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Oncolytic Virus Therapy in Solid Tumors: Clinical Translation Challenges and Strategies

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ABSTRACT
Oncolytic viruses (OVs), as a type of tumor-targeted immunotherapy, show great potential in solid tumor treatment by selectively infecting and lysing tumor cells, while activating the host's anti-tumor immune response. Although products like H101 and T-VEC have been approved, their clinical translation still faces a core dilemma: feasibility of the mechanism does not equal clinical efficacy. Currently, the clinical translation of oncolytic viruses faces three major challenges. First, the preclinical-to-clinical translation dilemma, as existing animal models are unable to accurately predict the replication efficiency and immune response of the virus in the human body; second, the challenges at the clinical development stage, due to the lack of effective biomarkers to guide patient selection; and third, delivery and pharmacokinetics issues, where intratumoral injection is only suitable for superficial tumors, while systemic administration faces dual barriers from immune and physical obstacles in the tumor microenvironment. To address these challenges, the article proposes corresponding optimization strategies: first, optimizing viral vectors to enhance virus targeting and immune evasion capabilities; second, upgrading delivery systems to achieve systemic targeted delivery of the virus; and third, optimizing dosing regimens and combination therapies to induce immunogenic cell death and improve the tumor microenvironment. In the future, with advancements in precision medicine and delivery technologies, oncolytic virus therapy is expected to bring new breakthroughs in solid tumor treatment.

KEYWORDS
Oncolytic virus; Clinical translation; Challenges; Strategies

1 Introduction

Oncolytic viruses (OVs), as a tumor-targeting immunotherapy, have received extensive attention in recent years. It is a type of virus that can selectively infect and kill tumor cells, achieving selective infection and replication of tumor cells through multiple mechanisms. Within tumor cells, oncolytic viruses can replicate efficiently and eventually lead to the lysis and death of tumor cells. This selective replication mechanism not only directly kills tumor cells but also reduces damage to normal cells, thereby lowering the side effects of treatment. During the process of infecting and killing tumor cells, oncolytic viruses can induce immunogenic cell death (ICD) and activate the host's immune system, especially the anti-tumor immune response. Since the systemic immune response activated by oncolytic viruses can recognize and attack tumor cells throughout the body, it can also produce the abscopal effect, that is, it can have therapeutic effects on tumor lesions far from the treatment site. Through genetic engineering technology, oncolytic viruses can be modified to express immune regulatory factors, cytotoxic factors or other proteins with therapeutic effects. This engineerable feature enables oncolytic viruses not only to be direct tumor-killing tools but also to serve as multifunctional gene therapy vectors, achieving the synergistic effect of multiple therapeutic mechanisms.

In addition, the treatment of solid tumors has multiple unique complexities. First, solid tumors show significant intratumoral and inter-tumor heterogeneity. Unlike hematological malignancies, solid tumors lack universal antigens that can be safely targeted. The microenvironment of solid tumors is usually immunosuppressive, infiltrated by regulatory T cells (Tregs), tumor-associated macrophages (Tams), and myeloid-derived suppressor cells (MDSC). These cells produce various immunosuppressive mediators, inhibit dendritic cell maturation, reduce the proliferation of cytotoxic T cells, and weaken the effector immune response. Second, the extracellular matrix (ECM) of solid tumors is dense, physically hindering the penetration of immune cells and reducing the spread of therapeutic drugs to the tumor core. Vascular abnormalities in solid tumors restrict the entry and migration of immune cells, maintaining the immune rejection or immune desert phenotype of solid tumors. Last, tumor cells in hematologic malignancies circulate freely in the blood, while solid tumors create a highly complex cellular microenvironment. This structural difference makes it more difficult for immune cells to infiltrate and attack solid tumors. Hematologic cancers have clearly defined lineage-restricted surface antigens that can be targeted for CAR T-cell therapy; in contrast, the expression of tumor antigens in solid tumors is heterogeneous, requiring the strategic selection of multiple antigens as therapeutic targets for each tumor type. Additionally, many target antigens in solid tumors are also expressed in healthy tissues, which may lead to "targeted on-target" toxicity.

2 Current Situation

As of now, several oncolytic virus therapies have successfully completed clinical translation and received market approval worldwide, marking an important milestone in the transition of this field from theory to clinical application. Among them, H101 is a recombinant human type 5 adenovirus that was approved in China in 2005 for the treatment of advanced nasopharyngeal carcinoma. It directly acts on the tumor lesions through intratumoral injection, releasing viral particles that lyse tumor cells and activate the body's immune response, thereby enhancing the efficacy of radiotherapy; T-VEC (Imlygic) is a genetically modified herpes simplex virus that received FDA approval in 2015 for unresectable melanoma. Through injection into the tumor, it selectively infects melanoma cells, releasing GM-CSF to activate the immune system and generate a lasting anti-tumor immune response; DELYTACT (Teserpaturev) received conditional approval in Japan in 2022 for recurrent malignant glioma by directly acting on tumor cells to induce their apoptosis, exerting anti-tumor effects. The successful translation of these products is primarily based on their ability to selectively infect and lyse tumor cells while activating systemic anti-tumor immune responses.

Currently, various OVs are undergoing clinical trials worldwide, with a focus on exploring combination treatment strategies involving oncolytic viruses and PD-1/PD-L1 inhibitors, CTLA-4 antibodies, radiotherapy, or targeted drugs. These combinations have shown synergistic potential in multiple solid tumors, such as melanoma, triple-negative breast cancer, and non-small cell lung cancer. These combination therapies enhance the tumor-killing effects through synergy, providing new insights for the treatment of solid tumors and advancing the clinical application of oncolytic viruses.

The successful clinical translation of oncolytic virus therapy relies on the synergistic interaction of multiple key factors. First, a clear biomarker-driven approach is central to achieving precise treatment. By screening sensitive patients through the detection of biomarkers such as DSG2, we can significantly enhance efficacy and response rates. Second, the design of a rational drug delivery method is crucial; intratumoral injection can effectively increase the local viral concentration in tumors, while exploring systemic delivery strategies such as intravenous or arterial infusion holds promise for overcoming the physical barriers of solid tumors and expanding treatment indications. Additionally, multidisciplinary collaboration provides strong support, as the deep integration of virology, oncology, immunology, and pharmacology drives full-chain innovation from mechanistic research to clinical validation, offering systematic assurance for the optimization and implementation of oncolytic virus therapy.

3 Challenges

Clinical transformation refers to the process of converting basic research results into applicable diagnostic, therapeutic or preventive strategies. This process involves multiple stages, from basic research in the laboratory to clinical application, and needs to go through a series of strict steps, including preclinical research, clinical trials, and ultimately clinical application and regulatory approval. In the process of clinical transformation, there exists a core contradiction: mechanism feasibility does not equal clinical effectiveness. This means that even if the mechanism of a certain treatment method is proven feasible in the laboratory, it may not necessarily achieve the expected results in the clinical setting. The core challenges in clinical translation can be roughly divided into three categories based on the stages of translation: challenges in the transition from preclinical to clinical, challenges in the clinical development phase, and challenges in delivery and pharmacokinetics.

3.1 Challenges in the Transition from Preclinical to Clinical

First of all, animal models have limitations. Although the immune-competent mouse model can simulate the basic biological characteristics of tumors, its immune system differs significantly from that of humans. Taking patient-derived tumor xenografts (PDX) as an example, they lack a complete adaptive immune system, and sometimes even the innate immune system is not fully functional. More importantly, the tumor microenvironment in this model is artificially constructed, with tumor cells being implanted rather than spontaneously generated, which may introduce species-specific and virus tropism issues. This refers to a virus optimized for one species potentially showing reduced infectivity or altered replication profile in another species. These factors significantly affect the evaluation of oncolytic virus therapy's anti-tumor efficacy[1]. In spontaneous tumor models, animal tumor cells are generally less susceptible to human viruses (including HSV-1) than human tumor cells, which can lead to an underestimation of the viral replication efficiency[1]. Additionally, although syngeneic models retain a complete immune system and natural microenvironment, the tumor biological characteristics differ greatly from those of humans, making it difficult to accurately predict the intensity of immune responses[1].

Moreover, in the process of optimizing drug dosages to achieve the best therapeutic effects, we face numerous challenges that become increasingly complex due to variations in tumor types, stages, and the immune status of patients. Despite extensive research, determining the optimal dosing strategy remains a significant challenge. Furthermore, data from veterinary clinical trials indicate that dosage requirements can vary significantly between different species; for

example, the optimal dosing regimen for canine patients may differ greatly from that for felines and humans[2]. Therefore, conducting comprehensive pharmacokinetic (PK) and pharmacodynamic (PD) analyses across species is particularly important. Additionally, the lack of standardized conversion formulas for extrapolating drug dosages from mouse models to human clinical applications, along with difficulties in accurately predicting dosing frequency and the intensity of immune responses, adds to the uncertainties surrounding dose optimization. These uncertainties further complicate the challenge of optimizing dosages. Moreover, the differences in viral replication dynamics between preclinical models and actual human conditions impose higher demands on our drug dosage strategies.

3.2 Challenges in the Clinical Development Phase

The development of clinical trials also faces several key challenges. First, the inconsistency in patient selection criteria is a major issue. Currently, there is a lack of effective biomarkers to guide patient enrollment. For example, the expression levels of viral receptors such as nectin-1 and MXRA8 are associated with the sensitivity to HSV-1 and the entry of M1 viruses, respectively, but standard methods to detect these biomarkers have not yet been established[3]. Similarly, high tumor mutational burden (TMB) is often associated with better immune responses, but its relationship with overall efficacy still needs further clarification. Baseline CD8+ T cell infiltration levels, while also clinically significant, require biopsy for detection, making it a more complex procedure. The characteristics of the gut microbiome are also an emerging biomarker, but evidence for its correlation with treatment response is still limited. A 2025 meta-analysis suggested that composite biomarkers integrating genomics, immunity, and the microbiome are crucial for optimizing patient selection and achieving precise viral immunotherapy[3].

Secondly, the current efficacy evaluation system also reveals a delay. The traditional Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) struggles to keep up with the unique response patterns of immunotherapy. For example, the appearance of new lesions does not always indicate disease progression, a phenomenon known as pseudoprogression. In response to this, the immune Response Evaluation Criteria in Solid Tumors (iRECIST), published by the RECIST working group in 2017, propose that new lesions must be confirmed before being classified as progression, and suggest considering clinical stability as a factor in continuing treatment[4]. However, most phase III clinical trials still use RECIST 1.1 as the primary endpoint, while iRECIST is only used for exploratory analysis[4]. Imaging evaluations also face challenges, such as the inflammatory response after oncolytic virus therapy, which may be misinterpreted as disease progression.

Finally, individual differences in efficacy should not be overlooked. The density of tumor stroma, such as increased collagen deposition and hyaluronic acid content, can physically hinder the spread of the virus. The degree of immune infiltration, such as immune rejection-type microenvironment and the dominance of myeloid cells, indicates resistance to treatment. The level of antiviral antibodies, especially the variation in titers of pre-existing neutralizing antibodies (NAb), can affect the systemic delivery of the virus. Gender differences may also influence the prognosis of cancer immunotherapy and should be objectively assessed as a potential confounding factor. Furthermore, the number of treatment lines a patient has undergone can also impact efficacy, with previous chemotherapy or radiotherapy potentially damaging innate immune cells and reducing anti-tumor immunity[5].

3.3 Challenges in Delivery and Pharmacokinetics

The primary challenge lies in the limitations of local delivery. Intratumoral injection, currently the most common method of administration, faces clear bottlenecks. Specifically, this method is only suitable for superficial or palpable tumors, such as skin and subcutaneous metastases[6]. For deep tumors like those in the lungs, liver, pancreas, and brain, intratumoral injection becomes difficult to implement and typically requires image guidance or surgical intervention, which undoubtedly increases technical difficulty and the consumption of medical resources. Moreover, intratumoral injection cannot address multifocal diseases and widespread metastases, limiting its broad clinical application.

Systemic delivery also faces challenges. In the process of systemic delivery, immune barriers and the physical barriers of the tumor microenvironment together form the primary obstacles. Regarding immune barriers, the complement system inactivates viral particles, preventing the virus from being delivered to the tumor before it is cleared. Pre-existing neutralizing antibodies limit the virus's delivery and replication at the tumor site, while red blood cells further reduce systemic exposure by sequestering viral particles and targeting their clearance[6]. The first-pass effect of the liver and the uptake by the reticuloendothelial system also significantly impact delivery efficiency. The physical barriers of the tumor microenvironment are equally complex. The dense collagen network obstructs viral penetration, the high hyaluronic acid (HA) content increases interstitial fluid pressure (IFP), and abnormal blood vessel structures affect drug extravasation[7]. Furthermore, tight junctions between tumor cells limit the spread of the virus towards the tumor center. These factors collectively hinder drug delivery and distribution[7].

In conclusion, these challenges severely impact the therapeutic efficacy and scope of the medication, necessitating the development of new strategies and technologies to overcome these barriers and achieve more effective cancer treatment.

4 Strategies

Through precise virus design, intelligent delivery systems, and optimized combination strategies, the evolution of oncolytic virotherapy from a 'single weapon' to a 'multi-functional platform' is expected to overcome core challenges in clinical translation.

4.1 Viral Vector Optimization

First, there is the modification of the serotype and capsid. In the modification of adenovirus hexon proteins, various innovative methods can be employed to evade the immune system's recognition. Specifically, researchers replace Ad5 with serotypes that have lower pre-existing immunity in the population (such as Ad11, Ad35, and Ad48), a strategy known as serotype switching[8]. In addition, modifications can also be made to the viral capsid, including PEGylation and glycosylation, among others. These modifications are aimed at masking key immunogenic epitopes[9].

Next is the genetic engineering strategy. Among them, tumor-specific promoters achieve selective killing of tumor cells by controlling viral replication. For example, the AFP promoter targets alpha-fetoprotein-positive hepatocellular carcinoma[10]; CEA promoter targets carcinoembryonic antigen-positive colorectal and lung cancers[11]; The E2F-1 promoter targets various cancer cells with defects in the pRb pathway[11]. The hTERT-CMV fusion promoter combines the hTERT promoter and the CMV enhancer fragment, retaining tumor specificity while significantly enhancing transcriptional activity[12].

4.2 Delivery System Optimization

The optimization of oncolytic virus delivery systems is a key step in advancing from localized treatment to systemic immunotherapy, with nanocarriers and biomaterial delivery systems showing broad application prospects. Lipid nanoparticles (LNPs) and polymer encapsulation techniques effectively shield neutralizing antibodies through physical encapsulation or electrostatic complexation, prolong the circulation time of the virus, and enhance its tumor tropism. For example, liposomes can encapsulate complete viruses or genomes, achieving immune evasion[9]; PEGylation significantly extends the half-life, but may impact viral infectivity[9]. Cationic polymers such as polyethyleneimine (PEI) can enhance transduction efficiency, but are limited due to their high toxicity and poor degradability[9]. In addition, hydrogels and scaffold-based sustained release systems, such as alginate hydrogels, can continuously release OV within tumors, reducing antiviral immune responses while enhancing CD4+/CD8+ T cell infiltration, thereby exerting stronger antitumor immune effects[13].

In the field of cell carrier delivery strategies, mesenchymal stem cells (MSCs) have become the ideal 'living carriers' due to their strong tumor tropism, immune evasion properties, and virus protection abilities. MSCs can not only deliver viruses precisely to tumor sites but also act as 'virus factories,' continuously releasing progeny viruses, enhancing their spread within the tumor. Multiple clinical trials have confirmed their safety and feasibility in brain tumors, ovarian cancer, and gliomas[14]. Immune cell carriers such as T cells, dendritic cells (DCs), neutrophils, and macrophages each have their own advantages. They can not only deliver viruses but also synergistically activate immune responses, such as the dual targeting achieved by combining CAR-T with OVs[14]. A more cutting-edge approach is the tumor-targeted bacterial delivery system, such as attenuated Salmonella and Clostridia, which can colonize the anaerobic core of tumors. In particular, the CAPPSID system developed by Columbia Engineering in 2025 hides oncolytic viruses within attenuated Salmonella. By leveraging the bacteria's natural tropism, it achieves tumor-specific delivery. The virus only matures at the tumor site under the action of bacterial enzymes, greatly enhancing both safety and efficacy, offering a novel path for systemic treatment of metastatic tumors[15].

4.3 Optimization of Dosing Regimen and Combination Therapy

Focusing on scientifically driven combination therapy and precise drug administration design, the optimization of oncolytic virus therapy's clinical efficacy aims to achieve synergistic effects. In terms of combination strategies, synergy with immune checkpoint inhibitors (ICIs) is a core direction, with the key being precise control of the timing. Research shows that OV infection can upregulate the PD-L1 expression in tumor cells and release tumor antigens[16]. Delayed administration of ICI (such as days to weeks after viral therapy) often yields better results than simultaneous administration. Multiple clinical trials (e.g., NCT03003676, NCT02263508) are exploring the optimal interval to maximize survival benefit [16].

The research focuses on capturing the dynamic window of immune response and optimizing the dosage in the refined design of the administration scheme. The ideal strategy is usually divided into the 'induction phase' and the 'effector phase': during the induction phase, high-dose virus injections are administered early to achieve sufficient viral replication, tumor antigen release, and DC activation; during the effector phase, fractionated dosing is used to maintain continuous immune system activation and T cell expansion. At the same time, pre-treatment with cyclophosphamide to reduce Tregs, or administering viruses after low-dose radiotherapy, can further eliminate immunosuppressive cells, induce ICD, create space for viral replication, and enhance immune response[16]. These programs are continuously being validated through

preclinical research and clinical trials, aiming to achieve the best balance between efficacy and safety.

All in all, these engineering modifications and delivery strategies demonstrate the evolution of oncolytic virotherapy from a 'single weapon' to a 'multi-functional platform.' With precise virus design, intelligent delivery systems, and optimized combination therapies, they are expected to overcome the core challenges in clinical translation.

5 Future Perspectives and Conclusions

Oncolytic virus therapy has undergone decades of development and has made substantial breakthroughs in the treatment of solid tumors, but overall, it is still in the 'early maturity phase'. In the future, with continuous advancements in technology, this therapy is rapidly evolving toward greater efficiency, precision, and safety.

On a technical level, advancements in viral genetic engineering will endow oncolytic viruses with stronger targeting capabilities and multifunctionality, enabling them to not only efficiently lyse tumor cells but also deeply activate systemic anti-tumor immunity. The innovation in delivery technologies, particularly breakthroughs in systemic drug delivery methods such as intravenous injection and cell carrier delivery, will effectively overcome the limitations of conventional intratumoral administration and address the challenges in treating deep-seated and metastatic tumors. Moreover, the combined use of immune checkpoint inhibitors, radiotherapy, chemotherapy, and other therapies will further amplify the synergistic effects, overcoming the bottleneck of resistance.

In clinical applications, biomarker-based precision medicine is expected to become mainstream. By screening patients with specific gene expressions or immune features, precise stratification and personalized treatment can significantly improve response rates and survival benefits. Furthermore, as regulatory science continues to improve and the industrialization process accelerates, the entire chain, from oncolytic virus production quality control to clinical application standards, will become more standardized. International collaboration and the deepening of multi-center clinical trials will also drive this achievement worldwide, bringing new hope to cancer patients globally.

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