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REVIEW

Enhancing Oncolytic Virus Therapy with Nanomedicine: A Review of Progress, Challenges, and Future Directions in a New Frontier of Cancer Treatment

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Abstract: Oncolytic viruses (OVs) are a new generation of tumor-specific biological agents that can selectively kill cancer cells. They replicate uniquely within tumors, showing significant potential for the advancement of precision cancer therapy. OVs have a dual action: they directly lyse malignant cells through selective viral replication in tumor tissues and activate the host's systemic antitumor immune response, thereby creating a comprehensive immune defense network. However, their clinical efficacy is often limited by rapid systemic clearance, poor tumor tissue penetration, and off-target effects. Nanotechnology has emerged as a transformative strategy to overcome these delivery barriers. This review highlights how intelligent nanocarriers enhance OV therapy through improved pharmacokinetics, active targeting, and controlled release within the tumor microenvironment. We further discuss rational combination strategies with conventional therapies (e.g. chemotherapy, radiotherapy) and immunomodulatory agents to achieve synergistic antitumor efficacy. Finally, we critically examine the current challenges and future translational prospects of nano-engineered OVs, providing a framework for advancing these innovative platforms toward clinical application and the development of next-generation cancer therapeutics.

Keywords: oncolytic virus, nanomedicine, anti-tumor, targeting delivery, immune activation

Introduction

Currently, the global burden of cancer morbidity and mortality is escalating at an alarming rate. The treatment paradigm for cancer has evolved from traditional approaches such as chemotherapy, radiotherapy, and surgery to more integrative multimodal therapies that encompass targeted therapies, immunotherapy, epigenetic therapies, and precision medicine. Nevertheless, conventional treatments—namely chemotherapy and radiotherapy—remain the first-line options for numerous cancers. The limitations of conventional therapies, such as their low specificity, systemic toxicity, and issues of drug or radioresistance, have catalyzed the development of novel therapeutic strategies.

Oncolytic viruses (OVs) are emerging as promising biotherapeutic agents in precision cancer therapy because of their unique ability to selectively replicate within tumor cells.[1] This selective replication leads to direct lysis of cancer cells and triggers a systemic antitumor immune response, creating a positive feedback loop of "viral tumor lysis-immune

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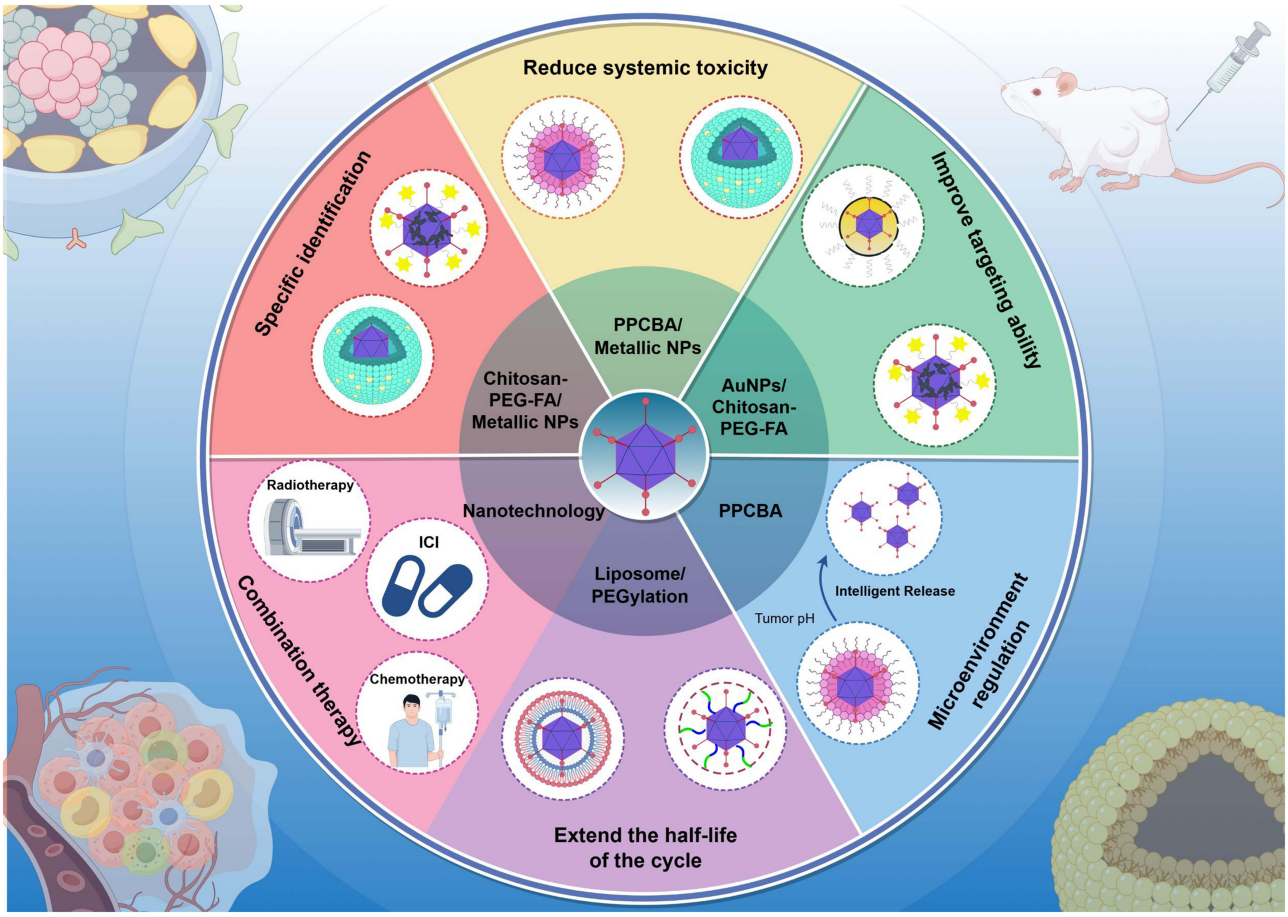
Graphical Abstract



activation"[2] This multimodal approach offers innovative strategies for cancer treatment that extend beyond traditional cell death paradigms.[3] However, the clinical application of oncolytic viral therapy faces significant challenges.[4,5] The circulation half-life of the virus is greatly reduced by humoral immune clearance, limiting its effective duration of action.[6,7] Additionally, the complex tumor microenvironment (TME)—characterized by hypoxia, acidic pH levels, and high interstitial pressure—impedes viral replication efficacy.[8–10] Off-target effects from nonspecific distribution and physiological barriers (eg., blood-brain barrier) further diminish the therapeutic effectiveness of OVs.[11,12] Recent advancements in nanotechnology have provided new solutions to these limitations.[13–15] The application of biomimetic design principles in intelligent nanocarrier systems offers a promising strategy to enhance key attributes of OVs, including their circulation half-life, tumor-targeting capability, and safety profile. This review critically evaluates recent advancements in these nano-engineered OV platforms, with a focus on how intelligent nanocarrier design can overcome existing delivery barriers and improve therapeutic outcomes. Furthermore, it explores combination strategies with conventional therapies and discusses the future translational prospects of this rapidly evolving field, providing a framework to guide future research and clinical development.

Oncolytic Virus Antitumor Mechanisms

Selective Cytotoxicity Against Tumor Cells

OVs exhibit unique tumor-targeting properties, either inherently[16–19] or through genetic modifications. Research by Toshiyoshi's team designed an adenoviral vector (telomere lysin, OBP-301), which not only permits preferential expression

of the viral genes in tumor cells, but also leads to selective viral replication and tumor cell death.[20] Genetic optimization of key adenovirus (AdV) proteins and design of an adenovirus death protein (ADP) overexpression complex (ADP-HAdV) enhances tumor cell lysis and immune escape.[21,22] These viruses selectively and effectively replicate within cancer cells, leading to proliferation and induction of tumor cell lysis due to increased internal pressure. Lysed tumor cells subsequently generate new viral particles that infect and destroy neighboring cancer cells, resulting in a devastating cascading effect (Figure 1). Following infection by OVs, tumor cells undergo various forms of cell death, including apoptosis (type I), autophagy (type II), and necroptosis (type III). A critical aspect of OV therapy is the interplay between these distinct death modalities, which can occur sequentially or simultaneously to create a synergistic antitumor effect.[23,24] The preference for a particular pathway is influenced by the virus type,[25] the specific tumor cell line, and the tumor microenvironment.

Apoptosis is triggered by both endogenous (mitochondria) and exogenous (death receptors) pathways, and is ultimately accomplished by executioner caspases.[26,27] The endogenous pathway is initiated by non-receptor-mediated cellular stressors (eg. radiation, hypoxia, DNA damage and oxidative stress) and subsequently triggered by MOMP (mitochondrial outer membrane permeabilisation), which induces the leakage of cytochrome c, leading to the formation of apoptotic vesicles and activation of caspase 9.[27] Exogenous apoptosis is activated by linking death components such as FAS-L, TNF-α and TRAIL cytokines to FASR, TNF-R1, TRAIL-R1 and TRAIL-R2 receptors, a process that stimulates caspases 8 and 10.[28] Meanwhile, exogenous apoptosis is usually interlinked with endogenous apoptosis via pro-apoptotic Bcl-2 family members. Both pathways ultimately activate executioner caspases 3, 6, and 7, which cleave cytoplasmic and nuclear proteins.[29] Autophagy is a biochemically programmed intracellular degradation process that is mainly regulated by LC 3B proteins, which are essential for autophagy and undergo conformational changes from LC 3B-I to LC 3B-II throughout the cellular autophagy process.[30] OVs also induce a non-caspase-dependent programmed cell death pathway, necroptosis, which exhibits morphological features such as cell swelling and plasma membrane rupture, and the presence of necroptotic cells is usually associated with inflammation.[31,32] Receptor-interacting protein kinases 1 and 3 (RIP1 and RIP3) are key molecules in necroptosis.[33,34] Collectively, these diverse modes of cell death create a complex network of antitumor effects.[30] When apoptosis is

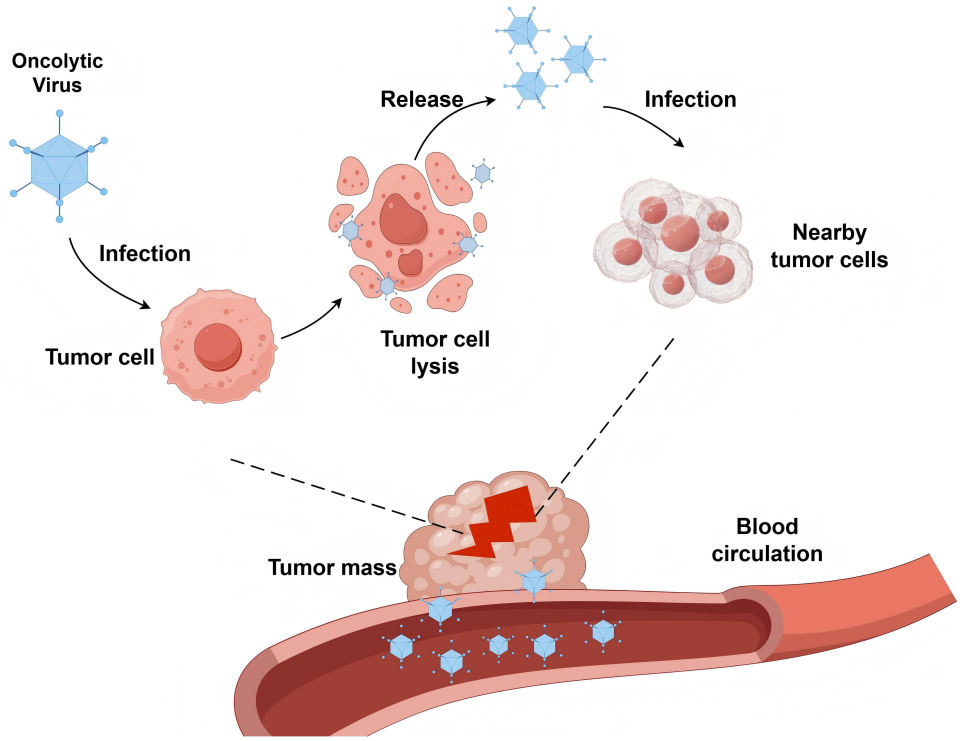


Figure 1 Mechanisms of oncolytic virus selective cytotoxicity against tumor cells. The schematic illustrates the process of OV infecting a tumor cell, selectively replicating within it, leading to cell lysis and the release of new viral particles to infect adjacent cells, creating a cascading antitumor effect.

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compromised, OVs can often induce necroptosis, a caspase-independent programmed necrosis characterized by cell swelling and membrane rupture, which is mediated by RIP1 and RIP3 kinases and is inherently pro-inflammatory.[35]

The synergy between these pathways is key to OV efficacy. For example, the inflammatory nature of necroptosis can potentiate antitumor immunity and augment the effects of apoptosis-induced immunogenic cell death.[36] Furthermore, the ability of OVs to engage alternative death pathways like necroptosis serves as a crucial mechanism to overcome apoptotic resistance in cancer cells. Therefore, the complex network of cell death mechanisms induced by OVs not only directly lyses tumor cells but also stimulates a robust and sustained systemic antitumor immune response, highlighting the multi-mechanistic strength of this therapeutic approach.[1]

Eliciting Systemic Antitumor Immune Responses

OVs invade tumor cells and initiate complex biological processes that elicit systemic antitumor immunity. Viral infection leads to the lysis of tumor cells, resulting in the release of tumor-associated antigens, which are subsequently captured by dendritic cells (DCs) and presented to T cells, thereby locally activating antitumor immune responses.[37] Activated T cells migrate to tumor tissues, attracting additional immune cells and facilitating immune infiltration into tumors, ultimately enhancing the therapeutic efficacy.[1] Moreover, viral infections generate viral pathogen-associated molecular patterns(PAMP), cellular danger-associated molecular patterns(DAMP), and cytokines that promote the maturation of antigen-presenting cells (APCs), including DCs. Mature APCs effectively deliver T-cell antigens and amplify antitumor immune responses (Figure 2)[1,38].

Limitations of Oncolytic Viruses

Limitations of Physical Barriers

The oncolytic virus must navigate several barriers to reach the tumor site in solid tumors. The virus must traverse the endothelium to access the target cells.[11] The abnormal lymphatic network and vascular hyperpermeability present in tumors, along with the robust extracellular matrix characteristic of solid tumors, may lead to interstitial hypertension.[39–41] This condition can impede viral infiltration and limit viral dissemination within the tumor core.[8,42]

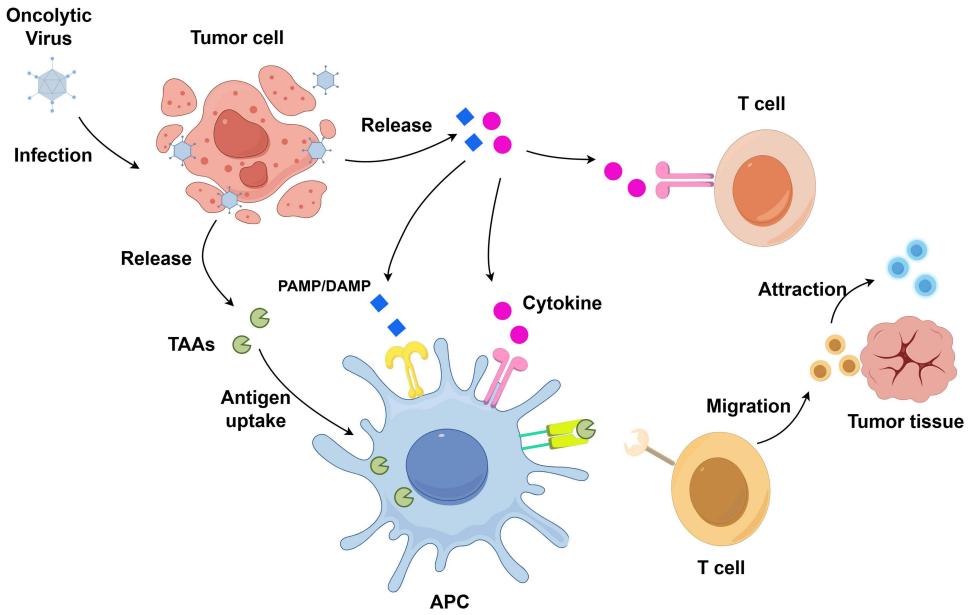

Figure 2 Schematic representation of OVs eliciting systemic antitumor immune responses. Following tumor cell lysis, OVs promote the release of tumor-associated antigens (TAAs) and danger signals, leading to dendritic cell (DC) maturation and subsequent activation of T cells, which mount a systemic immune attack against the tumor.

Interference with the Host Immune System

OVs can provoke robust innate immune responses, interact with APCs, and activate host immunological defense mechanisms. However, strong antiviral immunity, pre-existing circulating antibodies, and various blood components, such as coagulation factors FIX and FX and complement protein C4BP, can facilitate viral clearance. Furthermore, both coagulation factors and the complement system play roles in destabilizing viral integrity.[8,43]

Development of an Immunosuppressive Tumor Microenvironment

Chemokines and cytokines released by solid tumors (eg., IL-10, TGF-β, and arginase) compromise the functionality of immune cell populations[44] and attract immunosuppressive cells (eg., regulatory T cells, myeloid-derived suppressor cells, and tumor-associated macrophages), thereby diminishing antitumor responses.[3,44,45] Furthermore, the overexpression of immunological checkpoints (eg., PD-1 and CTLA-4) exacerbates the immunosuppressive TME and facilitates immune evasion.[46–49] Consequently, there is also a growing interest in enhancing immune infiltration by combining OVs with agents that block immunosuppressive signals or remodel the TME.[50–55]

Tumor Heterogeneity and Pharmacological Resistance

Aberrant tissues and structures within the tumor vasculature compromise the blood supply, resulting in a hypoxic and acidic microenvironment.[10,56] These detrimental microenvironments may hinder tumor cell apoptosis, promote angiogenesis, and elevate levels of tumor growth factors.[11,57] Consequently, this exacerbates the TME and induces cross-resistance of tumor cells to conventional therapies, such as radiotherapy, cytotoxic agents, and immunotherapy.[11,57,58]

Strategies for the Implementation of Nanotechnology in Oncolytic Viral Treatment

Design and Fabrication of Nanocarrier Systems

Prolongation of Circulation Half-Life

Through techniques such as PEGylation and cell membrane camouflage, nanocarriers can establish an immune evasion layer on the surfaces of viral particles.[59] This effectively allows them to evade detection and elimination by the monocyte-macrophage system, thereby prolonging the presence of viral particles in the systemic circulation. Notably, liposome-encapsulated adenoviruses have demonstrated a significant extension of their in vivo circulation time and a markedly enhanced accumulation at tumor sites (Figure 3). With the aid of the cationic liposomal vectors, the oncolytic Ads genome can arrive at the tumor foci through the systemic circulation and then translocate into the nucleus and subsequently replicate, generating infectious oncolytic Ads progenies within tumor cells. These newly generated oncolytic Ads subsequently lyse the cancer cells and infected adjacent cells, thereby enhancing the overall oncolytic efficacy. Experimental results demonstrated the superior performance of the liposome-encapsulated, armed oncolytic Ads: treated mice exhibited a viral genome tumor-to-liver ratio that was 934 times and 27 times higher than that in the naked oncolytic Ads and naked armed oncolytic Ads groups, respectively. Concurrently, this strategy triggered a potent antitumor response, reducing tumor volume by more than 90% compared to the control group.[60] However, a well-documented limitation is the potential for anti-PEG antibodies to induce an accelerated blood clearance (ABC) phenomenon upon repeated administration, which can compromise the efficacy of subsequent doses.[61] Furthermore, excessive surface modification can sometimes hinder the virus's intrinsic ability to infect target cells, necessitating a delicate balance between stealth properties and bioactivity.

Attaining Tumor-Specific Identification and Profound Infiltration

Nanocarriers can incorporate TME-responsive targeting motifs, thereby endowing OVs with enhanced "intelligent navigation" capabilities. These targeting moieties selectively identify indicators of tumor neovascularization or specific receptors present on the surface of tumor cells, allowing them to penetrate the dense mesenchyme and achieve significant tumor infiltration. Chitosan-PEG-FA-modified adenovirus nano complexes facilitate the targeted delivery of OVs through folate receptor-mediated endocytosis.[60,62] A significant challenge, however, arises from inter- and intra-tumoral

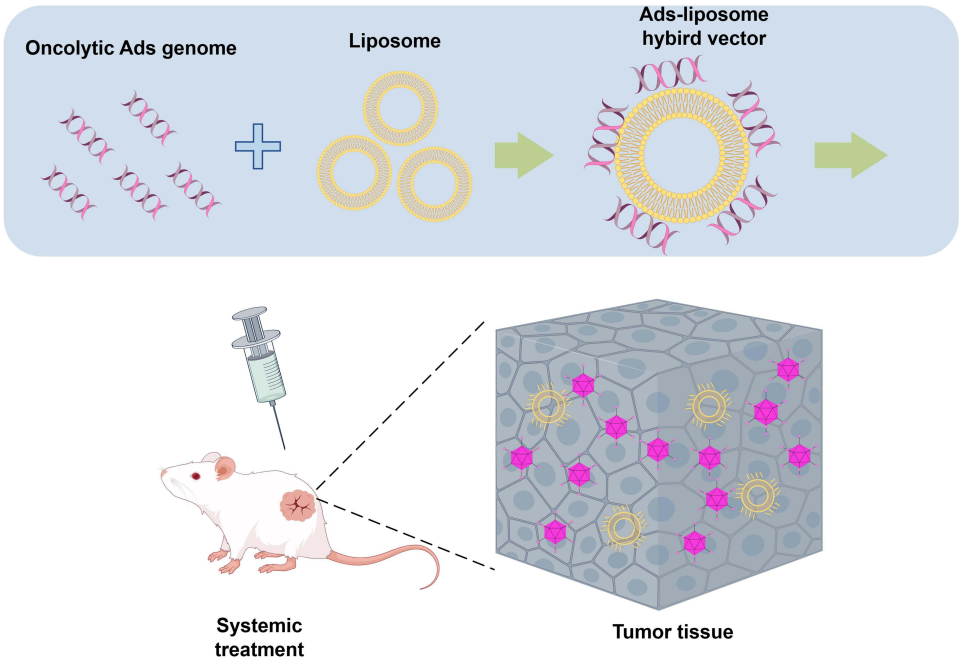

Figure 3 Mechanism of liposome-encapsulated adenovirus in tumor therapy. With the aid of cationic liposomal vectors, the oncolytic Ads genome is delivered to the tumor foci via systemic circulation. The genome then translocates into the nucleus and replicates, generating new infectious viral progenies within tumor cells, leading to cell lysis and infection of neighboring cells.

heterogeneity, where variable expression levels of the target antigen can lead to inconsistent therapeutic outcomes. Additionally, the dense fibrotic stroma characteristic of many solid tumors remains a formidable physical barrier to deep penetration, even for actively targeted nanocarriers.[63]

Mitigating the Risk of Off-Target Toxicity

Through spatiotemporally controlled viral release mechanisms, nanocarriers can precisely deliver viral loads to tumor sites, significantly reducing the risk of off-target damage. Adenoviruses encapsulated in the pH-sensitive polymer PPCBA can target the acidic microenvironment characteristic of tumors and release viruses under low pH conditions.[64] Moreover, Tseng, S. J. et al designed nanoparticles containing LOX, which exhibit high reactivity with lactic acid in the TME and provide positive guidance for the targeted and precise release of OVs, while reducing the risk of off-target toxicity.[65] The key advantage is the substantial reduction in systemic toxicity and enhanced therapeutic index achieved through this precise, stimulus-responsive control.[66] The limitations primarily concern the reliability of the triggering stimulus; for instance, the pH gradient between the tumor and healthy tissue may not be sufficiently sharp in all cases, potentially leading to incomplete or untimely viral release.[67] Furthermore, the biocompatibility and degradation kinetics of the smart polymer materials themselves require rigorous evaluation to ensure long-term safety.[68]

Nanotechnology in Targeted Delivery Systems

OVs have attracted considerable attention because of their unique antitumor properties. However, their clinical application faces numerous challenges, including inefficient transport, rapid immune clearance, and a complex TME. These limitations significantly hinder the therapeutic efficacy and applicability of OVs in cancer therapy. Nanocarrier technology has emerged as a novel approach for the targeted delivery of OVs to address these challenges. By employing a triple mechanism comprising passive, active, and stimulus-responsive targeting, nanocarrier technology effectively mitigates the challenges associated with oncolytic virus delivery. This advancement markedly enhances the accumulation efficiency at tumor sites and improves anticancer efficacy.

Passive Targeting: Utilizing Tumor Characteristics for Preliminary Enrichment

Passive targeting primarily relies on the increased permeability of tumor vasculature and the enhanced permeability and retention (EPR) effect, which selectively concentrates nanoparticles at the tumor sites.[69] Lipid-encapsulated nanosystems represent a widely utilized strategy to prolong the circulation time of OVs in vivo while simultaneously increasing their concentration at tumor locations. Lipid-encapsulated membranes provide a protective barrier for OVs against immune system clearance, significantly enhancing their distribution within tumor tissues. Furthermore, liposome-encapsulated adenoviruses demonstrated extended circulation times in vivo and markedly improved accumulation at the tumor site, presenting a promising approach for systemic drug delivery.[60] The main advantage is its broad applicability across different nanocarrier types without the need for complex ligand engineering. However, the clinical relevance of the EPR effect in humans has been debated, with high heterogeneity observed among patients and tumor types.[70] Moreover, high interstitial fluid pressure within solid tumors often hinders the uniform distribution of nanocarriers, limiting their efficacy in the tumor core.[71]

Active Targeting: Accurate Localization to Enhance Infection Efficiency

Active targeting enhances the affinity of nanoparticles for tumor cell receptors by modifying ligands, such as folate and peptides, thereby improving infection efficiency.[72] Gonzalez et al encapsulated adenovirus (Ad) vectors with gold nanoparticles (AuNPs) featuring quaternary groups and RGD peptides to create biocompatible complexes, significantly boosting transporter efficacy.[73] Chitosan-PEG-FA-modified adenovirus nanocomplexes exploit the high expression of folate receptors in various tumors for targeted delivery of OVs.[62] The integration of magnetic nanoparticles with OVs enables distant targeted delivery, while a magnetic field-guided approach increases OV accumulation in tumors and reduces nonspecific infections. Additionally, incorporating photosensitive protein genes into adeno-associated virus type 2 (AAV2) facilitates photodynamic therapy (PDT), significantly decreasing tumor proliferation.[74] Howard's team synthesized biocompatible magnetic nanoparticles from magnetized bacteria combined with herpes simplex viruses to develop magnetized viruses (MAG-OV).[75] These can be directed toward tumors using an external magnetic field to enhance viral replication and improve antitumor efficacy. This strategy not only promotes viral replication within tumors, but also boosts antitumor immunity and induces apoptosis in immune cells, contributing to tumor reduction. A significant drawback, however, is the "binding-site barrier" effect, where strong binding near blood vessels can prevent deeper penetration into the tumor mass.[76] There is also the potential for immune recognition of the targeting ligands, which could accelerate clearance.

Stimulus Response Targeting: Intelligent Release to Mitigate Systemic Toxicity

Stimulus-response targeting utilizes specific conditions in the TME or external stimuli to activate nanoparticles for targeted drug release at the lesion site, thereby minimizing systemic toxicity. Recent studies have developed oncolytic adenoviruses encapsulated in calcium carbonate and manganate (MnCaCs) to create biomineralized nanoparticles (OA@MnCaCs).[77] These nanoparticles protect the virus from immune elimination and extend its circulation time. In an acidic environment, MnCaCs dissolve to release Mn^{2+}, which catalyzes the conversion of endogenous H_2O_2 into oxygen, enhancing tumor activity and promoting OA replication, thereby significantly improving the antitumor efficacy. Elevated levels of Mn^{2+} and oxygen also facilitate T1-modality magnetic resonance imaging and photoacoustic imaging (Figure 4). Additionally, Moon CY's al. engineered pH-sensitive polymer PPCBA-coated adenoviruses that target the acidic TME. These viruses are released under low pH conditions, increasing their cytotoxic effects on tumor cells.[64] Moreover, the surface modification of nanoparticles with specific ligands in photodynamic virotherapy enhances the selectivity and solubility of photosensitizers, thereby boosting therapeutic efficacy.[78]

Nanotechnology-Enhanced Oncolytic Viral Combination Therapy

Combination Therapy of Chemotherapy and Oncolytic Viruses

The combination of chemotherapeutic agents with OVs effectively overcomes tumor treatment resistance through a dual mechanism.[79] Chemotherapy induces apoptosis in tumor cells,[80] while OVs lyse cancer cells and activate the immune system via tumor-specific replication.[81] Nanotechnology significantly enhances this synergistic effect via multifunctional integration.

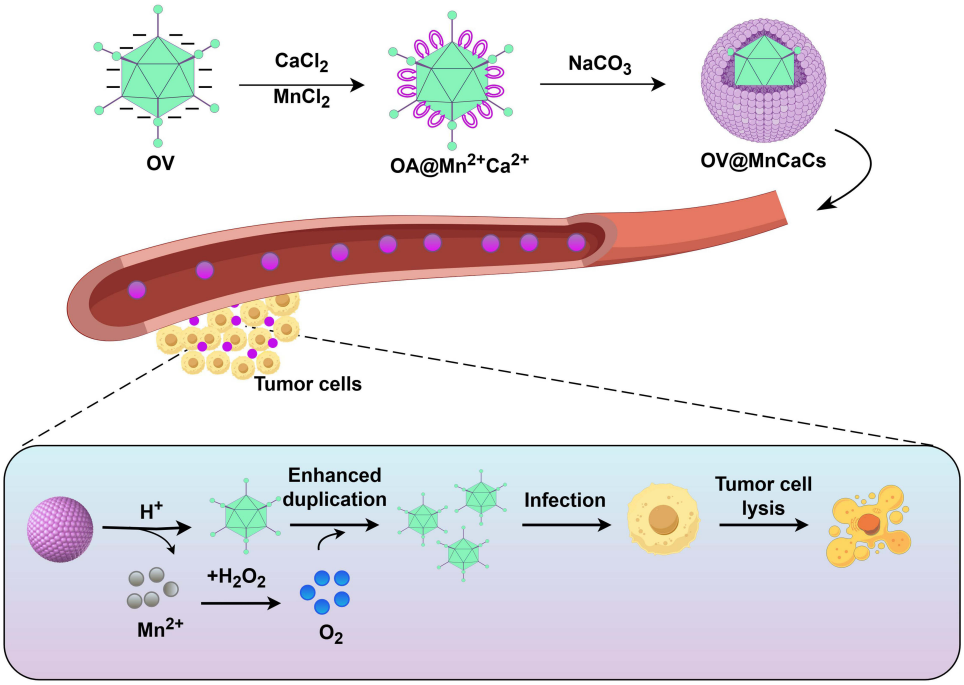

Figure 4 Function of biomineralized oncolytic adenovirus nanoparticles (OA@MnCaCs). The diagram depicts the structure of OA@MnCaCs and their responsive behavior in the acidic tumor microenvironment (TME), including the release of $Mn^{2+}$and O_2, enhancement of OA replication, and application in bimodal imaging.

Amini et al developed a doxorubicin (DOX)-based nano-targeted delivery system that reversed multidrug resistance in tumor cells by inhibiting P-glycoprotein expression and promoting $CD8^+$ T cell infiltration to strengthen the antitumor immune response.[82] Professor Zhu Y further enhanced this response by co-loading DOX with IDO1 inhibitors using DNCaNPs, neutralizing the acidic TME, inducing immunogenic cell death, and inhibiting Treg proliferation to transform the immune environment from cold to hot.[83] Yang Y's research team created a magnetic-driven FTNP to boost the antitumor immune response by enhancing CD8+ T cell infiltration.[84] Their innovative Fe/DOX@SL nanorobot technology utilizes intelligent delivery mechanisms for precise magnetic targeting under an applied magnetic field, demonstrating significant antitumor efficacy and favorable biosafety profiles. However, the combination can lead to complex pharmacokinetic interactions, and the long-term biosafety of co-delivery nano-systems requires extensive investigation.[85]

Combination Therapy of Radiotherapy and Oncolytic Viruses

The integration of radiation therapy with OVs can enhance antitumor immunity through various mechanisms.[86] This synergistic approach increases the radiosensitivity of tumor cells while stimulating immune activation.[87–89] Additionally, nano-radiation sensitization technologies improve the localized effects of radiotherapy and modify the TME.[90] Apoptosis and Enhanced Radiosensitivity: Xiao L found that gold-based nanoparticles ($Au@AgBiS_2$) significantly inhibited metastasis in triple-negative breast cancer by inducing reactive oxygen species (ROS) production and activating pyroptosis-related proteins alongside radiotherapy.[91] Moreover, Zhang et al developed iron-based nanosystems ($Au\text{-}Fe_3O_4$ nano-heterodimers) that generated substantial ROS under X-ray irradiation, creating a synergistic effect between radiotherapy and chemodynamic therapy.[92] The research results of Professor Salehiabar M are also similar to the above research results.[93]

Combination Therapy of Immune Checkpoint Blockade and Oncolytic Viruses

The integration of immune checkpoint inhibitors (ICIs) with oncolytic viruses has demonstrated significant antitumor efficacy in clinical settings.[94–97] OVs enhance ICIs by converting the "cold" TME into a more immunogenic environment, and nanotechnology further boosts the effectiveness of this combination therapy.[98]

Clinical studies indicate that Puzanov I et al found that combining T-VEC with the CTLA-4 inhibitor ipilimumab significantly improved the objective remission rate (ORR) in patients with melanoma while being well tolerated.[99]

Additionally, Professor Ribas A utilized T-VEC alongside the PD-1 inhibitor pembrolizumab to induce a systemic antitumor response by increasing $CD8^+$ T-cell infiltration and reducing regulatory T-cells (Treg) relative to effector T-cells (Teff).[100] Foundational studies have revealed additional possibilities for this. Prof. Ren X developed bispecific aptamer nano-assemblies to deliver GLUT1 inhibitors, shifting Treg metabolism from immunosuppressive to immunostimulatory states, thus enhancing the antitumor immune response.[101] Moreover, Wang-Bishop's team discovered that SLR-LNPs nanoparticles significantly improved tumor responses to ICIs and increased tumor immunogenicity through RIG-I pathway activation.[102] The major advantage is the potential to achieve robust and durable systemic antitumor immunity by combining the antigen release triggered by OVs with the T-cell reinvigoration provided by ICIs. The primary limitation is the risk of exacerbating immune-related adverse events (irAEs). Furthermore, the efficacy of this combination is highly dependent on the host's immune status and may be limited in severely immunosuppressed patients.[103]

Opportunities and Obstacles for the Clinical Utilization of Nanoengineered Oncolytic Viruses

Advancements in nanotechnology indicate that nanoengineered OVs hold significant promise for precision tumor therapy.[104,105] The convergence of biomimetic design, intelligent responsiveness, and multifunctional integration within nanoplatforms is paving the way for viruses that can dynamically adapt to the tumor microenvironment, thereby maximizing oncolytic potency while minimizing systemic toxicity.[106] This evolution positions nano-engineered OVs not merely as improved delivery vehicles but as programmable therapeutic systems capable of transforming the oncology treatment landscape. The creation of intelligent nanoplatforms, along with the optimization of various mechanisms and faster clinical translation, positions these viruses as next-generation therapeutic agents in oncology, capable of transforming the treatment landscape. Clinical decision-making will evolve by considering two key aspects: (1) tailored treatment strategies: customizing plans based on patients' unique characteristics, such as tumor type and immune status, can improve outcomes while reducing side effects;[107,108] (2) combination therapies: using a variety of modalities, such as chemotherapy, radiotherapy, and immunotherapy, can create a synergistic approach to enhance antitumor efficacy.[104,109]

Despite their potential, nanoengineered OVs face several challenges in clinical application.[110–112] A primary obstacle lies in the precise engineering of nanocarriers to achieve optimal biodistribution and intracellular delivery; even minor variations in size, charge, or surface chemistry can drastically alter pharmacokinetics and tumor accumulation profiles.[113] Furthermore, the inherent heterogeneity of human tumors means that preclinical models often fail to accurately predict therapeutic efficacy and potential toxicities in diverse patient populations.[114] This biological complexity is compounded by manufacturing hurdles, where achieving batch-to-batch consistency and scalable production of these complex biological-nanomaterial hybrids remains a significant technical and regulatory challenge.

Improving the biosafety, stability, and targeting capabilities of nanocarriers is therefore crucial. Additionally, patient heterogeneity complicates the design of robust clinical trial protocols and reliable outcome evaluations. Moreover, navigating the complex regulatory approval process for new anticancer drugs poses another significant hurdle that must be addressed to facilitate timely market entry.[115–119] Regulatory agencies currently lack specific guidelines for these combination products, requiring a new framework that adequately addresses their unique safety and efficacy considerations.

Conclusions and Future Perspectives

As novel antitumor biological agents, OVs have demonstrated significant potential in precision tumor therapy. However, the journey from a potent concept to a mainstream clinical reality is fraught with biological and technological barriers that conventional virotherapy alone cannot overcome. Nanotechnology offers innovative solutions to address these obstacles. Intelligent nanocarrier systems, developed through bionanotechnology, enable OVs to achieve multiple functional enhancements, such as immune evasion, deep tumor penetration, and spatiotemporally controlled replication, indicating substantial promise for application in precision tumor therapy.[120]

The continuous advancement of nanotechnology and interdisciplinary collaboration position nano-engineered OVs as potential next-generation therapeutic agents in oncology, heralding a transformative shift in treatment approaches. To realize this paradigm shift, future research must extend beyond demonstrating efficacy in model systems to solving the

core translational challenges. It is crucial to address the technical bottlenecks, challenges associated with clinical trials, and regulatory approval issues that nanoengineered OVs encounter during their clinical applications. This focus is essential for facilitating timely integration into clinical practice and providing new hope for patients with cancer.

Looking forward, the clinical translation of nano-engineered OVs will depend on several key developments. Future efforts should prioritize: (1) refining nanocarrier design to optimize biosafety, stability, and scalable manufacturing, with a focus on biodegradable materials and simplified fabrication processes to ease regulatory approval;[121] (2) validating combinatorial approaches with immunotherapy, radiotherapy, and chemotherapy in physiologically relevant models, such as patient-derived organoids and humanized mouse models, to better predict clinical synergy;[122] (3) establishing clear regulatory pathways for these complex therapeutic platforms through early and continuous dialogue with agencies, defining critical quality attributes for these combination products. Addressing these priorities will be essential to fully realize the potential of nano-engineered OVs, ultimately facilitating their timely integration into clinical practice and offering new hope for cancer patients.

Data Sharing Statement

This is a review article and does not contain original research data. All discussed information is based on previously published studies cited in the reference list.

Ethics Statement

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Consent for Publication

All authors have given their consent for publication.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

All authors claim that there are no potential conflicts of interest in the study.

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