ISSN: 2755-0125

Journal of Virology Research & Reports

SCIENTIFIC Research and Community

Review Article

Open Access

Oncolytic Viruses: A Selective and Innovative Therapy in Cancer Treatment

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ABSTRACT

Immunotherapy strategies, formulated as alternatives to conventional cancer therapies like surgery, chemotherapy, and radiotherapy, provide unique techniques that align with the tumor microenvironment, enhance targeted immune responses, and minimize systemic toxicity. These advanced therapeutic techniques has the capability to selectively identify tumor antigens, modify the tumor microenvironment, and eradicate immunosuppressive processes. Oncolytic virus therapy induces direct cell lysis through tumor-specific viral multiplication and activates adaptive immunity through virus-induced immunogenic cell death. Molecules including damage-associated molecular patterns (DAMPs) and pathogen-associated molecular patterns (PAMPs) generated after immunogenic cell death stimulate dendritic cells and other antigen-presenting cells, facilitating the recognition and targeting of tumor-specific antigens by cytotoxic T lymphocytes. This facilitates the development of an anticancer immune response in both local tumor tissue and metastatic locations. Oncolytic viruses provide a different approach for solid tumors that are resistant or refractory to traditional therapy, hence enhancing their clinical significance. This article discusses the molecular foundation of oncolytic virus therapy, the characteristics of the viral vectors employed, application tactics, clinical research outcomes, and prospective future applications in a comprehensive manner.

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Received: July 24, 2025; **Accepted:** July 28, 2025; **Published:** September 27, 2025

Keywords: Oncolytic Virus, Cancer, Therapy, Mechanism

Entrance

Cancer remains a prominent cause of mortality globally, affecting both industrialized and developing nations. In 2020, there were 19.3 million new cancer diagnoses globally, and around 10 million individuals succumbed to the disease [1]. While surgery, chemotherapy, and radiotherapy remain the primary approaches to cancer treatment, these treatment modalities generally have limited success rates and are often insufficiently therapeutic, particularly in advanced or metastatic cases. Furthermore, these traditional treatments affect healthy cells alongside tumor cells, leading to serious systemic toxicities, immune suppression, and a decreased quality of life [2].

However, many tumor types can develop resistance to classical chemotherapeutic agents over time, and cells with increased DNA damage repair capacity can become refractory to treatment. This has highlighted the need for new treatment strategies that are more specific, targeted, and able to interact with the immune system. Immunotherapy approaches developed in recent years allow the immune system to be reactivated against the tumor and target-specific cytotoxic responses are generated [3]. Among these approaches, oncolytic virus therapy stands out because it can selectively infect cancer cells, replicate only in the tumor environment, and subsequently directly reduce tumor burden through cell lysis. Furthermore, the tumor antigens, damage-associated molecular patterns (DAMPs), and viral patterns (PAMPs) released during this process activate antigen-presenting cells, promoting the generation of tumor-specific T-cell responses. Thus, oncolytic virus therapy provides both a direct cytotoxic effect and triggers a systemic adaptive immune response [4,5].

This dual effect of oncolytic viruses makes them not only an alternative but also a powerful agent that can be combined with immunotherapy. Therefore, oncolytic virus therapy is currently being evaluated with increasing interest not only in preclinical research but also in clinical trials, and is particularly promising in patients resistant to immune checkpoint inhibitors (anti-PD-1, anti-CTLA-4) [6].

Mechanism of Action of Oncolytic Viruses

Oncolytic virus therapy is based on the principle that viruses selectively infect cancer cells, multiply, and cause cell lysis. During this process, the viruses hijack the host cells' protein synthesis mechanisms, promote the production of viral products, and then multiply and spread to surrounding tumor cells. The antitumor effect of oncolytic virus is not limited to direct cell killing; they also activate the immune system, making the tumor microenvironment immunogenic [7]. Oncolytic virus -infected cells trigger innate and adaptive immune responses by secreting danger signals and tumor-specific antigens. Tumor evasion mechanisms can limit the effectiveness of oncolytic virus . Therefore, genetic weaponization of Oncolytic virus (e.g., insertion of genes encoding cytokines such as IL-12 and IFN-β) is widely used to increase their immunogenicity [8-10].

The tumor microenvironment and extracellular matrix (ECM) can hinder the spread of the virus. Combining oncolytic virus therapy with ECM-degrading enzymes or immunosuppressive agents (e.g., sunitinib) can overcome these barriers and increase treatment efficacy. However, with systemic administration, the innate immune system can neutralize the virus, preventing Oncolytic virus from reaching the tumor. A combination of histone deacetylase inhibitors and immunomodulatory drugs is recommended to overcome this problem [11].

Oncolytic viruses elicit their anticancer effects through two principal mechanisms: Oncolytic viruses utilize two primary mechanisms for cancer elimination: Direct cellular lysis and the enhancement of antitumor immunity.

The initial method exploits the virus's inherent life cycle. Following tumor infection, the virus proliferates, resulting in cell lysis and death. Subsequently, viral particles invade adjacent cells, sustaining the lytic cycle and generating a limited, self-reinforcing therapeutic impact inside the tumor area [12]. This cycle persists until immune responses inhibit viral multiplication or exhaust the reservoir of vulnerable host cells [12].

The second method employed by oncolytic viruses is the stimulation of antitumor immunity [13-15]. Oncolytic viruses cause the lysis of tumor cells, resulting in the release of tumor-associated antigens and neoantigens [6].

The released antigens become available to antigen-presenting cells that infiltrate the tumor, specifically dendritic cells and macrophages. Dendritic cells process captured tumor-associated antigens and tumor antigenic neoepitopes and deliver them to T cells, thereby beginning a tumor-specific T cell response. This response targets a broad spectrum of circulating antigens and enhances the immune assault on the tumor [6]. Furthermore, oncolytic viruses possess a notable capacity to induce immunogenic cell death, hence eliciting a robust immune response [16]. Induction of immunogenic cell death by oncolytic viruses triggers a sequence of events [17]. This involves the release of damage-associated molecular patterns (DAMPs) and pathogen-associated molecular patterns (PAMPs). The surface presentation of calreticulin on tumor cells, along with the release of high-mobility group box 1 and the synthesis of adenosine triphosphate, are considered critical features of immunogenic cell death. The generated adenosine triphosphate concurrently serves as a signal that allows immune cells to recognize and infiltrate the tumor microenvironment, thereby augmenting their presence within the tumor. The extracellular release of **High Mobility Group Box 1 protein** recruits more immune cells to the tumor microenvironment, provoking an inflammatory response [18].

The concurrent release of these molecules, known as DAMPs, is recognized by pattern recognition receptors, in conjunction with the release of viral components such as nucleic acids, proteins, and capsid elements, collectively dubbed PAMPs. This definition leads to improved concentration and development of tumor-specific T lymphocytes within the tumor microenvironment [19,20].

Major Oncolytic Viruses

Oncolytic viruses are viruses used in cancer treatment that selectively infect and destroy tumor cells. Today, various types of oncolytic viruses are used in research and clinical applications. Among the most commonly used are herpes simplex virus (HSV), adenovirus, reovirus, vesicular stomatitis virus (VSV), and Newcastle disease virus (NDV) [21]. The herpes simplex virus has been modified using genetic engineering techniques to enhance its ability to both directly kill tumor cells and activate the immune system [22]. Adenoviruses are frequently preferred, especially for gene therapy and oncolytic activity, and their different types and modifications allow for targeted tissue-specific treatment. Reovirus stands out for its natural ability to selectively infect certain cancer cells. Vesicular stomatitis virus and Newcastle disease virus, with their strong immunostimulant properties, contribute to treatment efficacy by enhancing the immune response in the tumor microenvironment [23] . Each of these viruses is being investigated in different cancer types and treatment combinations, showing promising results in clinical trials in terms of efficacy and safety.

Many different types of viruses have oncolytic potential [24]. The prominent viruses in clinical and preclinical studies are:

- Herpes Simplex Virus (HSV-1): Tumor selectivity has been increased through genetic modification.
- Reovirus: Shows selective replication in RAS-mutant tumors [25].
- Adenovirus: Suitable for targeted genetic loading due to its large DNA carrying capacity.
- Vaccinia virus: It is an effective vector for both gene expression and replication capacity.

Clinical Applications

Oncolytic viruses have significant clinical applications in cancer treatment by activating the immune system and selectively targeting tumor cells. First, Talimogene laherparepvec (T-VEC), a herpes simplex virus-based therapy, has been approved by the FDA for the treatment of advanced melanoma and has been shown to trigger a systemic antitumor immune response in addition to its direct cytotoxic effect on local tumors [8]. Teserpaturev (G47Δ), a modified herpes simplex virus used in the treatment of glioblastoma in Japan, significantly increased survival rates in phase II clinical trials [26]. In liver cancer, the oncolytic virus Pexastimogene devacirepvec (JX-594) slowed tumor growth and strengthened the immune response through intratumoral and intravenous applications [27]. Reolysin (Pelareorep), a reovirus-based oncolytic virus, has been shown in clinical trials to increase its efficacy when combined with gemcitabine in difficult-to-treat cancers such as pancreatic cancer, and to have tolerable side effects [28]. Additionally, Seneca Valley Virus (SVV-001) has been found safe in phase I trials for neuroendocrine tumors such as small cell lung cancer, and some antitumor effects have been reported [29-31]. In bladder cancer, Coxsackievirus A21 (CAVATAK) has shown positive results such as complete response and stable disease in patients with intravesical applications [32]. These studies show that oncolytic viruses hold promise in both monotherapy and combination therapies for different cancer types; however, challenges remain, such as viral distribution, optimization of immune responses, and management of side effects. In the future, the aim is to increase the effectiveness of these treatments through combinations of virus engineering and immunotherapy [4].

CombinationTherapies

Oncolytic viruses not only directly destroy tumor cells but also activate the immune system. However, in some tumors, the effectiveness of immunotherapies may be limited due to immune suppression mechanisms. At this point, oncolytic viruses enhance the effectiveness of checkpoint inhibitors like PD-1/PD-L1 inhibitors by making the tumor microenvironment "hot" (i.e., by attracting immune cells to the tumor region). For example, the combination of Talimogene laherparepvec (T-VEC) and pembrolizumab (a PD-1 inhibitor) has shown higher response rates and longer survival times in clinical trials in patients with

advanced melanoma compared to pembrolizumab alone [33].

Oncolytic Virus and Chemotherapy Combinations

The combination of oncolytic viruses and chemotherapy enhances tumor cell lysis and mitigates the immunosuppressive effects of chemotherapy. The amalgamation of Reolysin (a reovirus-derived oncolytic virus) with gemcitabine has demonstrated encouraging outcomes in phase II clinical trials for pancreatic cancer treatment; this combination has been successful even in chemotherapy-resistant patients [28].

Oncolytic Virus and Radiotherapy Combinations

Radiotherapy triggers cell death by causing DNA damage in tumor cells, while its combination with oncolytic viruses increases the immune response in the tumor microenvironment and strengthens the local control of radiotherapy. Especially in difficult-to-treat tumors like glioblastoma, the combination of HSV-based oncolytic viruses and radiotherapy has increased tumor shrinkage in preclinical models [34].

Oncolytic Virus and Targeted Therapy Combinations

Combining oncolytic viruses with certain targeted drugs can both facilitate the virus's entry into tumor cells and more effectively inhibit tumor growth. For example, there is preclinical data suggesting that the combination of BRAF inhibitors and oncolytic viruses increases treatment success in BRAF-mutated melanoma [35].

These combinations not only increase treatment efficacy but also help reduce side effects and prevent treatment resistance. However, as each combination can elicit a different response in the patient, clinical trials are ongoing to determine the optimal dose and timing.

Nano-Based Oncolytic Virus Therapies

Nanotechnology-assisted oncolytic virotherapy has emerged as a promising strategy in cancer treatment in recent years. It has been shown that the limitations of oncolytic viruses, such as elimination from systemic circulation, limited penetration into the tumor microenvironment, and antiviral immune responses, can be overcome through surface modifications and delivery systems using nanomaterials [36].

Oncolytic viruses, particularly those coated with polymers such as PEG or complexed with nanoparticle systems, both increase their circulation time and improve tumor targeting. This increases the replication capacity of oncolytic viruses, and their immune system activation potential can be used more effectively [37].

In another study conducted in this context, Newcastle disease virus (NDV) combined with gold nanoparticles (GNP) demonstrated potent antitumor activity in breast cancer cell lines. Combination therapy has been reported to induce apoptosis in tumor cells by increasing the expression of apoptosis-related genes p53 and caspase-9 and significantly reduce colony formation. Furthermore, the NDV-GNP combination has been reported to exhibit more pronounced cytotoxic and anti-proliferative effects than either agent administered alone. These findings suggest that the synergistic use of oncolytic viruses with nanoparticles can enhance both direct tumor lysis and indirect antitumor effects via the immune system in cancer treatment [38-42].

In conclusion, combining oncolytic viruses with nanotechnology is considered an innovative approach that can increase the effectiveness of cancer treatment through multiple mechanisms, including bioavailability, targeting accuracy, immunogenic cell death, and immune system reorganization.

Future Perspective

Despite the significant potential offered by oncolytic viruses in clinical applications, several biological and immunological hurdles that limit their therapeutic efficacy have not yet been fully overcome. Therefore, a priority goal of future research should be to further investigate the interactions of oncolytic viruses with immunosuppressive factors in the tumor microenvironment. Furthermore, designing oncolytic viruses tailored to patient-specific tumor profiles through advanced genetic engineering approaches is crucial for personalized treatment strategies. Determining the optimal dose, timing, and sequence of administration for combination therapies stands out as a critical area of research for improving therapeutic efficacy. Furthermore, there is a growing need for large-scale randomized clinical trials to evaluate the efficacy of various oncolytic virus and treatment combinations across different cancer types. Furthermore, developing effective immune modulation strategies to manage antiviral immune responses to oncolytic virotherapy is an important goal for supporting treatment success.

In addition to directly targeting and eliminating cancer cells, oncolytic viruses have been shown to trigger an antitumor immune response by inducing potent immunogenic cell death. In this context, the integration of oncolytic viruses with immunotherapies is considered an innovative approach that contributes to immune system restructuring. The success of oncolytic virotherapy depends on viral replication capacity, effective access to the tumor, accurate targeting of the immune system, and overcoming obstacles in the tumor microenvironment. Therefore, combining oncolytic viruses with genetic engineering techniques and immunotherapy strategies will significantly contribute to the development of more effective, safe, and targeted cancer treatments in the future.

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