

Applications of Oncolytic Virotherapy in Malignant Tumors

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Abstract. Oncolytic virotherapy, an emerging cancer immunotherapy modality, has attracted much attention in recent years due to its power to selectively infect and eradicate tumor cells while simultaneously activating host anticancer immune responses. This review systematically summarizes the basic concepts, mechanisms of action, major classifications, and research advances regarding representative oncolytic viruses. Emphasis is placed on the engineering strategies and current clinical research status of typical oncolytic viruses from the Herpesviridae, Adenoviridae, Poxviridae, and Picornaviridae families. Additionally, the synergistic effects of oncolytic virotherapy are investigated, both as a stand-alone treatment and in combination with immune checkpoint inhibitors, chemotherapy, and radiation. Oncolytic virotherapy has a favourable safety profile and preliminary efficacy in a range of solid tumours. However, hurdles such as inefficient delivery, antiviral immune clearance and an immunosuppressive tumour microenvironment remain. In the future, with advances in synthetic biology, artificial intelligence-assisted design, and novel delivery systems, oncolytic virotherapy is expected to evolve into an "intelligent multifunctional platform" and emerge as an integral component of comprehensive cancer treatment.

Keywords: tumors, oncolytic viruses, cancer therapy, combination therapy

1. Introduction

Malignant tumors represent a major challenge to human health. Current therapeutic modalities include surgery, radiotherapy, chemotherapy, and emerging targeted therapy and immunotherapy. But there are still problems like metastasis and recurrence and negative effects of treatment, and the overall therapeutic efficacy remains suboptimal. Immune checkpoint inhibitors, which have garnered significant attention in recent years, have demonstrated remarkable efficacy in "hot" tumors such as melanoma, but show limited effectiveness in "cold" tumors like glioblastoma. Oncolytic viruses, as a novel cancer immunotherapy, can specifically reproduce in and destroy tumor cells, stimulate anticancer immune responses, and cause minimal harm to normal tissues [1].

By the 21st century, the progressive maturation of genetic engineering technologies propelled the rapid advancement of oncolytic virotherapy. In 2005, China sanctioned the application of recombinant human adenovirus type 5 (H101) alongside chemotherapy for the management of nasopharyngeal cancer [2]. The approval of talimogene laherparepvec (T-VEC) for the treatment of recurrent melanoma after first surgical intervention by the U.S. Food and Drug Administration (FDA) in 2015 was a major milestone in oncolytic virotherapy [3]. The oncolytic herpes simplex

virus G47 Δ was conditionally approved for malignant glioma therapy in Japan in 2021 [4]. Oncolytic virotherapy has now become a highly active research area and has successfully transitioned from bench to bedside.

Against this backdrop, this review thoroughly summarises the research advancements and applications of oncolytic virotherapy in malignant tumours. Emphasis is placed on representative viruses from the Herpesviridae, Adenoviridae, and Poxviridae families, covering their engineering strategies, mechanisms of action, and current clinical research status. Combination therapy strategies and future directions are also discussed. This review seeks to serve as a reference for subsequent research and clinical implementation of oncolytic virotherapy.

2. The action mechanisms of oncolytic viruses

Oncolytic viruses exhibit their antitumor activity through multiple synergistic methods such as direct oncolysis, activation of antitumor immunity, disruption of tumor vasculature, and synergy with gene therapy [5].

After entering the body, oncolytic viruses preferentially target tumor cells for infection, where they undergo vigorous replication, ultimately causing cell lysis and the release of progeny virions that can then infect adjacent tumor cells. This entire process is termed oncolysis. This tumor selectivity stems largely from the genetic mutations commonly present in cancer cells. To sustain rapid proliferation, tumors often harbor abnormalities in pathways such as p53 or RAS, which compromise their antiviral defenses and render them increased vulnerability to viral infection [6]. Moreover, certain viral entry receptors are often overexpressed on the surfaces of tumor cells. The measles virus can utilize the overexpressed CD46 and SLAM receptors on tumor cells to enhance cellular entrance [7].

Oncolytic viruses can provoke immunogenic cell death (ICD) and mount antitumor immune responses [8]. Subsequent to the destruction of tumor cells, substantial amounts of offspring oncolytic viruses, tumor-associated antigens, and tumor-specific antigens are liberated [9]. These chemicals are identified and internalized by dendritic cells in the body, which then deliver them to T cells, so provoking adaptive immunity [10]. An essential implication is that oncolytic viruses can convert a tumor microenvironment of the "cold" phenotype, featuring low immune cell recruitment and multiple immunosuppressive factors, into a "hot" niche rich in T cells and cytokines.

Tumour vascular endothelial cells can be selectively infected and destroyed by oncolytic viruses, thereby reducing the expression of angiogenic factors [11]. Intravenously administered vesicular stomatitis virus (VSV) infects and obliterates tumor vasculature, replicates within the tumor neovasculature, spreads into the tumor mass, and triggers inflammatory responses [12].

Oncolytic viruses can be employed not only for the direct death of tumour cells but also as vectors for gene therapy, delivering therapeutic genes into tumor cells. Researchers can enhance oncolytic viruses through genetic engineering by including diverse therapeutic genes, including suicide genes, pro-apoptotic genes, immunostimulatory genes, and genes that encode immune checkpoint inhibitors [12].

3. Classification and examples of oncolytic viruses

Oncolytic viruses are highly diverse, and a systematic classification framework can be established based on viral family, genomic characteristics, and engineering strategies.

3.1. Herpesviridae

3.1.1. T-VEC

T-VEC (talimogene laherparepvec) is the inaugural oncolytic virus sanctioned by the U.S. FDA, designated for injectable but unresectable melanoma of the skin or lymphatic nodes. Derived from HSV-1 JS1 strain, this viral agent undergoes genetic manipulation: two RL1 (ICP34.5) and US12 (ICP47) gene copies are knocked out to grant its tumour-specific weak virulence, alongside an inserted coding sequence for granulocyte-macrophage colony-stimulating factor (GM-CSF). Following tumor lysis, GM-CSF is released to augment antitumor immunity [13]. Findings from the phase III OPTiM clinical study demonstrated that monotherapy with T-VEC yielded a 16.3% durable response rate (DRR), versus merely 2.1% observed within the control cohort; this therapeutic regimen also prolonged the median overall survival period from 18.9 months up to 23.3 months. Combination regimens incorporating immune checkpoint inhibitors have demonstrated enhanced efficacy. In a phase II study, T-VEC plus ipilimumab (anti-CTLA-4) yielded an objective response rate (ORR) of 39%, versus 18% for ipilimumab alone. Separately, a phase Ib trial combining T-VEC with pembrolizumab (anti-PD-1) produced an ORR of 62%, together with a complete remission (CR) rate of 33%. T-VEC has shown early safety and efficacy in human trials in head and neck cancer, pancreatic cancer and other cancers; yet, intratumoral injection continues to present hurdles for treating deep or metastatic tumors [14].

3.1.2. G47Δ

G47Δ is the inaugural oncolytic virus sanctioned for glioblastoma (GBM), designated for recurrent or persistent malignant glioma. G47Δ, derived from the second-generation oncolytic HSV-1 G207, incorporates three principal modifications: the deletion of the γ 34.5 gene and the insertion of lacZ to disrupt the ICP6 gene (UL39), facilitating selective viral replication in proliferating tumor cells; the deletion of the α 47 gene to bolster antitumor immunity; and the transformation of the US11 gene into an immediate-early gene, whose protein product compensates for the absence of γ 34.5, thereby enhancing replication capacity and oncolytic efficacy [15, 16]. An interim review of a Japanese phase I/II study and a phase II trial indicated that the one-year survival rate for 13 patients was 92.3%, in contrast to 15% in historical controls. Following a maximum of six intracerebral injections, no serious adverse events of grade ≥ 3 were noted, with just two instances of grade 2 fever reported, so affirming a strong safety profile [17].

3.1.3. Other herpesviruses

G207 is the antecedent of G47Δ. Deletion of γ 34.5 gene and insertion of lacZ in the ICP6 gene allow selective viral replication in tumour cells. G207 with radiation in a phase Ib trial resulted in a 23-month median overall survival among individuals with relapsed glioblastoma with increased infiltration of CD3+/CD8+ T cells. In a phase I trial involving pediatric high-grade gliomas, G207 combined with radiotherapy exhibited no significant adverse events [18-20]. HSV1716 is an oncolytic strain of HSV-1 that has undergone a deletion of the γ 34.5/RL1 gene to reduce neurovirulence. HSV1716 administered by intravenous infusion was well tolerated in paediatric and adolescent patients with extracranial solid tumours; nevertheless, clinical results varied significantly among individuals, and the virus has not yet obtained marketing approval [21-23]. HF10 is a naturally occurring mutation of HSV-1. In a phase I trial for unresectable pancreatic cancer, 66% of

patients exhibited stable disease or partial remission, accompanied by heightened CD8⁺ T cell infiltration at the injection site. When administered in conjunction with erlotinib and gemcitabine, over 70% of patients exhibited a therapeutic response, two cases demonstrated complete pathological response post-surgery, and no significant side effects were recorded [24].

3.2. Adenoviridae

3.2.1. H101

H101 is the inaugural oncolytic virus to obtain marketing authorization, having been authorized in 2005 by Chinese regulators for treating nasopharyngeal cancer [25]. It is a modified adenovirus derived from Ad5, including a deletion of the E1B-55kD gene. In normal cells, the E1B-55kD protein associates with and inactivates p53, thus obstructing apoptosis; however, in roughly fifty percent of malignant tumors, p53 is either mutated or inactivated. Thus, H101 can effectively multiply and lyse p53-deficient tumor cells, while failing to replicate in normal cells, hence facilitating selective tumor cell destruction. In a phase III trial for nasopharyngeal cancer, H101 in conjunction with cisplatin and 5-fluorouracil attained an objective response rate of 78.8%, against 39.6% with chemotherapy alone [2]. In gastric cancer, the H101-chemotherapy combination outperformed monotherapy [26], and in hepatocellular carcinoma, H101 combined with conventional transarterial chemoembolization (cTACE) prolonged both overall survival and progression-free survival [27].

3.2.2. DNX-2401

DNX-2401 is an oncolytic adenovirus produced from Ad5 and is being developed for the treatment of malignant glioma. The modifications consist of two parts. First, a 24-bp deletion in the E1A gene impairs Rb-binding by the protein, thereby confining viral propagation to tumour cells that have a defective Rb pathway. Second, an RGD motif is incorporated into the fibre protein, which re-directs the virus toward integrins $\alpha\beta3$ and $\alpha\beta5$, thus overcoming the barrier imposed by low CAR expression [28]. As a phase I trial involving 37 patients with recurrent glioblastoma, participants receiving two intratumoral injections had a median overall survival (OS) of 13.0 months, as contrast to 9.0 months for those with a single injection, with no identified dose-dependent harm [29]. A multicenter phase I/II trial with 49 patients revealed that intratumoral administration of DNX-2401 combined with pembrolizumab resulted in a median OS of 12.5 months (95% CI, 10.7-13.5) and a 12-month OS rate of 52.7% (significantly surpassing the predetermined benchmark of 20%), and three enduring responses lasting 45, 48, and 60 months. Complete responses were exclusively noted in patients exhibiting "moderate" inflammatory infiltrate, indicating that immunological state is a critical factor influencing treatment results [30]. In a juvenile diffuse intrinsic pontine glioma (DIPG) trial, the intracerebellar infusion of DNX-2401 resulted in a median overall survival of 17.8 months, in contrast to a historical control of under 12 months [31]. DNX-2401 exemplifies the design evolution from "pure attenuation" toward "active targeting" and provides an important paradigm for oncolytic virotherapy of brain tumors.

3.3. Poxviridae

3.3.1. JX-594

JX-594 is an oncolytic virus originating from the Wyeth strain of vaccinia virus, characterised by a deletion of the thymidine kinase (TK) gene and the integration of the GM-CSF gene. The loss of TK restricts viral replication to tumor cells harboring elevated nucleotide pools, while GM-CSF enhances local immune activation. The virus also replicates with greater efficiency in tumors with EGFR overexpression or KRAS mutations [32, 33]. The phase IIb TRAVERSE trial involving patients with advanced hepatocellular carcinoma who had either progressed on or were intolerant to sorafenib demonstrated that intravenous JX-594 in conjunction with low-dose cyclophosphamide was safe and well tolerated, effectively activating T-cell immunity; however, overall survival did not show significant improvement, potentially due to limitations imposed by pre-existing or rapidly developed antiviral immunity [34]. In the neoadjuvant treatment of colorectal cancer liver metastases, a solitary preoperative intravenous infusion of JX-594 was well tolerated and resulted in heightened intratumoral production of IFN- α and chemokines, indicating immune activation [35].

3.3.2. Other poxviruses

GL-ONC1 has exhibited a positive safety profile and initial anticancer efficacy in various phase I/II trials, encompassing advanced solid tumors, peritoneal carcinomatosis, and head and neck malignancies. The TG6002 is a genetically engineered vaccinia virus, which combined with 5-fluorocytosine (5-FC) is currently in phase I/II clinical trials for recurrent glioblastoma and brain cancer (NCT03294846). GC001 is an attenuated strain of modified vaccinia virus Ankara (MVA) and is now being tested in a phase I clinical trial in high-grade glioma (NCT06660650) [36].

4. Clinical applications of oncolytic virotherapy

In clinical practice, oncolytic virotherapy as monotherapy often has limitations: it is difficult not only to completely eliminate tumor cells but also to achieve substantial improvement in patient prognosis and quality of life. Combination therapies can significantly enhance antitumor activity and produce synergistic effects. Moreover, given their highly engineerable nature, oncolytic viruses serve as ideal combination therapy platforms and can be synergistically combined with immune checkpoint inhibitors, chemotherapy, radiotherapy, and other therapeutic modalities.

4.1. Monotherapy

To date, several oncolytic viruses have received approval for localized clinical treatment: H101 (China, for nasopharyngeal carcinoma), T-VEC (FDA, for unresectable melanoma), and G47 Δ (Japan, for malignant glioma), collectively validating the viability of virotherapy in the treatment of brain tumors. Nonetheless, the objective response rates of these medicines as standalone therapy remain constrained, prompting the advancement of combination techniques.

4.2. Synergistic combination with radiotherapy and chemotherapy

Radiotherapy and chemotherapy exert synergistic effects when combined with oncolytic viruses: chemotherapeutic agents can suppress antiviral immunity and prolong viral persistence, and the resulting DNA damage may enhance viral replication efficiency [37]; radiotherapy can activate

signaling pathways in tumor cells, upregulate relevant gene expression, and potentiate viral replication [38].

Clinical studies have validated such synergies: in patients with nasopharyngeal carcinoma, H101 combined with cisplatin plus 5-FU showed superior efficacy compared with chemotherapy alone [2]; in lung cancer, the recombinant adenovirus ATV combined with cisplatin demonstrated synergistic tumor suppression [39]; in pancreatic cancer, oncolytic measles virus combined with gemcitabine enhanced therapeutic efficacy [40]; and in glioma, G207 combined with radiotherapy prolonged survival and increased T-cell infiltration [41].

4.3. Combination with immunotherapy

The integration of oncolytic viruses with inhibitors of immune checkpoints signifies a highly promising domain of contemporary study. Oncolytic viruses lyse tumour cells, releasing tumour antigens and damage-associated molecular patterns (DAMPs), so converting a "cold" tumour microenvironment into a "hot" one [36]. Concurrently, viral infections might enhance PD-L1 (programmed death-ligand 1) levels on tumor cells, hence increasing the targets for immune checkpoint inhibitors [42]. Immune checkpoint inhibitors, in turn, unleash T cells from suppression and enhance their killing activity [43]. Together, they produce a synergistic antitumor effect that is greater than the sum of their parts.

In summary, combination strategies offer new avenues for overcoming immune escape, although the optimal regimens and their sequencing remain to be explored.

5. Conclusion

This review systematically summarizes the research progress on representative viruses from the Herpesviridae, Adenoviridae, Poxviridae, and Picornaviridae families, and describes their engineering strategies, mechanisms of action, and current clinical research status.

Several oncolytic virus therapies like T-VEC, G47 Δ and H101 have been commercially approved till now, demonstrating the safety and efficacy of this mode of treatment. Viruses such as DNX-2401 and JX-594 have also shown promising potential in the therapy of solid tumours, including glioma, hepatocellular carcinoma, and colorectal cancer. Combining oncolytic viruses with chemotherapy, radiotherapy, and immune checkpoint inhibitors has improved anticancer efficacy and provided new strategies to overcome tumour heterogeneity and immunosuppressive microenvironment.

However, oncolytic virotherapy still faces considerable challenges. With regard to delivery efficiency, most viruses require intratumoral injection, which has limited efficacy against deep or metastatic lesions, whereas intravenous administration is susceptible to neutralization by pre-existing antibodies. In terms of antiviral immunity, the host antiviral response may prematurely clear the viral vector, restricting viral replication and limiting repeated administration. Within the tumor microenvironment, the dense extracellular matrix, aberrant vascular architecture, and immunosuppressive cells constitute both physical and functional barriers that impede viral spread as well as immune cell infiltration.

Looking ahead, the future advancement of oncolytic virotherapy will be directed upon the following key directions: first, the design of more intelligent viruses; second, more precise combination strategies; and third, overcoming the delivery bottleneck.

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