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Current Opinion in Virology

Oncolytic herpes simplex virus interactions with the host immune system

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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.

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Current Opinion in Virology 2016, **21**:26–34

This review comes from a themed issue on **Viral gene therapy vector-host interactions**

Edited by **David Markus** and **Roland Herzog**

http://dx.doi.org/10.1016/j.coviro.2016.07.007

Introduction

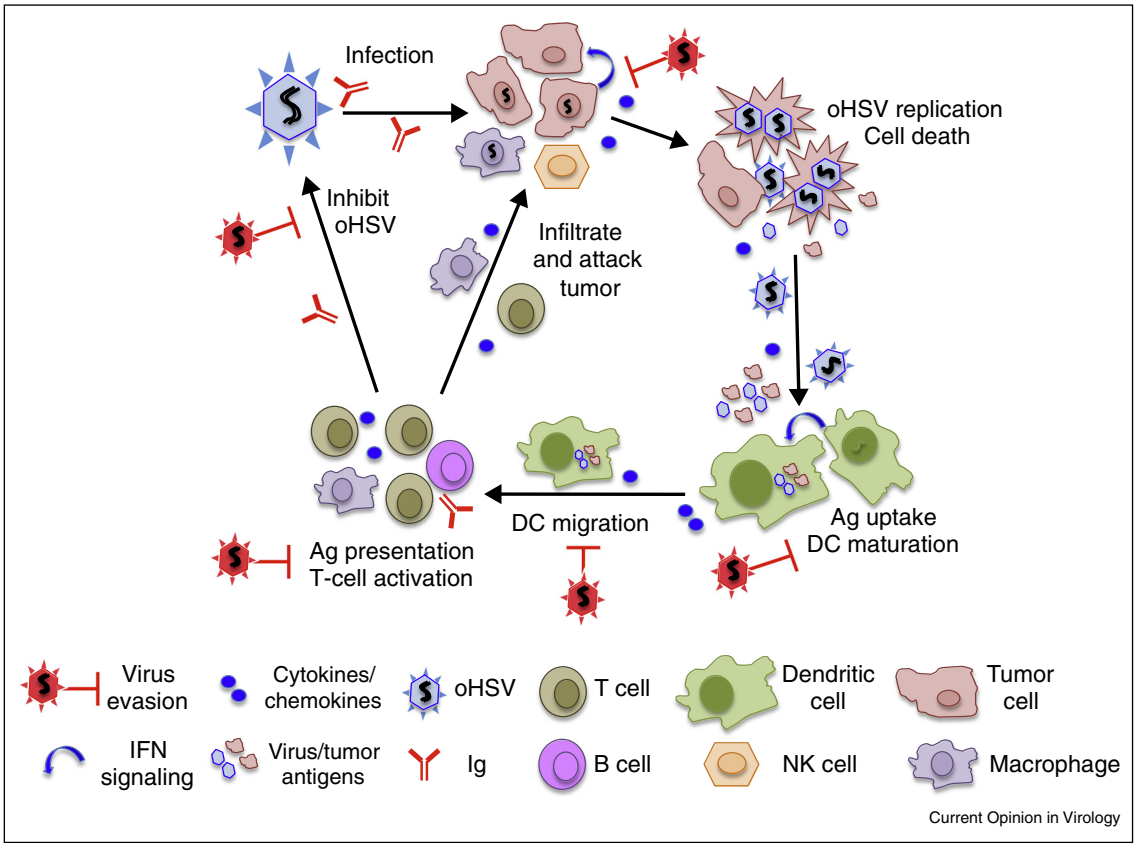
Oncolytic viruses (OVs) are a new and unique class of cancer therapeutics, with cancer cell selective replication, cytotoxicity, and spread, that is often coupled to anti-tumor immunity (immunovirotherapy) [1•,2]. Herpes simplex virus type 1 (HSV-1) was the first genetically engineered OV, originally 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., γ34.5, ICP0, Us3) and pathogenicity (i.e., γ34.5, UL56, 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-sero-negative humans, rats and mice can specifically bind to oHSV, while pretreatment with anti-IgG or anti-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

Figure 1



Graphic representation of HSV–host immune interactions.

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-κB), 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-κB and IRF pathways occur when HSV glycoprotein H/L complex interacts with the αvβ3-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-κB and transcription of immunomodulatory cytokines, such as IL-1β, 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-κB 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