically engineered to selectively replicate in and kill cancer cells, while sparing normal cells. Initial OV infection, cell death, and subsequent OV propagation within the tumor microenvironment leads to a cascade of host responses (innate and adaptive), reflective of natural anti-viral immune responses. These host-virus interactions are critical to the balance between OV activities, anti-viral immune responses limiting OV, and induction of anti-tumor immunity. The host response against oHSV is complex, multifaceted, and modulated by the tumor microenvironment and immunosuppression. As a successful pathogen, HSV has multiple mechanisms to evade such host responses. In this review, we will discuss these mechanisms and HSV evasion, and how they impact oHSV therapy.

Graphical abstract

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Introduction

Oncolytic viruses (OVs) are a new and unique class of cancer therapeutics, with cancer cell selective replication, cytotoxicity, and spread, that is often coupled to anti-tumor immunity (immunovirotherapy) [1*,2]. Herpes simplex virus type 1 (HSV-1) was the first genetically engineered OV, originally developed for glioma [3]. An enveloped virus with a 152 kb DNA genome, HSV-1 is a human pathogen that is endowed with oncolytic activity by mutating non-essential genes involved in virus growth in post-mitotic cells (i.e., thymidine kinase, ribonucleotide reductase (ICP6)), counteracting innate anti-viral responses (i.e., γ 34.5, ICP0, Us3) and pathogenicity (i.e., γ 34.5, UL56, ribonucleotide reductase (ICP6)) [3]. In 2015, the FDA approved the first OV, an oncolytic HSV (oHSV), talimogene laherparepvec (T-VEC, Imlygic), for advanced melanoma [4]. Cancer treatment with oHSV, like other OVs, induces a variety of immune and inflammatory responses, both beneficial and detrimental. However, it has become increasingly recognized that OV-induced anti-tumor immunity plays a vital role in effective OV therapy of cancer [1*]. The cascade of host responses against HSV infection, which applies to oHSV, includes: serum factors (complement proteins and innate immunoglobulins); innate cytokine/chemokine cascades; recruitment and activation of innate immune cells; and induction of adaptive immune responses [5,6] (Figure 1). As a successful pathogen, HSV has multiple mechanisms to evade such host responses: inactivation of complement and immunoglobulins by viral glycoproteins; inhibition of interferon (IFN) responses and cytokine/chemokine production from infected cells [5]; blocking maturation of antigen presenting cells (APCs) [6]; escape from host immune surveillance through down-regulation of MHC class I expression [7]; and inhibition of apoptosis and cytotoxic T lymphocyte (CTL)-induced cell death [8]. A better understanding of the complex landscape of virus-host interaction is thus essential to refine oHSV strategies to improve therapeutic outcomes and understand oHSV immune vulnerabilities. In this review we will discuss different innate and adaptive anti-viral mechanisms elicited by a host in response to HSV-1 infection, and how HSV-1 overcomes the host's anti-viral defensive mechanisms.

Host responses against HSV infection

Complement proteins and immunoglobulins

Serum complement proteins play an important role in limiting the HSV-1 infection [9]. Sera originating from HSV-1 sero-negative humans inactivate more than 88% of oHSVs, while sera from HSV-unexposed mice also showed nearly identical anti-HSV potency [10]. The effect of complement can be partially ablated by treatment with cobra venom factor (CVF), such that intravascular delivery of oHSV to intracerebral tumors was greatly enhanced by CVF treatment [11]. Innate immunoglobulins IgG and IgM present in the sera of HSV-seronegative humans, rats and mice can specifically bind to oHSV, while pretreatment with anti-IgG or -IgM antibodies significantly depleted the ability of human or rat, but not mouse serum to inactivate oHSV [10,12]. Exposure to cyclophosphamide (CPA) acutely can partially suppress this IgM effect, while at longer times CPA suppresses neutralizing antibodies [12]. CPA in combination with CVF further improves oHSV propagation [11].

HSV-IgM complexes activate C1q, a subcomponent of C1 complement complex, and the classical complement pathway, which was sufficient to neutralize HSV [13].

Cytokine/chemokine signaling pathways

Once HSV enters into tumor cells, it replicates, kills the tumor cells, and subsequently propagates within the tumor microenvironment. During this process, HSV can activate multiple signal transduction pathways, including Nuclear Factor kappa B (NF- κ B), interferon (IFN) Regulatory Factors (IRFs) and Mitogen-Activated Protein Kinase (MAPK) pathways, resulting in induction of cytokine production in HSV-infected cells [14,15]. Stimulation of NF- κ B and IRF pathways occur when HSV glycoprotein H/L complex interacts with the α v β 3-integrin signaling pathway, which results in induction of type I IFNs [16]. HSV infection activates pathogen recognition receptors (PRRs) like Toll-like receptor (TLR) 2 and 9 in dendritic cells (DCs), which in turn induce downstream activation of NF- κ B and transcription of immunomodulatory cytokines, such as IL-1 β , IL-6, IL-8, IL-10, IL-12, TNF- α , and IFN- γ [17]. HSV infection of human monocytes induces IL-15 expression due to TLR2 signaling [18]. Engagement of TLR3 and activation of NF- κ B also occurs following HSV infection of neuronal cells and astrocytes, resulting in up-regulation of cytokines IL-6 and TNF- α [5]. A variety of other cytokines have also been detected in HSV-infected tissues of both mouse and human, including; IFN- α , IFN- β , IL-1, IL-2, IL-4, IL-5, and IL-23 [19].

Cytokines and chemokines derived from oHSV-infected tumor cells or cells of the tumor microenvironment limit oHSV replication and spread within the tumor and further induce stronger innate immune responses [20,21]. Chemokines CXCL9 (MIG) and CXCL10 (IP-10) are important in limiting HSV infections, recruiting natural killer (NK) and CD8⁺ T cells to the CNS [21]. OHSV 1716 infection of ovarian carcinomas induced CXCL9 and CXCL10 from monocytes and DCs, which led to the infiltration of NK and CD8⁺ T cells and the inhibition of tumor growth [22]. HSV-1 infection of macrophages and fibroblasts induces chemokine RANTES/CCL5 expression through a PKR-dependent mechanism [23]. Aside from its chemokine activity, RANTES binds directly to HSV virions via glycoprotein B (gB), damaging the virions [24]. The type I IFN (IFN- α/β) signaling pathway is critical in suppressing HSV replication and pathogenicity [25**], and orchestrating innate immune responses [15]. STAT1 activation in infected malignant peripheral nerve sheath tumor (MPNST) cells, with induction of IFN-stimulated genes (ISGs), was associated with reduced oHSV R3616 (γ 34.5) replication, while JAK inhibitor ruxolitinib increased virus yield [26]. STAT3, as opposed to STAT1 and STAT2, is an important negative regulator of type I IFN signaling and is activated in many tumors [27]. Activation of STAT3 by HDAC inhibitor VPA or IL-6 enhanced oHSV replication in glioma cells, through inhibition of type I IFN signaling, whereas inhibition of STAT3 reduced replication [20].

Innate cellular immune responses

Cytokines and chemokines recruit innate immune cells (macrophages, NK, NKT, $\gamma\delta$ T cells) to the site of HSV infection, and activate them for further production of cytokines and chemokines, leading to a toxic cycle for HSV [28,29]. For example, IL-15 produced from peripheral blood mononuclear cells up-regulates the cytotoxic activity of NK cells against

HSV infections *in vitro* [30]. CPA treatment decreased innate cytokine expression (IFN α / β , TNF α , IL-15) in mononuclear cells and increased oHSV spread in brain tumors and extended survival [31]. IL-18 produced from activated macrophages induced IFN- γ production by NK cells and protected mice from HSV infections [32]. IFN- γ is also produced from activated macrophages and $\gamma\delta$ T cells in response to HSV infections, which further stimulates macrophages to produce TNF- α , which activates NK cells for HSV control [33]. Depletion of macrophages with clodronate liposomes or modulation of the tumor microenvironment with CPA (reducing IFN- γ expression and infiltration of macrophages) improves oHSV intratumoral spread and efficacy in brain tumors [34]. OHSV infections lead to increased infiltration of M1 type macrophages into the tumor, which produce significant amounts of TNF- α , resulting in TNF- α -induced apoptosis in infected tumor cells and inhibition of viral replication [35]. IL-6 produced from macrophages, has also been shown to control HSV-1 infection and immunopathology [36], in contrast to the effects of IL-6 in enhancing oHSV replication in glioma cells [20]. Microglial IL-6 expression was protective to neural progenitor cells after HSV-1 infection *in vitro*, while contrarily IL-6 and phospho-STAT3 were found to be elevated in HSV encephalitic brain, illustrating dependence on cell context [37].

HSV can trigger NK recognition of infected fibroblasts due to up-regulation of ligands for natural cytotoxicity receptors (NCR; NKp30, NKp46) [38]. Interestingly, this ligand up-regulation also occurs in oHSV-infected glioblastoma cells, which mediates NK lysis of oHSV-infected cells and decreased oHSV efficacy [29]. Identification of the ligands could provide a target to enhance anti-tumor activity. TGF- β , an immunosuppressive cytokine, has been shown reverse NK cell and macrophage mediated inhibition of oHSV replication in glioblastoma cells *in vitro* and to improve oHSV efficacy *in vivo* [39*]. Transgenic mice expressing dominant negative TGF- β receptor in CD11c innate cells, but not CD4⁺ T-cells, had reduced virus replication in the eye, while expression in CD4⁺ T-cells resulted in reduced leukocyte infiltration [40].

Adaptive immune responses

DCs are professional APCs that coordinate innate and adaptive immune responses. They are key to protecting against HSV; immature DCs sense HSV and efficiently take-up and process antigens leading to their maturation and migration to lymph nodes where they prime and activate T-cells [6]. DCs express a broad array of PRRs that recognize HSV pathogen-associated molecular patterns (PAMPs) [14]. HSV gH/gL and gB bind to TLR2 and activate NF- κ B [41]. Activated DCs stimulate IFN- γ secretion from HSV-specific CD4⁺ and CD8⁺ T-cells [42]. OHSV infection of tumor cells leads to immunogenic cell death and the release of viral and tumor-associated antigens (TAAs), which can be cross-presented by DCs [1*]. Both CD4⁺ Th1 cells and CD8⁺ effector T-cells play a role in limiting HSV disease. HSV-specific CD8⁺ T-cells can clear established lytic infections, but are less effective at blocking the initial spread of virus [43]. HSV has also been shown to activate T regulatory cells (Tregs), including upregulation of OX40 and CTLA-4, which suppress effector and memory CD8⁺ cells [44]. Cancer cell specific CTL activity and anti-tumor efficacy is increased by CPA after oHSV treatment of syngeneic tumors [45]. B cells are also important in controlling HSV infection, through both innate (IgM) and adaptive (APCs activating CD4⁺

T-cell responses) immunity [46]. B cells cooperated with DCs in Th1 memory CD4⁺ T-cell recall responses, with immunized mice succumbing to HSV-2 pathogenicity in their absence [47]. A schematic overview of host responses against HSV infection is provided in Figure 2.

HSV evasion of host antiviral responses

While HSV induces anti-viral innate and adaptive immune responses, it also expresses proteins that inhibit both the induction and activity of those responses, allowing the virus to evade the immune system and establish both a productive and latent infection [5,15] (Figure 1). In the context of oHSV immunovirotherapy, some of these viral genes can be detrimental or beneficial. The immune evasion functions of HSV genes are listed in Table 1. In addition, pharmacological manipulation of different immune pathways or cell types can enhance oHSV efficacy [2].

Evasion of host initial defense mechanisms

HSV envelope glycoproteins not only function for virus entry, but also to escape humoral defense mechanisms. HSV gC binds and inactivates complement protein molecules (C3b, C5, and properdin), protecting HSV from complement-mediated virus neutralization induced by natural IgM [13] and antibody-independent complement neutralization [48]. Glycoprotein E and gI encode Fc receptors (FcγR) that bind IgG, with gE/gI binding monomeric IgG and gE binding IgG complexes [49]. This binding blocks antibody-mediated complement activation and antibody-dependent cellular cytotoxicity and contributes to pathogenicity *in vivo* [50]. Glycoprotein D (gD) down-regulates CD112, a ligand for the DNAM-1 (DNAX accessory molecule 1) receptor of activated NK cells, resulting in NK inability to bind and lyse HSV-infected or gD-transfected cells [51]. HSV reduces the expression of CD1d molecules on the surface of APCs, impairing their stimulation of NKT cells [52].

Inhibition of IFN signaling and cytokine/chemokine signaling pathways

HSV expresses several immune evasion genes to escape the host's anti-viral immune surveillance mechanisms [5,15] (Table 1). Because of defects in those pathways in cancer cells, mutations in many of these genes endow oncolytic activity to HSV [3]. Type 1 IFN production and its signaling pathway is key to antiviral innate immunity and thus HSV targets multiple steps in the pathway: (i) TLR signaling pathway; TLR3 and TLR2 signaling to TRAF6 are inhibited by Us3 [53], TRAF3 is inhibited by UL36 deubiquitinase [15], MyD88 and NF-κB subunits P50 and P65 are inhibited by ICP0 [54], nuclear translocation of NF-κB is inhibited by UL42 and Us3 [55,56], and ICP27 blocks NF-κB by binding to IκBα [57]. (ii) RIG-I-like receptor (RLR) signaling pathway; Us11 binds to PACT, RIG-I and MDA-5 to inhibit interaction with MAVS [58,59*], γ34.5 binds to TBK1 and inhibits IRF3 phosphorylation [60*], as does VP24 [61], Us3 hyper-phosphorylation of IRF3 blocks activation [62], ICP0 inhibits IRF3 translocation to the nucleus [63], and VP16 interferes with IRF3-CBP complex to inhibit transcription [15]. (iii) DNA sensor signaling pathway; IFI16 is inhibited by ICP0 in a dynamic fashion in the nucleus [64]. (iv) IFN-stimulated genes: UL41 (vhs) inhibits viperin, ZAP, and tetherin through mRNA degradation [15,65], and Us11 inhibits OAS [66] and PKR [67]. PKR phosphorylates eIF2α, which shuts down

protein synthesis. γ 34.5 activates protein phosphatase 1 α to dephosphorylate p-eIF2 α and restore protein synthesis [14], and overcomes IFN-induced anti-viral mechanisms [14]. ICP27 prevents STAT-1 phosphorylation and activation [68]. Several of these immune evasion genes (γ 34.5, ICP0, Us3) have been deleted/mutated in oHSV [3], because cancer cells tend to be defective in IFN signaling [1*].

Inhibition of adaptive immune responses

HSV has evolved numerous mechanisms to block DC function [6]. HSV efficiently infects both immature and mature human DCs, which leads to an inability to mature or down-regulation of maturation, but not cytokine secretion, and induces apoptosis early after infection [6]. γ 34.5, through targeting TBK1 and IKK α/β , inhibits DC maturation and interferes with antigen presentation through inhibition of autophagy [14,69]. HSV activates β 2 integrins in infected mature human monocyte-derived DCs, which enhances adhesion, and down-regulates expression of CCR7, which mediates CCL19 chemotaxis to lymph nodes, thereby impeding migration and T-cell activation [70]. ICP0 induces degradation of CD83, a marker of DC maturation, resulting in reduced T-cell stimulation [71]. ICP47 down-regulates MHC I-peptide presentation by blocking transporter associated with antigen presentation (TAP) in infected human cells, including cancer cells [7]. This results in no MHC I-mediated antigen presentation to CD8⁺ T-cells and escape from immune surveillance [7]. Inhibition of mouse TAP with oHSV expressing bovine herpes virus UL49.5 improved anti-tumor efficacy in syngeneic tumor models, dependent on CD8⁺ T-cells, and with increased virus [72*]. The MHC II processing pathway in CD4⁺ T cells is down-regulated by HSV-1 through reduction in invariant chain (Ii) expression and binding of gB to HLA-DM and -DR [73]. Both γ 34.5 and UL41 block accumulation of MHC class II proteins on the cell surface of glioblastoma cells, resulting in interference in antigen presentation to CD4⁺ T cells [74].

HSV infection also modulates T cells. Us3 interrupts TCR signaling by inhibiting the linker for activation of T cells (LAT) [53]. In T cells, HSV inhibits NF- κ B activation and synthesis of pro-inflammatory cytokines like IL-2 and TNF- α , while activating STAT3 and the MAPK p38 and JNK pathways, and IL-10 synthesis [75]. Co-culture of T cells with HSV-infected fibroblasts or direct infection induced apoptosis [76]. For cancer therapy in immunocompetent models, oHSV acts as an *in situ* vaccine, with T-cells playing a critical role as immune cell mediators of efficacy [2,77]. Both in mice and T-Vec melanoma responders, oHSV treatment led to a reduction in Tregs [77,78]. In the T-Vec phase III clinical trial durable responses were observed not only in injected lesions, but also non-injected, with 11% of patients having complete responses, strongly suggestive of robust immune responses [1,78*]. Augmenting this with immune modulators like immune checkpoint inhibitors or expression of immune modulatory transgenes like IL-12 is actively being pursued [3,77,78].

Autophagy is a major cellular degradative pathway, including for cellular pathogens like HSV, as well as for MHC I and II presentation in APCs [79]. γ 34.5 binds beclin 1, preventing autophagosome formation [80**]. HSV-1 with γ 34.5 deleted for the beclin 1 binding domain has increased autophagy in culture and is attenuated for neuropathogenicity,

but is able to dephosphorylate eIF2 α and replicate similar to wild-type virus in culture [80*,81]. As opposed to γ 34.5-deleted oHSV, oHSV lacking the beclin 1 binding domain, 68H-6, is able to replicate in glioblastoma stem cells [81]. Us11 is also able to block autophagy through its interaction with PKR [82*].

Inhibition of cell death

Several HSV genes, such as Us3, Us5 (gJ), gD, and ICP6 are involved in the inhibition of apoptosis of HSV-infected cells, thus allowing HSV-infected cells to survive long enough to complete viral replication [8] (Table 1). Us3 inhibits apoptosis through multiple interactions; inhibiting cytochrome c and caspase-3 activation, programmed cell death protein 4 (PDCD4) [83], and pro-apoptotic proteins Bad and Bid [84]. Because of this, Us3-deleted HSV has oncolytic properties [85]. Glycoprotein J antagonizes the Fas ligand- and granzyme B-mediated pathways of CTL-induced apoptosis [86]. HSV deleted for Us12 or Us3 were defective in preventing T cell mediated lysis but not apoptosis, while gJ-deleted HSV was defective in both [87]. Necroptosis is another form of regulated cell death that occurs in the absence of caspases. HSV-1 ICP6 and HSV-2 ICP10 suppress apoptosis by blocking TNF- α - and Fas ligand-mediated caspase 8 [88], as well as blocking TNF-induced necroptosis in human cells by inhibiting the interactions between RIP1 and RIP3 [89]. In mice, ICP6 has the opposite effect, binding to RIP3 to activate necroptosis [8,90*].

Conclusions

HSV-host interactions are complex and accumulating evidence suggests that the interaction impacts the therapeutic outcome of oHSV therapy of cancer. Successful use of HSV as an oncolytic agent requires molecular and cellular understanding of HSV-host immune interactions, involving an array of signaling pathways and host cell types. HSV utilizes various immune evasion mechanisms to evade host anti-viral responses and promote virus replication. To minimize pathogenicity and ensure tumor selectivity, oHSV have deletions of genes with immune-modulating functions such as γ 34.5, ICP6, and Us3. Such genetic alterations may elicit increased innate immune responses and attenuate viral replication and spread within the tumor, which in turn could reduce the magnitude of viral oncolysis and release of tumor antigens and other danger signals. Achieving a robust and smooth transition from innate to adaptive tumor-specific immunity is key to optimizing oHSV therapy of cancer. The immune responses can be further modulated pharmacologically (i.e., CPA, immune checkpoint inhibitors) and by arming oHSV with immunomodulatory transgenes that affect the tumor microenvironment, host immune defense mechanisms, and anti-tumor immunity to enhance anti-tumor efficacy. Further elucidation of mechanisms relating to HSV-host interactions will facilitate the design of next generation oHSV for improved cancer therapy.

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* of special interest

** of outstanding interest

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Highlights

- oHSV infection induces anti-viral responses that limit efficacy
- HSV encodes multiple proteins that inhibit innate and adaptive immune responses.
- oHSV antitumor immunity is a balance between immune stimulation and evasion

Figure 1.
Graphic representation of HSV-host immune interactions. [Graphical Abstract]

Figure 2.
Schematic overview of host immune responses to oHSV infection.

Table 1

Immune evasion mechanisms of HSV.

HSV genes or proteins	Functions	References
Glycoprotein B	Down-regulation of MHC II processing pathway in CD4 ⁺ cells	[73]
Glycoprotein C	Inactivates serum complement proteins	[13]
Glycoprotein D	Down-regulates NK receptor ligand and NK-mediated lysis; inhibition of apoptosis	[8,51]
Glycoproteins E and I	Inactivate circulating immunoglobulins	[49]
Us3	Inhibits NF- κ B activation and reduces cytokine expression, such as IL-8; inhibits induction of apoptosis; hyperphosphorylates IRF3 to block activation of RLR signaling pathway	[8,56,62]
Us5 (gI)	Antagonizes Fas ligand- and granzyme B-mediated CTL-induced apoptosis; inhibits perforin- or UV-induced cell death and apoptosis	[86,87]
VP16	Inhibits NF- κ B activation and blocks IRF3 pathway and IFN- β production	[15]
VP24	Inhibits IRF3 phosphorylation	[61]
Us11	Inhibits RLR signaling, PKR-induced eIF-2 α phosphorylation and autophagy; blocks OAS	[58,59*,66,67,82*]
ICP0	Blocks NF- κ B-mediated transcription of immunomodulatory cytokines, and IRF3- and IRF7-induced anti-viral signaling pathways; inhibits IRF3 translocation to the nucleus; inhibits IFI16; degradation of mature DC marker (CD83)	[54,63,64,71]
ICP6	Blocks TNF- α - and Fas ligand-mediated apoptosis through interacting with caspase 8 and necroptosis	[88,89]
ICP27	Blocks NF- κ B and IRF3 signaling pathways; blocks STAT1 activation and its translocation to the nucleus	[68]
γ 34.5	Suppression of PKR/eIF-2 α signaling pathway and IFN-induced anti-viral mechanisms; inhibits DC maturation and antigen presentation; blocks MHC class II accumulation on the cell surface; autophagy inhibition	[14,69,80**]
UL36	Inhibits TRAF3 of TLR pathway	[15]
UL41 (vhs)	Inhibits IFN-stimulated genes viperin, ZAP, and tetherin; blocks DC activation and maturation; blocks MHC class II accumulation on the cell surface	[14,65,74]
UL42	Inhibits nuclear translocation of NF- κ B	[55]
ICP47	Down-regulates MHC class I by inhibiting TAP	[7]