Oncolytic Herpes Simplex Virus ICP47 Deletion Reverses Tumor Immune Evasion

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Abstract
Herpes simplex virus (HSV) is an enveloped, double-stranded DNA virus that has been used with modification as oncolytic viruses (OVs) against a number of tumor types. OVs represent a new class of therapeutic agents that promote anti-tumor responses through a dual mechanism of action that is dependent on selective tumor cell killing and the induction of systemic anti-tumor immunity. Among OVs, HSVs preferentially replicate in and lyse cancer cells, leading to in situ autovaccination, adaptive anti-virus and anti-tumor immunity. Suppression of antitumor immunity after OV therapy has been observed and the molecular and cellular mechanisms of action are recently reported. ICP47, a small protein produced by the herpes simplex virus, is considered as an important factor in the evasion of cellular immune responses in HSV-infected cells. Therefore, reviewing the research status of ICP47 is certainly helpful to improve the anti-tumor effect of oncolytic HSVs (oHSVs). Here, this review will focus on the following contents: 1) Anti-tumor mechanism of OVs; 2) Functions of early HSV genes; 3) The mechanism of immune escape of ICP47; 4) Recombinant HSV against cancer; 5) The functional verification of ICP47 deletion. This review highlights the current understanding of recombinant HSVs against cancers.

Keywords
Oncolytic Virus, HSV, ICP47, Anti-Tumor Immunity

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1. Introduction

Tumors are originated from transformed cells in tissues or organs, which contain heterogeneous cancer cells, such as tumor stem cells etc. [1] [2] [3] [4] [5], and tumor stromal cells, for instance immune cells etc., in tumor microenvironment [6]. And cancer is still a serious danger to human health [7]. Conventional chemotherapy and radiotherapy achieve limited efficacy leading to the search for novel ways to treat cancer [8]. The concept of using viruses as a cancer treatment drug dates back to the beginning of the last century, when it was observed that patients with different kinds of malignant tumors who underwent rabies vaccination or experienced viral diseases exhibited spontaneous tumor regression [9]. However, the use of wild-type viruses for cancer therapy was associated with serious adverse events. So with genetic-engineering of virus vectors to reduce pathogenicity, oncolytic virus (OV) therapy became a promising therapeutic strategy [10]. Replication-competent oncolytic HSV (oHSV) vectors target actively dividing neoplastic cells while sparing normal cells and can be exploited as a therapeutic strategy for the selective destruction of tumors without damaging adjacent normal tissue [11]. The infected neoplastic cells, which are killed by the replicating viruses, release progeny virions [12]. This model of viral amplification and lateral cell-to-cell transmission lead to the further destruction of surrounding cancer cells. As these viruses destroy tumor cells by oncolysis, cross-resistance with other therapy approaches, such as radiotherapy, chemotherapy and hormonal therapy, typically does not arise [13]. Thus oHSV selectively propagates in cancer cells while displaying minimal adverse effects in healthy cells, making it one of the most promising treatments [14]. Thus, the research of the ICP47 status, involving in both viral replication and immune escape, is beneficial to the function enhancement of oHSV.

2. Anti-Tumor Mechanism of Oncolytic Virus

Oncolytic viruses are therapeutically useful viruses that selectively infect and damage cancerous tissues without causing harm to normal tissues [15]. It can kill infected cancer cells in many different ways, ranging from direct virus-mediated cytotoxicity through a variety of cytotoxic immune effector mechanisms [16]. Oncolytic viruses typically takes over and controls the molecular cell death machinery of the infected cancer cells, allowing death to occur only after available cellular resources have been maximally exploited for the replication and assembly of new viruses [17]. In addition to killing infected cells, oncolytic viruses can mediate the killing of uninfected cancer cells through indirect mechanisms such as destruction of tumor blood vessels, amplification of specific anticancer immune responses, or the specific activity of proteins expressed from engineered viruses encoded by transgenes [18] (Figure 1).

3. Functions of Early HSV Genes

HSV transcription is complexly regulated by both viral and cellular factors [19].

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Figure 1. Infection and killing of tumor cells by an oncolytic virus. (a) An oncolytic virus cannot replicate in normal, healthy cells; (b) An oncolytic virus targets a cancer cell, multiplying within the cells before destroying them, and virus replication leads to cell lysis (direct effect) and the release of progeny virions, resulting in virus spread throughout the tumor, causing the body's immune response.

There are five immediate-early proteins in HSV: infected cell polypeptide (ICP)0, ICP4, ICP22, ICP27 and ICP47. The first four are involved in the regulation of viral transcription [19]. ICP4 is a transcription factor that recruits cellular complexes, including TFIID, to viral DNA to enhance transcription initiation and can also function to repress transcription of some viral genes [20]. ICP0 is an immediate early viral protein crucial in both lytic and latent HSV-1 infection [21]. The main function of ICP0 is to offset the cellular frontline antiviral defenses and consequently to enhance downstream viral gene expression. The most important functional domain of ICP0 is a RING-type E3 ubiquitin ligase located in its second exon, which targets several host factors for proteasome-dependent degradation. Some of the ICP0 E3 substrates are part of the host intrinsic defenses. Their degradation contributes to the augmentation of viral DNA expression and DNA replication [22]. ICP27 is involved in the nuclear export of viral mRNAs and has a role in recruiting RNA Pol II to viral genes. ICP27 is the first viral protein shown to activate cryptic polyadenylation signals (PASs) in introns [23]. ICP22 plays a role in recruiting elongation factors like the complex to the HSV-1 genome to allow for efficient viral transcription elongation late in viral infection and ultimately infectious virion production. In the absence of ICP22, viral production is reduced globally in the late stages [24]. ICP47 effectively blocks the major histocompatibility complex class I (MHC I) antigen presentation pathway. ICP47 binds with high affinity to the human transporter associated with antigen presentation (TAP) and blocks its binding of antigenic peptides [25]. Association of ICP47 precludes substrate binding and prevents nucleotide-binding domain closure necessary for ATP hydrolysis. By blocking viral antigens from entering the endoplasmic reticulum, HSV is hidden from cytotoxic T lymphocytes (CTL), which may contribute to establishing a lifelong infection in the host [26].
4. The Mechanism of Immune Escape of ICP47

Cellular immunity against viral infection and tumour cells depends on antigen presentation by MHC I molecules [27]. Intracellular antigenic peptides are transported into the endoplasmic reticulum by the TAP and then loaded onto the nascent MHC I molecules, which are exported to the cell surface and presented to the immune system. CTL recognize non-self peptides and kill the infected or malignant cells. Defects in TAP account for immunodeficiency and tumor development. To escape immune surveillance, some viruses have evolved strategies either to down regulate TAP expression or directly inhibit TAP activity [28]. HSV evades CD8+ T-cells by producing ICP47, which limits immune recognition of infected cells by inhibiting TAP [29]. ICP47 is targeted at TAP, one of the important proteins that determine the efficiency of antigen presentation by MHC-I. ICP47 through competition with immunological peptides in combination with the TAP peptide binding sites, reduces the peptide transport function of the TAP, resulting in instability of no-load MHC I molecules. The expression of MHC I on tumor cell surface was significantly decreased, which directly interferes with the MHCI mediated CTL activation. Then HSV avoid the host immune clearance, even become a virus of reserve in the body [30] (Figure 2).

5. Recombinant HSVs against Cancers

HSV offers particular advantages for use as an oncolytic virus. The engineered
oHSVs have demonstrated remarkable safety in clinical trials, with some evidence of efficacy [31]. The first recombinant HSV strain directed against cancer, dlsptk, was generated through the deletion of the UL23 gene encoding thymidine kinase (TK) [32]. TK processes nucleotides to facilitate replication of viral DNA. In the absence of HSV TK, HSV-1 infecting normal cells would fail to replicate at a rate sufficient to sustain infection. While the efficacy and selectivity of dlsptk established a proof of principle for the use of HSV-1 genome deletions to achieve tumor selectivity through selective attenuation, the TK deletion was ultimately problematic from the standpoint of clinical application, as it rendered the strain impervious to first-line anti-herpes medications. This resistance represented to many the loss of a crucial safety control for clinical experimentation with viral therapies [33]. Thus, dlsptk and its TK deletion were abandoned. HSV-G207 features a single deletion of UL39 (ICP6) and double deletion of RL-1 (ICP34.5). ICP34.5 is the major gene determinant of HSV neurovirulence [34]. ICP34.5 precludes the shut-off of host protein synthesis in infected cells [35]. ICP6 is the large subunit of viral ribonucleotide reductase, a key viral enzyme for DNA synthesis that is necessary for virus replication in normal non-dividing cells. These two generations of oHSVs are designed to reduce viral replication in non-cancer cells. A third-generation oHSV vector, G47Δ, was created by adding to the UL39 and RL1 deletions of G207 a deletion of the HSV-1 gene α47 (ICP47) (Figure 3).

![Figure 3](image_url)

**Figure 3.** Recombinant HSVs against cancers. The first recombinant HSV strain directed against cancer, dlsptk, was generated through the deletion of the UL23 gene encoding thymidine kinase (TK). HSV-G207 features a single deletion of UL39 (ICP6) and double deletion of RL-1 (ICP34.5). A third-generation oHSV vector, G47Δ, was created by adding to the UL39 and RL1 deletions of G207 a deletion of the HSV-1 gene α47 (ICP47).
6. The Functional Verification of ICP47 Deletion

Because the ICP47 inhibits TAP, which translocates peptides across the endoplasmic reticulum, the down-regulation of MHC class I that normally occurs in human cells after infection with HSV-1 does not occur when the \( \alpha 47 \) gene is deleted. G47\( \Delta \)-infected human cells in fact presented higher levels of MHC class I expression than cells infected with other HSV-1 vectors [36]. Further, human melanoma cells infected with G47\( \Delta \) were better at stimulating their matched tumor-infiltrating lymphocytes \textit{in vitro} than those infected with G207. The deletion also places the late US11 gene under control of the immediate-early \( \alpha 47 \) promoter, which results in suppression of the reduced growth phenotype of \( \gamma 34.5 \)-deficient HSV-1 mutants including G207. In the majority of cell lines tested, G47\( \Delta \) replicated better than G207, resulting in the generation of higher virus titers, and exhibiting greater cytopathic effect [37]. Therefore, the verification of ICP47 deletion is particularly complex and important. There are two main methods: start with the HSV DNA/RNA sequence to verify the integrity of HSV and verify the functional changes of oHSV to indirectly prove whether ICP47 is deleted [36] (Figure 4).

**Southern Blot:** southern blot is a method used in molecular biology for detection of a specific DNA sequence in DNA samples. Southern blotting combines transfer of electrophoresis-separated DNA fragments to a filter membrane and subsequent fragment detection by probe hybridization. Thus, it validates the presence of the ICP47 deletion in HSV.

**Virus Yields of Replication:** because of the overlapping transcripts encoding ICP47 and US11, the deletion in \( \alpha 47 \) also places the late US11 gene under control of the immediate-early \( \alpha 47 \) promoter. This alteration of US11 expression enhances the growth of \( \gamma 34.5 \) mutants by precluding the shutoff of protein synthesis. Therefore, deletion of ICP47 facilitates virus replication.

![Figure 4. The functional verification of ICP47 deletion.](image)
Cytopathic Effect of G47Δ in Vitro: G47Δ, a third-generation oHSV vector, was created by adding to the UL39 and RL1 deletions of G207 a deletion of the HSV-1 gene α47. Therefore, G47Δ should be significantly more efficient at destroying tumor cells than G207.

MHC I Expression in G47Δ-Infected Cells: ICP47 inhibits the function of TAP in translocating peptides across the endoplasmic reticulum in human cells. Thus, G47Δ-infected cells should have no down-regulation of MHC I expression.

G47Δ-Infected Cells Stimulate T Cells in Vitro: due to the strong affinity between ICP47 and TAP, and will be preferentially bound, resulting in the emergence of empty carrier MHC I. Therefore, CD8+ T cells could not recognize infected cells, and HSV could avoid the immune killing effect [31]. However, G47Δ, deletion of ICP47, infected tumor cells would stimulate T cells to a greater extent than G207-infected tumor cells.

Antitumor Efficacy of G47Δ in Vivo: ICP47 deletion restores MHC I and allows tumor cells to present antigens to T cells in response to infection. Therefore, the antitumor effect of G47Δ would be enhanced.

G47Δ has been shown efficacious in animal tumor models of a variety of cancers including brain tumors, prostate cancer, breast cancer and schwannoma [36] [38] [39] [40]. Moreover, the above seven methods have been used in detail by researchers, and compared with G207, G47Δ have enhanced the anti-tumor effect [36].

7. Conclusion

To enhance oncolytic efficacy, yet maintain safety, a third-generation vector, G47Δ, was constructed from G207 by a deletion within the nonessential ICP47 gene. Normally, HSV-1 infection causes down regulation of MHC I expression on the surface of infected cells, with the binding of ICP47 to TAP blocking antigenic peptide transport in the endoplasmic reticulum and loading of MHC I molecules [41]. ICP47 binds to TAP in a species-specific manner, with the affinity for murine TAP being about 100-fold less than for human TAP. Disruption of ICP47 results in increased MHC I expression in G47Δ-infected cells compared with G207-infected cells, with enhanced stimulation of antiviral and antitumor T cell activity; and enhanced virus growth and cytotoxicity in a variety of tumor cell lines in culture and in glioma xenograft models in vivo because of deletion-associated immediate-early expression of the late US11 gene [42]. Currently, accumulating evidence indicated that ICP47 was associated with viral replication and immune escape. Therefore, deleting ICP47 of oncolytic virus will exert promising anti-tumor effects in cancer therapy. Indeed, an ICP47 deletion mutant has been approved for clinical usage [43] [44].

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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