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# THE EVOLUTION OF CANCER TREATMENT THROUGH ONCOLYTIC VIRUS IMMUNOTHERAPY

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## INTRODUCTION

*Oncolytic viruses (OVs) offer new and promising therapeutic options for patients with cancers resistant to traditional therapies. These OVs, which can be natural or genetically modified, are multifaceted tumor killers. They directly destroy tumor cells while sparing normal cells and, indirectly, enhance antitumor immunity by releasing antigens and activating inflammatory responses in the tumor microenvironment. However, some limitations, such as limited penetration of OVs into tumors, short persistence, and the host antiviral immune response, are hindering the broad application of oncolytic virotherapy in the clinic. If these challenges can be overcome, combination therapies, such as OVs plus immune checkpoint blockade (ICB), chimeric antigen receptor (CAR) T cells, or CAR natural killer (NK) cells, may provide powerful therapeutic platforms in the clinic.*

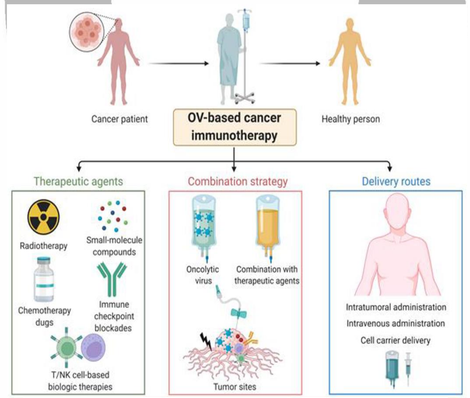
## OVERVIEW OF ONCOLYTIC VIRUSES FOR CANCER THERAPY

*For over a century, viruses have been used to induce cell death. In the 1990s, researchers proposed using viruses to specifically target and destroy tumor cells, leading to the discovery of oncolytic viruses (OVs). OVs are designed to selectively replicate within and kill tumor cells, unlike gene therapy vectors which don't replicate. OVs fall into two categories: naturally occurring (e.g., measles, Newcastle disease, and reovirus) and genetically modified (altered to enhance anti-tumor effects). The FDA approved the first OV, T-VEC, for metastatic melanoma in 2015, and Japan approved DELYTACT for malignant glioma in 2021. Studies show that OVs can be effective alone or with other therapies, though the balance between antiviral responses and anti-tumor immunity is still being understood. This review explores the unique aspects of OVs, their therapeutic potential, delivery methods, and the future of combining OVs with other immunotherapies for improved cancer treatment.*

## MECHANISMS OF ACTION OF ONCOLYTIC VIROTHERAPY

*Oncolytic viruses (OVs) initially exert their therapeutic effects through the direct lysis of tumor cells. This direct oncolytic activity is complemented by an indirect mechanism involving the induction of systemic anti-tumor immunity. OVs can stimulate the immune system by causing the release of tumor antigens and activating inflammatory responses, which help counteract tumor-induced immune suppression and evasion. The selectivity of OVs for tumors is driven by several factors. First, viral entry into tumor cells is mediated by virus-specific receptors, such as SLAM/CD150 and CD46, which facilitate the recognition of oncolytic measles virus (MV). Additionally, modifications to viral surface proteins can enhance the ability of OVs to target tumor-specific receptors, such as the epidermal growth factor receptor (EGFR), improving viral infection and replication within tumor cells. Tumor cells, with their high proliferation rates and elevated metabolism, provide a favorable environment for OV replication. Engineering OVs to include tumor-specific promoters or combining them with microRNAs can further enhance their replication within tumor cells. Moreover, tumor cells often exhibit dysfunctional immune responses, particularly in type I interferon (IFN) signaling pathways, which impedes viral clearance and allows OVs to replicate without harming healthy cells. Nonetheless, resistance to OV infection may occur in tumors with IFN pathway mutations, necessitating further investigation into these mechanisms.Following viral replication, OVs induce immunogenic cell death, characterized by the release of danger-associated molecular patterns (DAMPs) and tumor-associated antigens (TAAs). This process activates both innate and adaptive immune responses. Natural killer (NK) cells and macrophages are activated, producing cytokines that enhance the immune response. Dendritic cells (DCs) also play a crucial role by presenting antigens and stimulating T-cell responses, which contribute to the systemic eradication of tumors.The tumor microenvironment (TME) can be categorized as immunologically "cold" or "hot" based on the presence of inflammatory immune cells and overall immune activity. OVs have the potential to convert "cold" tumors, which are poorly responsive to immune therapy, into "hot" tumors by inducing inflammation and recruiting immune cells. However, excessive inflammation can lead to adverse effects, such as autoimmune responses.Combining OVs with immune checkpoint inhibitors (ICBs) has shown clinical promise, particularly in cases of metastatic melanoma. For example, the combination of T-VEC with pembrolizumab demonstrated significant responses. Nevertheless, the timing of therapy administration is crucial; differing outcomes have been observed based on whether OV therapy was administered before or simultaneously with ICBs. Optimizing treatment protocols is essential for achieving the maximum therapeutic benefit.*

## COMBINATION STRATEGIES WITH ONCOLYTIC VIROTHERAPY




## CONCLUDING REMARKS

*This review explores the role of oncolytic viruses (OVs) in cancer immunotherapy, both as standalone treatments and in combination with other therapies. Combining OVs with immune checkpoint blockers (ICBs), chemotherapy, or other strategies generally improves survival outcomes in experimental models, and clinical trials show promise with minimal additional toxicity. Better understanding the interactions between immune responses, viral pathogens, and tumor cells will improve OV design. Selecting the right OV vectors, such as HSV, Ads, and VACV, which can sustain transgene production, is crucial for converting a "cold" immunosuppressive tumor microenvironment into a "hot" inflammatory one. Future research should aim to balance reducing antiviral activity with enhancing anti-tumor effects to develop more effective and safer therapies. OV-based virotherapy holds promise but faces challenges like limited OV persistence, viral replication, and safety concerns. Addressing these issues through improved understanding of OV interactions may lead to more innovative and effective treatments.*

## CONTACT INFORMATION

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