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Nanoparticle-mediated delivery of oncolytic viral genomes: an innovative strategy for tumor-targeted immunotherapy

Junhan Yang[1] and Binlei Liu[1*]

*Correspondence:
liubl@hbut.edu.cn

[1] National "111" Center for Cellular Regulation and Molecular Pharmaceutics, Key Laboratory of Fermentation Engineering (Ministry of Education), Cooperative Innovation Center of Industrial Fermentation (Ministry of Education & Hubei Province), Hubei Key Laboratory of Industrial Microbiology, School of Life and Health Sciences, Hubei University of Technology, Wuhan 430068, China

Abstract

Nanoparticle (NP)-mediated delivery of oncolytic viral genomes (vGenomes) represents an innovative strategy to overcome the limitations of conventional oncolytic virotherapy. While traditional live virus delivery systems face substantial challenges including immune-mediated clearance and complex manufacturing workflows, our analysis reveals that encapsulating viral genomes (vGenomes) within surface-functionalized nanoparticles establishes a robust delivery platform. By encapsulating vGenomes within functionalized NPs, this platform achieves tumor-targeted delivery via enhanced permeability and retention (EPR) effects or ligand-mediated active targeting. Intracellular release of vGenomes enables in situ production of viral progeny, inducing immunogenic cell death while evading pre-existing antiviral immunity. Preclinical studies demonstrate that NP-vGenome complexes achieve > 80% tumor regression in murine models and maintain efficacy even in neutralizing antibody-rich environments. This review synthesizes the mechanistic synergy between nanotechnology and oncolytic virotherapy, providing a roadmap for next-generation cancer immunotherapy.

Keywords: Oncolytic viruses, Nanoparticles, Viral genomes, Antitumor therapy, Tumor targeting

Background

Tumors are abnormal tissues formed by uncontrolled cell proliferation and are a major threat to human health. According to statistics from the World Health Organization, there were approximately 18.2 million new cases of cancer and approximately 9.6 million deaths from cancer in 2018 worldwide (Bray et al. 2018). Traditional tumor treatments mainly include surgery, radiotherapy, and chemotherapy, but these methods are often accompanied by serious side effects and the risk of recurrence. In recent years, with the development of biotechnology and immunology, some new tumor treatment methods have emerged, such as targeted therapy, immunotherapy, and gene therapy. These methods can kill tumor cells more accurately and effectively, and can regulate the body's immune system, thereby improving cure rates and survival. With the continuous

increase in tumor morbidity and mortality, finding more effective and safe tumor treatment methods is one of the major challenges facing the medical community today.

Oncolytic viruses are a new class of cancer therapeutics based on natural or genetically modified viruses (Bommareddy and Kaufman 2018) that selectively infect and kill tumor cells and induce anti-tumor immune responses (Deng et al. 2016). Currently, four commercial oncolytic viruses have been approved by different regulatory agencies worldwide (Muthukutty and Yoo 2023), and numerous clinical trials have also demonstrated the tolerance and effectiveness of oncolytic viruses (Dummer et al. 2008; Goins et al. 1144; Gupta et al. 2006; Hersey and Gallagher 2014; Mastrangelo et al. 1999; Senzer et al. 2009). Despite its many advantages, this emerging therapy still faces significant challenges such as route of administration, host immune response, and safety (Li et al. 2020). Since only systemic treatment can target lesions that are difficult to reach surgically, and the efficacy of simple intravenous injection of oncolytic viruses is easily limited by neutralizing antibodies and cellular immune responses produced against the virus, many recent studies have focused on the development of carriers that can systemically deliver oncolytic viruses to tumor lesions (Na et al. 2019). A typical example is the hybrid carrier system generated by combining oncolytic viruses with different nanoparticles (Grünwald et al. 2013; Jung et al. 2017). However, the complex production process and strong immunogenicity of live viruses have led to a therapy that combines the oncolytic virus genome with nanoparticles. Researchers replaced the live virus in the hybrid vector system with the oncolytic virus genome, which not only retains the conditional replication of the virus in tumor cells but also avoids unexpected immune responses (Kwon et al. 2011).

To comprehensively evaluate the clinical potential of NP-vGenome therapy, we present a key attributes comparison with conventional treatments (Table 1), Compared to the broad cytotoxicity of chemotherapy (clinical response rate 10–40% (Yalniz et al. 2018)), NP-vGenome achieves tumor-specific killing through viral replication, with preclinical response rates reaching 80%. Unlike immune checkpoint inhibitors, this therapy does not require pre-existing tumor immune infiltration and can activate T cells even in"cold tumor"models (see Fig. 3A). Furthermore, its modular production model reduces annual treatment costs.

Table 1 Comparison of NP-vGenome therapy with conventional cancer treatments

Therapy	Targeting	Efficacy	Toxicity	Key limitations	Refs.
Chemotherapy	Low	Moderate	High	Non-specific cytotoxicity	Cai et al. 2024; Gupta et al. 2018)
Immune Checkpoint Inhibitors	Moderate	High (select patients)	Moderate (immune-related adverse events)	Low response in "cold" tumors	Zhan et al. 2025)
Chimeric Antigen Receptor T-Cell Immunotherapy (CAR-T Cell Therapy)	High	High (select patients)	High (acute toxicity and long-term complications)	Cytokine storm, poor solid tumor penetration	Qi et al. 2022)
NP-vGenome Therapy	High	High (preclinical)	Low (theoretical)	Scalability and long-term safety	Kwon et al. 2011)

Nanoparticles have gained popularity in the field of cancer treatment due to their unique advantages such as biocompatibility, stability, adjustability, and low toxicity (Gavas et al. 2021). A wide variety of nanoparticle systems have been developed, including polymers, liposomes and metal particles (Surendran et al. 2018). In recent years, drug delivery platforms based on nanoparticles have developed rapidly. These nanoparticles with their distinct characteristics have been proven to be effective in many studies (Allen and Cullis 2013; Cheng and Lee 2016; Knudsen et al. 2015). However, compared with viral vectors, their lower gene transfection efficiency limits their clinical transformation (Li and Huang 2006). Fortunately, the conditional replication ability of oncolytic viral genomes is expected to provide a satisfactory solution (Fu and Zhang 2001). The combination of oncolytic viral genomes with nanoparticles cleverly utilizes the characteristics of viral and non-viral vectors, thereby effectively synergizing efficient viral vector-mediated therapy and non-viral vector-mediated systemic administration.

As summarized in Table 2, nanoparticle-mediated delivery of oncolytic viral genomes addresses critical limitations of traditional oncolytic virotherapy. By encapsulating vGenomes within functionalized nanoparticles, systemic immune clearance is minimized through nanocarrier shielding, while tumor-targeted delivery is enhanced via ligand modification or passive accumulation. This dual-modality strategy not only preserves the oncolytic potency of viral progeny but also leverages scalable nanomanufacturing platforms, such as lipid nanoparticles (LNPs) validated in mRNA vaccine production (Schoenmaker et al. 2021).

The oncolytic virus genome first avoids the neutralization of virus-specific antibodies in the host with the help of nanoparticles, reaches tumor lesions throughout the body through blood circulation, and then transcribes and translates in cancer cells, eventually generating infectious and complete progeny oncolytic viruses. These progeny viruses lyse cancer cells and continue to infect adjacent tumor cells, effectively retaining the efficacy of oncolytic viruses while avoiding their limitations. In addition, because the nanoparticle-modified oncolytic virus genome itself does not contain any viral capsid proteins, the body's humoral and cellular immune responses to these capsid proteins are reduced to varying degrees, which undoubtedly further enhances the safety and effectiveness of the combination therapy.

Table 2 Comparison between traditional oncolytic viruses and nanoparticle-delivered vGenomes

Criteria	Traditional oncolytic viruses	Nanoparticle-delivered vGenomes	Refs.
Immunogenicity	High (capsid-triggered immunity)	Low (nanocarrier shielding)	Bommareddy and Kaufman 2018; Li et al. 2020; Kwon et al. 2011)
Scalability	Low (live virus production)	High (synthetic nanocarriers)	Gavas et al. 2021; Surendran et al. 2018; Schoenmaker et al. 2021)
Tumor targeting	Limited (natural tropism)	Enhanced (ligand-mediated targeting)	Grünwald et al. 2013; Jung et al. 2017; Surendran et al. 2018)
Delivery efficiency	High (direct infection)	Moderate (release-dependent)	Kwon et al. 2011; Fu and Zhang 2001)
Safety	Moderate (off-target risks)	High (tumor-selective release)	Li et al. 2020; Kwon et al. 2011)

This article reviews the role and mechanism of oncolytic virus and nanoparticle anti-tumor therapy in cancer treatment. We also organized and summarized the application of nanoparticle-modified oncolytic virus genomes in cancer treatment. Finally, we discussed the potential value and future directions of this therapy in clinical translation.

Oncolytic viruses

At the end of the nineteenth century, a female leukemia patient experienced a significant decrease in the number of white blood cells in her body after being infected with the influenza virus (Tian et al. 2022). Subsequently, more and more cancer patients were reported to have lesions alleviated or even disappeared after being infected with the virus. Some scientists realized that there might be some connection between viruses and tumors, so from the 1950 s to the 1980 s, researchers began to use various wild-type viruses for clinical trials on tumor patients. Unfortunately, due to various limitations, the oncolytic potential of the virus was not effectively developed (Asada 1974; Moore 1952; Southam and Moore 1952). It was not until the end of the twentieth century that Ezzeddine et al. used a retroviral vector to deliver the thymidine kinase gene (TK) of herpes simplex virus type I (HSV-1) to rat gliomas and successfully inhibited tumor growth (Ezzeddine et al. 1991). Oncolytic viruses have experienced rapid development. At the beginning of the twenty-first century, various oncolytic viruses approved by regulatory agencies emerged internationally, including RIGVIR approved in Latvia in 2004 (Bilsland et al. 2016), H101 approved in China in 2005 (Garber 2006; Zhang et al. 2022), followed by T-VEC approved in the United States and Europe in 2015 (Kaufman and Bommareddy 2019), and Deltyact approved for marketing in Japan in recent years (Zeng et al. 2021). The successful launch of these drugs represents the gradual recognition of oncolytic virus therapy and marks the increasing maturity of oncolytic virus technology.

Many genetically modified oncolytic viruses with significant clinical efficacy have been reported (Macedo et al. 2020). However, these oncolytic viruses often only show good response rates against one or several types of cancer. This is usually caused by the high heterogeneity of tumor tissues and the high complexity of the tumor microenvironment. Therefore, the correct selection of different oncolytic viruses and efficient delivery methods are considered top priorities in the field of oncolytic virus therapy (Mondal et al. 2020).

Types of oncolytic viruses

Currently, two major categories of viruses have been developed for tumor therapy: DNA viruses and RNA viruses, some of which are mentioned in Tables 3, 4. Oncolytic DNA viruses (such as adenoviruses (Ads), herpes simplex virus (HSV), parvoviruses, and poxviruses) have certain advantages over RNA viruses due to their genome stability and ability to carry large amounts of exogenous gene fragments. In contrast, oncolytic RNA viruses (such as coxsackieviruses, measles virus (MV), reoviruses (RV), and retroviruses) are able to kill tumor cells more quickly because their nucleic acid replication occurs only in the cytoplasm (Zheng et al. 2019).

Table 3 A list of oncolytic viruses and their characteristics

Viruses	Structure (Capsid symmetry)	Virion	Baltimore classification (Size)	Replication site	Advantage	Disadvantage	Refs
Adenovirus (Ads)	Icosahedral	Naked	Group I: dsDNA (~ 35 kb)	Nucleus and cytoplasm	• Strong solubilizing activity Genetic manipulation possible • Able to infect a variety of cells (both dividing and non-dividing) • Enhanced tumor specificity • Physical and chemical stability of particles • High titer • Broad tissue tropism • Improving anti-tumor effects when combined with immunomodulators	• Limited tumor infection • Limited efficiency of antiviral immunity • Reduced virus transmission • Replication cannot be easily turned off	Lin et al. 2023; Niemann and Kuhnel 2017; Zhao et al. 2021)
Herpes simplex virus (HSV)	Icosahedral	Enveloped	Group I: dsDNA (~ 154 kb)	Nucleus and cytoplasm	• Fast replication • No receptor restriction, wide infection spectrum • Large genome, easy to modify and insert multiple foreign genes • Antiviral drugs can be used to control dosage	• May trigger the immune system to attack healthy cells • Requires precise dosing to avoid side effects	Ma et al. 2018; Scanlan et al. 2022)
Vaccinia virus (VACV)	Complex	Complex coats	Group I: dsDNA (160–190 kb)	Cytoplasm	• Highly effective in killing tumor cells • Excellent targeting ability • Fewer side effects • Multi-pathway tumor destruction	• Blood vessel closure may limit viral spread • May impede delivery of subsequent therapeutic drugs	Guo et al. 2019; Haddad 2017; Xu et al. 2023)

Table 3 (continued)

Viruses	Structure (Capsid symmetry)	Virion	Baltimore classification (Size)	Replication site	Advantage	Disadvantage	Refs
H-1 Parvovirus (H-1 PV)	Icosahedral	Naked	Group II: ssDNA (~ 5 kb)	Nucleus and cytoplasm	• High security • Induces immune system activation • Effective against a variety of tumor types	• Further clinical validation is needed • Dose-dependent toxicity may exist	Angelova et al. 2017; Hajda et al. 2021)

Antitumor activity of oncolytic viruses

It is generally believed that the anti-tumor effect mediated by oncolytic viruses mainly includes two pathways: the direct oncolytic effect of oncolytic viruses and the induction of systemic anti-tumor immunity by the various complex contents released during the oncolytic process.

Direct oncolysis by viruses

Most oncolytic viruses can directly cause tumor cell death after proliferation following infection. This is a complex process, which starts with the targeting and entry of the virus, followed by its ability to replicate and/or induce latency in the cell, and the interference of the host cell's own antiviral response elements with viral proliferation. All of these steps affect the direct oncolytic activity of the virus (Alvarez-Breckenridge et al. 2009; Uchida et al. 2013). Additionally, for different types of viruses, their dosage and tropism will cause differences in oncolytic ability.

The specific selection of oncolytic viruses for tumors is called tumor tropism, which can be determined by the natural tropism of the virus itself for certain specific cells or by artificial modification. Obviously, entering the target cell is the basis and prerequisite for direct viral oncolysis. Some viruses, such as Coxsackie virus, measles virus, and herpes simplex virus (HSV), have specific receptor-mediated entry (Holmes et al. 2023; Madavaraju et al. 2020; Shi et al. 2020). The virus directly adheres to the target cell by binding to the receptor, then triggers conformational changes of some proteins and membrane fusion, and finally the viral nucleic acid breaks through the cell membrane and enter the cell. Other viruses (such as NDV, vaccinia virus, etc.) enter the cell by endocytosis (Laliberte et al. 2011; Shi et al. 2024) (Fig. 1). Of course, these virus-specific receptors are not only present on the surface of tumor cells. On the contrary, numerous experiments have shown that some normal cells also have these receptor proteins. However, oncolytic viruses cleverly use mechanisms to ensure accurate targeting of cancer cells without harming healthy cells, including the use of abnormal signal transduction pathways in cancer cells, such as those involved in viral clearance signals or local interferon (INF) release pathways, including toll-like receptor (TLR), Janus kinase signal transducer and activator of transcription (JAK-STAT), and protein kinase RNA activation (PKR) pathways (Guo et al. 2017), which may cause defects in viral defense mechanisms and thus hinder viral clearance.

Table 4 Properties of select RNA viruses

Viruses	Structure (Capsid symmetry)	Virion	Baltimore classification (Size)	Replication site	Advantage	Disadvantage	Refs.
Reovirus (RV)	Icosahedral	Naked	Group III: dsRNA (23 kb)	Cytoplasm	• Intrinsic tumor selectivity • Can enhance anti-tumor response through chemothera-py • Clearer understanding of viral gene functions	• Challenges in genetic manipulation • Potential or mild toxicity • Limited clinical trial experience	Connolly et al. 2000; Errington et al. 2008)
Coxsackievirus	Icosahedral	Naked	Group IV: ssRNA (7.1 kb)	Cytoplasm	• Strong oncolytic activity • Can induce anti-tumor immune response • Can be delivered via a variety of routes	• May cause side effects such as myocarditis • Further safety studies are needed	Andtbacka et al. 2015; Au et al. 2007)
Seneca Valley Virus (SVV)	Icosahedral	Naked	Group IV: ss (+) RNA (7.2 kb)	Cytoplasm	• Highly selective infection of neuroendocr-ine tumors • Low toxicity • Induces anti-tumor immune response	• Further clinical validation is needed • Dose-dependent toxicity may occur	Burke 2016; Luo et al. 2022)
Poliovirus (PV)	Icosahedral	Naked	Group IV: ss (+) RNA (7.5 kb)	Cytoplasm	• Can penetrate the blood–brain barrier • Does not encode oncogenes • Will not integrate into the host genome • The function of viral genes is relatively clear	• Challenges in genetic manipulation • High pathogenicity in human neurons	Lin et al. 2023; McCarthy et al. 2019)

Table 4 (continued)

Viruses	Structure (Capsid symmetry)	Virion	Baltimore classification (Size)	Replication site	Advantage	Disadvantage	Refs.
Measles virus (MV)	Icosahedral	Enveloped	Group V: ss (−) RNA (16 kb)	Cytoplasm	• Strong oncolytic activity and tumor selectivity • Can induce anti-tumor immune response • Relatively stable genome • High safety profile	• Complexity of genetic engineering • Limited efficiency of antiviral immunity • Limited clinical trial data	Engeland and Ungerechts 2021; Wu et al. 2023)
Newcastle disease virus (NDV)	Helical	Enveloped	Group V: ss (−) RNA (15 kb)	Cytoplasm	• Low toxicity • Genetic engineering potential • Strong anti-tumor immune response • Broad spectrum anti-tumor activity	• May trigger immune system side effects • Limited clinical trial data	Numpadit et al. 2023; Schirrmacher and Fournier 2009)
Vesicular stomatitis virus (VSV)	Helical	Enveloped	Group V ss (−) RNA (11 kb)	Cytoplasm	• Strong immunogen-icity • Low antiviral immune response • Fast replication • Broad spectrum of tumor infectivity	• May cause neurological side effects • Relatively unstable genome • Limited clinical trial data	Lin et al. 2023; Zhang and Nagalo 2022)

Interestingly, viruses also manipulate abnormal signals within tumors to provide more time for their own life cycle. On the one hand, too rapid replication of the virus will lead to rapid death of the host, which is obviously not conducive to the massive proliferation of progeny viruses. On the other hand, too slow replication will increase the risk of the virus being discovered and cleared by the body's immune system. Achieving a balance between proliferation rate and proliferation quantity depends on the complex interaction between these opposing forces.

Massively replicating oncolytic viruses achieve direct oncolytic effects by inducing immunogenic cell death (ICD) in infected cells, which is characterized by the exposure of calreticulin (CRT) and heat shock proteins (HSPs) in the tumor microenvironment (TME) and the release of ATP and high-mobility group protein B1 (HMGB1) (Xia 2017). The signal represented by CRT facilitates phagocytosis, while ATP acts as a "*find me*" signal (Munck et al. 2017). HMGB1 promotes the production of cytokines and cross-presented antigens. These molecules recruit and activate

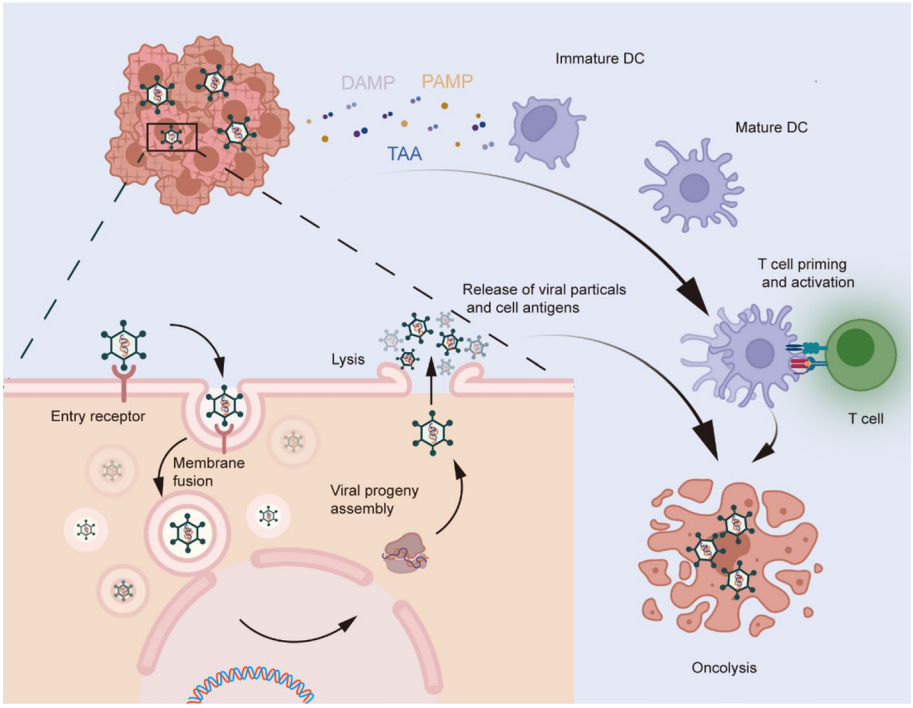

Fig. 1 Tumor tropism and direct oncolysis. Oncolytic viruses can specifically infect tumor cells through surface entry receptors, which is a prerequisite for oncolytic viruses as cancer immunotherapy. After the viral protein is assembled, OVs can directly lyse the tumor and release viral particles and tumor antigens. This process can also activate immune cells to kill cancer cells, characterized by the release of danger-associated molecular pattern signals (DAMPs), *PAMPs* pathogen-associated molecular patterns, and tumor-associated antigens (TAAs)

antigen-presenting cells (APCs), such as dendritic cells (DCs), to effectively activate naive T cells (Fig. 1).

Induced local and systemic anti-tumor immunity

The direct lysis of tumors by oncolytic viruses not only effectively controls the progression of cancer but also lays the foundation for further eradication of tumors. After the virus-infected cells die, they release a large number of tumor-associated antigens (TAAs). Upon detecting these TAAs, the immune system will respond quickly, and adaptive immunity is activated. The original immune environment of the TME is quite harsh. In addition to highly heterogeneous cancer cells, it is also filled with immunosuppressive cells, resting effector T cells, vascular endothelial cells, fibroblasts, matrix and vascular systems, which undoubtedly further enhances the immunosuppressive ability of tumors (Gujar et al. 2018). People figuratively call this type of tumor a "cold" tumor. Interestingly, the introduction of OV into the TME is expected to reshape the tumor environment by inducing acute viral infection, which can produce acute inflammation and drive immune cells to infiltrate the tumor site (Samson et al. 2018), turning it from "cold" to "hot". Of course, the composition of tumor-associated antigens is complex and is not yet fully understood. In addition, the viral pathogen-associated molecular patterns (PAMPs), cellular danger-associated molecular pattern signals (DAMPs), calreticulin, ATP and uric acid and various cytokines (e.g., type I IFN, tumor necrosis factor-α

(TNFα), IFNγ and interleukin-12 (IL-12)) released simultaneously during the process can further promote the maturation of APCs such as dendritic cells DCs, which can present these specific antigen information to $CD4^+$ and $CD8^+$ T cells for recognition. Once the recognition is successful, the activated $CD8^+$ T cells can rapidly expand into cytotoxic T lymphocytes and be directed to transfer to tumor lesions. This process is also effective for distant tumors that have not been exposed to the virus. In these places, cytotoxic effector cells initiate antigen-specific recognition and exert anti-tumor immunity (Fig. 2).

In addition, as an important component of the innate immune system, natural killer (NK) cells can be activated by various cytokines (*type I interferon (IFN-I), IFN-γ, TNF-α and IL-12*) and DAMPs produced during oncolysis. At the same time, OVs can also carry therapeutic genes to enhance the anti-tumor effect of NK cells, which lyse tumor cells by releasing granzyme B and perforin (Nicholson et al. 2019). It is foreseeable that OVs and NK cells will work together to produce stronger anti-tumor effects (Chaurasiya et al.

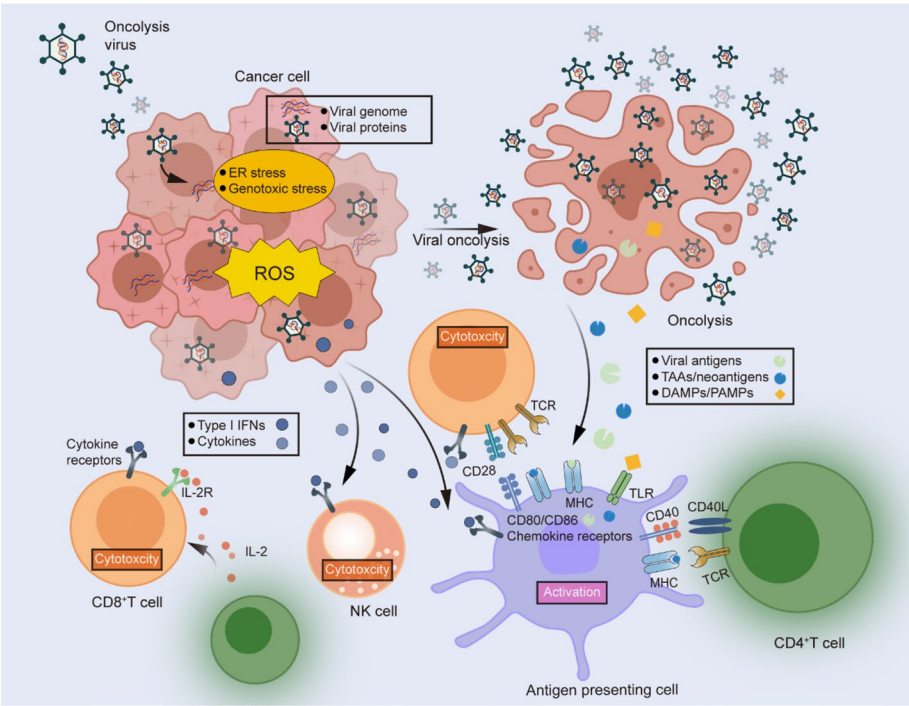

Fig. 2 Oncolytic viruses can exploit cancer immune evasion pathways. The therapeutic effectiveness of oncolytic viruses arises from both direct lysis of cancer cells and the indirect activation of antitumor immune responses. Upon infection with oncolytic viruses, cancer cells trigger an antiviral response characterized by endoplasmic reticulum (ER) and genotoxic stress. This response results in the increased production of reactive oxygen species (ROS) and antiviral cytokines. ROS and cytokines, particularly type I interferons (IFNs), are released from the infected cancer cells, thereby activating immune cells such as antigen-presenting cells, $CD8^+$ T cells, and natural killer (NK) cells. Oncolytic viruses then induce oncolysis, releasing viral progeny, pathogen-associated molecular patterns (PAMPs), danger-associated molecular patterns (DAMPs), and tumor-associated antigens (TAAs), including neoantigens. The release of viral progeny facilitates further infection by oncolytic viruses. PAMPs (comprising viral particles) and DAMPs (comprising host cell proteins) activate the immune system by engaging receptors like Toll-like receptors (TLRs). In this immunostimulatory environment, TAAs and neoantigens are released and captured by antigen-presenting cells. These processes collectively generate immune responses against virus-infected cancer cells and initiate new immune responses against TAAs/neoantigens on uninfected cancer cells. CD40L, *CD40 ligand*;

2018; Ramelyte et al. 2021). However, in addition to their anti-tumor function, NK cells also have antiviral capabilities. Premature detection and elimination of virus-infected tumor cells by NK cells may inadvertently impair the efficacy of oncolytic viruses. Therefore, a balance must be struck between immune-mediated viral clearance and anti-tumor immune induction, which is a topic worthy of further in-depth study.

Antigen spreading (epitope spreading)

Due to the high heterogeneity of solid tumors, the loss of target antigens greatly limits the effectiveness of immunotherapy. Epitope spreading, also known as "antigen spreading", refers to the phenomenon where the immune response triggered by a specific antigen can extend to other antigens. This process is continuous and dynamic and helping to address the immune escape problem caused by antigen loss during immunotherapy (Sundaresan et al. 2023; Twumasi-Boateng et al. 2018). During oncolytic virus therapy, APCs enhance autophagy by recognizing antigen signals presented by antiviral responses and further activate and mature DCs in the proinflammatory TME, facilitating antigen spreading. In addition, inflammatory cytokines and ICDs promote the extensive uptake of APCs, processing and presenting internalized proteins to T cells, thereby expanding the immune response from one antigen to multiple antigens (Twumasi-Boateng et al. 2018) (Fig. 3). In summary, the initial oncolytic therapy may target a single antigen, followed by a broader antitumor immune response against secondary epitopes that are neither part of the original treatment nor the target of the treatment.

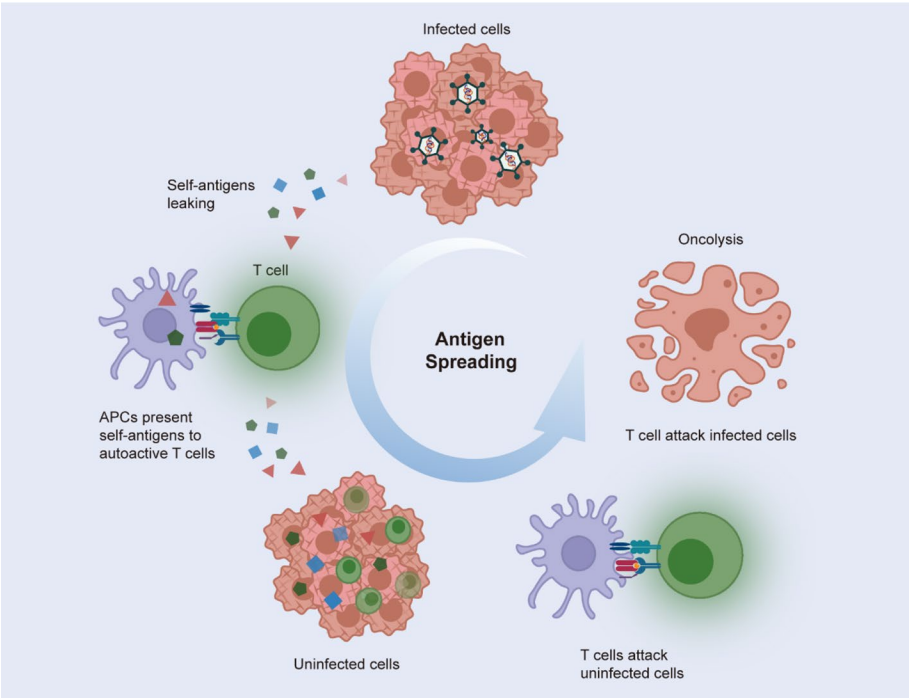

Fig. 3 Antigen spreading. Dendritic cells can specifically induce T cells to respond to antigens released by tumor cells. Self-antigens leaked from infected cells are presented to activated T cells which then attack uninfected cells and kill more tumor cells, thereby increasing the breadth of the immune response from one antigen to multiple antigens

OVs spread to cancerous tissue

A large amount of preclinical and clinical trial data show that the spread of OVs in the body greatly affects the effectiveness of treatment. Due to the heterogeneous nature of the virus, the immune system begins to respond to it and try to eliminate it from the moment it enters the human body. Even if it escapes the "*hunt*" of the immune system, whether OVs can continue to exist with the desired activity in the complex environment of the body is also a major challenge. Of course, there are far more obstacles. It is well known that the high heterogeneity inside tumors (especially solid tumors) makes them lack convective flow, which makes it difficult for OVs to penetrate deep into the tumor. To date, the most extensive and best therapeutic effect of OVs is still through intratumoral administration. However, the many disadvantages of intratumoral administration have forced researchers to actively seek new ways to solve this problem. Fortunately, with the help of new methods such as viral genome modification (Ylosmaki and Cerullo 2020), the use of nanoparticles (NPs), immunomodulators, and virus particle complexes (Yokoda et al. 2017), researchers have been able to improve the specificity and efficiency of OVs delivery to targets.

Nanoparticles

Like the problems faced by most diseases, a key point in cancer treatment is how to deliver therapeutic agents to the target site (Malik et al. 2022; Wilczewska et al. 2012). Naturally, designing a controllable drug delivery system to reduce the adverse effects of drugs on other organs and improve the safety and efficacy of treatment has become the goal pursued by researchers (Farjadian et al. 2022). In the past few decades, drug systems in the form of NPs have made significant progress in the treatment of various solid tumors (Pierce et al. 2021). NPs usually refer to substances with a size between 1 and 100 nm (Ferreira-Faria et al. 2022; Zare et al. 2022), which have special physical and chemical properties, including thermal, optical, and electromagnetic properties, enabling nanoparticles to produce surface effects, quantum ruler effects, and macroscopic quantum tunneling effects (Caratelli et al. 2022; Lan et al. 2020; Li et al. 2023; Rao and Shi 2022). Therefore, nanoparticles have become an ideal material for solving many difficult problems in the biomedical field, and have potential application value in diagnosis, chemical sensing, cell imaging, drug delivery, treatment, and tissue engineering (Mejia-Mendez et al. 2022). In 1995, the FDA approved the first nanoparticle for drug delivery, Doxil. This method of encapsulating the chemotherapy drug doxorubicin (DOX) in lipid nanoparticles optimized the drug's circulation time and toxicity in the body (Chanan-Khan et al. 2003). In the following decades, NP-based drug delivery systems have developed rapidly in the treatment of various solid tumors (Pierce et al. 2021). Researchers began to try to combine proteins, peptides, aptamers, nucleic acids and other biological molecules with NPs to improve efficacy (Chen and Liu 2016; Panigaj et al. 2019; Xin et al. 2017; Yousefi et al. 2022). Based on many promising preclinical and clinical data, in 2012, the FDA approved the anticancer drug Abraxane for the treatment of NSCLC patients (Sofias et al. 2017).

Nowadays, more and more nanomaterials are being developed and applied in cancer treatment (Bai et al. 2020; Guo et al. 2021; Han et al. 2022; Hou et al. 2018; Huang et al.

2020; Irvine and Dane 2020; Li and Burgess 2020; Liu et al. 2020a, 2020b; Xu and Liang 2020; Yamada et al. 2020; Zhang et al. 2021). In this process, many nanoparticles (such as metal and metal oxide nanoparticles) have been found to have unique anti-tumor properties that are different from other materials. They can be divided into two categories: organic (polymers, dendrimers, polymer micelles, nanospheres, nanohydrogels, liposomes, and lipid nanoparticles) (Yu et al. 2022; Zhu et al. 2022) and inorganic (non-metallic nanomaterials, metal nanomaterials, etc.) (Rethi et al. 2022). Next, we will discuss the mechanism of action of some common NPs used for tumor immunotherapy and their advantages and disadvantages.

Mechanism of action of nanoparticles in tumor therapy

In the development of cancer treatment, many drugs with significant efficacy have been developed and designed, but they often have some defects, such as excessive immunogenicity and weak stability, which greatly limit their effectiveness. Safely and stably delivering drugs to the ideal active site is a major challenge faced by researchers. Fortunately, NPs are expected to overcome this obstacle due to their unique properties.

Nanoparticle delivery strategies

Strategies for delivering nanoparticles to tumor sites include active and passive targeting (Petros and DeSimone 2010). In the process of passive targeting, due to the high EPR effect of nanoparticle carriers, the permeability of blood vessels in the tumor increases, causing the therapeutic drug to accumulate at the tumor site (Zein et al. 2020)(Fig. 4a). Active targeting relies on the biological interaction between the ligands on the surface of NPs and the cell targets, which not only minimizes the possible side effects of the

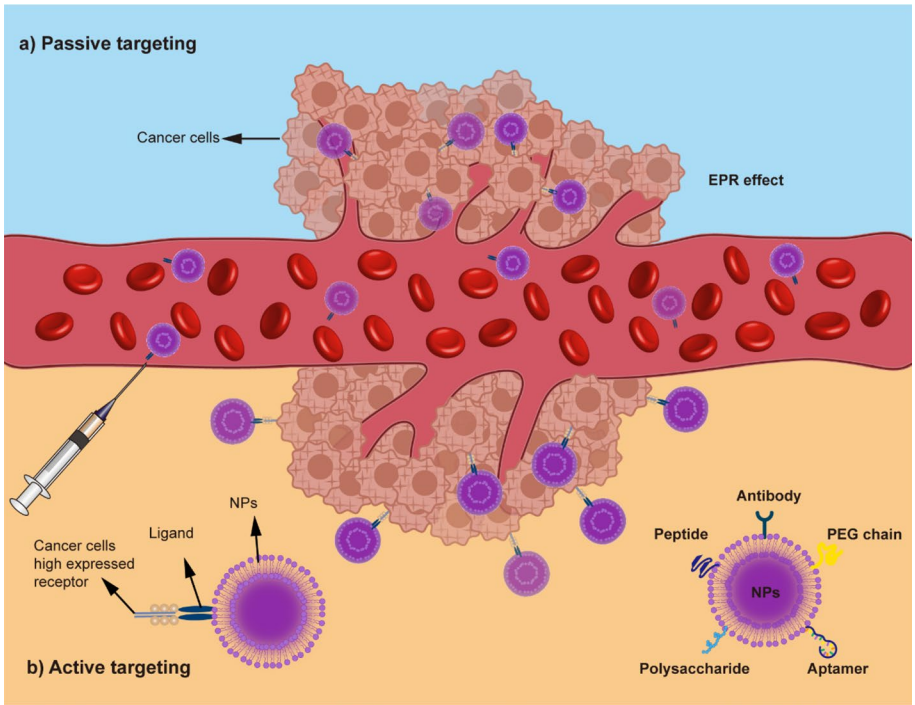

Fig. 4 Active and passive adsorption of nanoparticles

therapeutic agent, but also maximizes the concentration of the therapeutic drug in the lesion to enhance efficacy (Doroudian et al. 2019; Muhamad et al. 2018). Numerous biological ligands have been shown to promote the active targeting of NPs (Byrne et al. 2008), including proteins, polysaccharides, aptamers, peptides, and small molecules (Yoo et al. 2019) (Fig. 4b). Typically, active and passive targeting work simultaneously and do not conflict with each other (Zein et al. 2020).

Shielding and modification during drug delivery

As OVs research continues to deepen, the challenges of OVs therapy have gradually become clear. For example, due to the host's innate/adaptive immune response and the liver tropism of the virus, the non-targeted and passive accumulation of tumor tissues, the number of OVs reaching the tumor is insufficient, thereby reducing efficacy (Goldufsky et al. 2013). In view of this, researchers are no longer limited to improving the therapeutic effect of oncolytic viruses themselves. How to make therapeutic drugs have a "stealth" effect in the body has also become an important topic in OVs therapy. There are many types of existing therapeutic drug shielding strategies. Among them, nanoparticles have attracted widespread attention from researchers due to their unique advantages. As an important component, the research on polymers has made great progress. Polyethylene glycol (PEG) is one of the most commonly used polymer ligands for shielding nanoparticles. In high salt and extreme pH environments, PEG exhibits excellent hydrophilicity and biocompatibility, and these properties can maintain relatively long-term stability (Guerrini et al. 2018). Some researchers have used PEG to maintain the stability of oncolytic adenoviruses, prolong circulation time, and reduce liver toxicity (Kim et al. 2012). Also widely used is polyethyleneimine (PEI), a high molecular weight linear branched cationic polymer. Due to its charge characteristics, it is very suitable for binding to nucleic acids. Even in the absence of negatively charged nucleic acid counterparts, PEI will form a particle structure with a certain size and surface potential. In fact, PEI has been widely used for nucleic acid delivery in vivo and in vitro (Kubczak et al. 2022; Patnaik and Gupta 2013). Also, highly affine with nucleic acids are cationic liposomes (DOTAP/DOPE). Studies have applied them to deliver OVs genomes to tumor cells and successfully produced active progeny oncolytic viruses in situ. This method increases tumor penetration and preferential targeting of this therapy (Kwon et al. 2011). There are also some nanomaterials that need to be further developed, such as polyamidoamine dendrimers (PAMAM). As a dendritic polymer with monodispersity and controlled topology, it has the characteristics of small side effects, high biodegradability, and minimal nonspecific binding to blood proteins, which makes it quickly become a suitable carrier for drug application and gene transfer (Wong et al. 2023).

Diffusion of nanoparticles

After nanoparticles deliver the therapeutic drug to the desired site, accurately controlling the release of the drug is also an issue that needs attention. Obviously, too fast a drug release will cause the local concentration to be too high due to drug accumulation, thus producing side effects. However, too slow a drug release will lead to the nanoparticles being cleared by the body and provoke an unexpected immune response (Sanita et al. 2020). Currently, the means of controlling the diffusion of nanoparticles are generally

divided into two categories, namely, external stimulation through regulating temperature, light, and magnetism, and internal stimulation through pH changes and hypoxic environments (Fig. 5).

In external stimulation, temperature control plays a crucial role. When active drugs travel to target cells, they induce pore dilation by heating the lesion site. This is expected to facilitate further drug release while increasing blood flow (Petryk et al. 2013). Magnetic, electric, and ultrasonic waves are also effective means of elevating local temperature (Moradi et al. 2020). When magnetic nanoparticles are in an alternating magnetic field, the nanoparticles will rotate under the influence of the magnetic field to generate heat. Due to the lack of physical interaction with the patient, magnetic field stimulators are also considered one of the safest stimulators (Moradi et al. 2020). Tseng et al. utilized recombinant adeno-associated viruses coated with iron oxide nanoparticles to achieve remote delivery in a magnetic field (Tseng et al. 2016). In addition, since the output power of the irradiated light can be precisely controlled and the depth of light penetration can be ensured, the therapy has the advantages of minimal invasiveness and low toxicity, which makes light-responsive nanocarriers combined with photosensitizers likely to play an significant role in different malignant tumors (Raza et al. 2019). In the case of the current combination of photodynamic therapy (PDT) and viral therapy, appropriate photosensitizers are activated at specific wavelengths, causing photoresponsive nanoparticles to accumulate in the tumor, thereby killing cancer cells. At the same time, surface modification of nanoparticles with specific ligands (such as monoclonal antibodies, peptides, or PEG) can further improve the selectivity and solubility of photosensitizers, thereby significantly enhancing the efficiency of PDT (Lin et al. 2021).

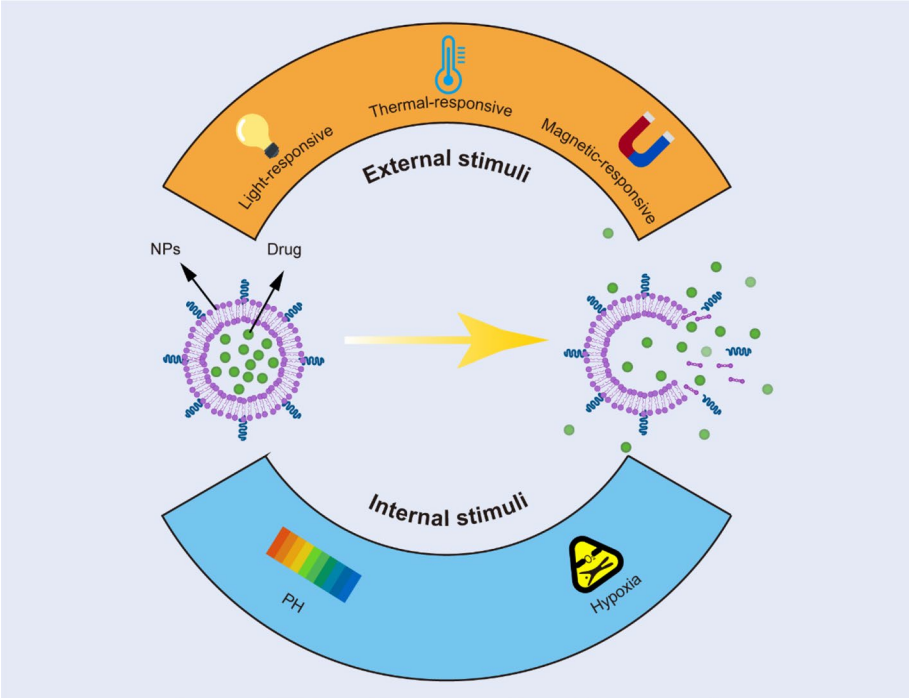

Fig. 5 External and internal stimuli-responsive drug delivery system. Nanoparticles are stimulated by various stimuli, leading to drug release in target tumor cells

For some solid tumors, an acidic environment often occurs simultaneously with hypoxia. This is because tumor acidosis is caused by the accumulation of lactic acid following extensive cell death within the tumor, and local hypoxia results from defects in the intratumoral vascular network and the interruption of oxygen supply to the tumor tissue. Based on this, pH-sensitive nanoparticles designed for acidic environments and the synthesis of nitroreductase (NI) and azoreductase substrates that depend on hypoxia at the nanoparticle level will achieve instantaneous and large-scale drug release at the tumor site (Moradi et al. 2020). Guo et al. reported a combined treatment strategy of pH-responsive polymer nanoparticle complexes containing chemical drugs, which showed promising clinical results, highlighting the great potential of synergistic therapy in the field of tumor treatment (Guo et al. 2020). Additionally, to enhance the cancer-specific killing ability of oncolytic viruses and leverage the characteristics of the tumor microenvironment, Moon et al. designed a pH-sensitive bioreductive polymer (PPCBA)-coated oncolytic adenovirus (Ads). This nanocomplex, which includes a bioreducible disulfide bond (methoxy-pegylated cystaminebisacrylamide), can release the viral particle payload in an acidic environment (Moon et al. 2015).

Engineered nanoparticle formulations for vGenome delivery

The design of nanoparticles for vGenome delivery requires careful consideration of material properties, surface modifications, and functional compatibility. Below, we systematically summarize key nanoparticle types, their modifications, core advantages and major challenges (Table 5).

Lipid-based nanoparticles (LNPs), exemplified by their success in mRNA vaccine delivery (Schoenmaker et al. 2021), offer high biocompatibility and scalability but face challenges in endosomal escape efficiency. Polymeric nanoparticles, such as PEI and PLGA, leverage cationic charges for enhanced nucleic acid binding, yet cytotoxicity remains a concern (Kubczak et al. 2022; Guo et al. 2020). Emerging exosome vectors enhance tumor homing via engineered membrane proteins (e.g., CD47)(Yang et al. 2020), but payload limitations remain unresolved. Inorganic nanoparticles (e.g., AuNPs) enable photothermal-controlled release but require optimization for biodegradability (Sendra et al. 2020).

Table 5 Engineered nanoparticles for vGenome delivery

Nanoparticle Type	Modifications	Advantages	Challenges	References
Lipid-based (LNPs)	PEGylation, ligand conjugation	High biocompatibility, scalable production	Risk of hepatic sequestration, variable endosomal escape efficiency	Kwon et al. 2011; Fu and Zhang 2001; Aoyama et al. 2017)
Polymeric (PEI, PLGA)	Cationic polymers, pH-sensitive	High nucleic acid loading, customizable functionalization	Potential cytotoxicity, unstable metabolic rates	Kubczak et al. 2022; Guo et al. 2020)
Exosomes	Engineered membrane proteins	Natural targeting, low immunogenicity	Limited payload capacity, purification challenges	Isaac et al. 2021; Pathania et al. 2021)
Inorganic (AuNPs)	Surface functionalization	Photothermal/imaging synergy, precise release control	Complex synthesis, poor biodegradability	Sendra et al. 2020)

Combination therapy

More and more smart nano drug delivery systems have been developed because they have improved the limitations of drugs in many aspects and indirectly enhanced efficacy by improving drug transmission and specific release (Doroudian and N.A. O', L.R. Mac, A. Prina-Mello, Y. Volkov, S.C. Donnelly 2021). As a rapidly emerging treatment method in recent years, oncolytic viruses have naturally been combined with various nanoparticles, including metal nanoparticles, various polymers, and biomineral shells. These combinations have also shown positive therapeutic effects, such as enhancing the proliferation and killing of viruses, avoiding the influence of blood factors, neutralizing antibodies, and liver in the body, achieving stronger targeting, prolonging the circulation time of oncolytic viruses in the blood, and reducing toxicity (Sendra et al. 2020; Choi et al. 2015; Gonzalez-Pastor et al. 2021; Kasala et al. 2017; Tang et al. 2018). Despite its many advantages, this combination still faces many problems in the process of transformation. Because live viruses are more complex than traditional drugs and have a series of safety issues, they have high requirements for personnel technology and environmental hardware in terms of quality control and purification, and concentration (Gujar et al. 2024; Ungerechts et al. 2016). Even if qualified viruses are produced, a series of tedious operations are still required to modify them. The various costs of this process will be huge, and the long preparation process will greatly increase the difficulty of quality control on the one hand, and on the other hand, it will also be a great challenge to the stability of the final product. Secondly, there are many types of oncolytic viruses, and their sizes are also varying. Therefore, it is difficult to find a single modification method that can modify different oncolytic viruses simultaneously. This personalized modification will undoubtedly greatly increase the cost of this type of drug.

Fortunately, the use of nanoparticles to modify oncolytic virus genes is expected to become a novel approach to solve the above-mentioned obstacles. This strategy not only retains the respective advantages of oncolytic viruses and nanoparticle delivery systems, but also addresses the pain points of existing virus production processes. For example, traditional live virus production requires extensive cell culture, virus infection (Grein et al. 2018), purification, freeze-drying, and other steps (Ungerechts et al. 2016). These steps are not only time-consuming and labor-intensive but may also affect the stability and activity of live viruses. The simple preparation of oncolytic virus genomes only requires the use of basic molecular biology techniques, such as PCR, electrophoresis, transfection. Since the final product is only nucleic acid, it can be modified using the same treatment method to a large extent. This process not only saves time and cost but also ensures the integrity and functionality of the oncolytic virus genome. During the delivering of the oncolytic virus genome to the target lesion, once the nanoparticle/viral genome complex is internalized and released into the cancer cell, the viral nucleic acid will begin to replicate and express, thereby producing a large number of infectious virus particles. These particles then begin to exert the anti-tumor advantages of the oncolytic virus itself and activate the body's immune system (Fig. 6). In recent years, significant progress has been made in this field, which we briefly introduce and analyze here.

At present, some articles have reported the use of nanoparticles to encapsulate different types of oncolytic virus genomes, such as RNA or DNA. To address the issue of neutralizing antibodies in the body during systemic administration of oncolytic virus

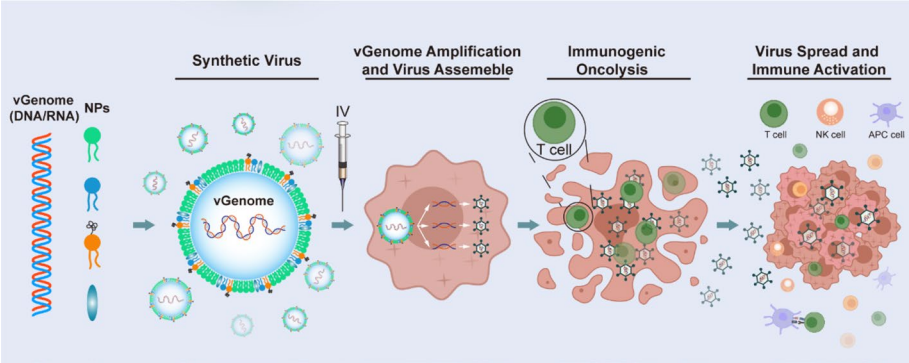

Fig. 6 Schematic illustration of the mechanism of action of nanoparticle-modified virus genome. Oncolytic nanoparticles are composed of vGenomes obtained in vitro using molecular biology techniques and nanoparticles with various functions. In tumor cells, the oncolytic viral genome modified by nanoparticles reproduces all stages of the viral life cycle, thereby replicating and generating a burst of infectious virions that spread locally, infect and kill tumor cells, thereby recruiting immune cells to the TME

therapy, Katsuyuki et al. described that as an oncolytic adenovirus drug suitable for systemic delivery, telomerase-specific oncolytic adenovirus (Lipo-pTS) genomic DNA expressing GFP can be encapsulated in lipid nanoparticles to counteract Ad-specific neutralizing antibodies (AdNAB) and thus achieve stealth against the body's immune system. In vivo and in vitro studies have consistently shown that Lipo-pTS with a diameter of 40–50 nm has good anti-tumor efficacy against the human colon cancer cell line HCT116, and this killing effect is independent of the tumor-specific receptors of the adenovirus. Additionally, after intravenous injection of Lipo-pTS into immune-competent mice, it was found that the production of AdNAB was significantly reduced compared with the control group, and even in the presence of AdNAB, it still had relatively high cytotoxicity (Aoyama et al. 2017). Fu et al. prepared three different forms of herpes simplex virus (HSV) vectors (purified viral DNA, HSV capsid, and intact viral particles) to study the feasibility of delivering HSV vectors through lipid nanoparticle formulations and tested the transfection efficiency of different forms of HSV in vitro and in vivo. The results showed that all three forms of HSV were able to effectively transfect cells and produce infectious viruses, and compared with HSV administered alone, the HSV DNA/liposome complex was more effective in evading the host's anti-HSV immune response and improving transfection efficiency. Therefore, it can be concluded that HSV can be systemically delivered through lipid nanoparticle formulations to achieve safe and repeated application of gene transduction or oncolytic therapy (Fu and Zhang 2001). Oh-Joon Kwon et al. reported a method of killing tumors using oncolytic viral genomes modified with lipid nanoparticles. They encapsulated oncolytic adenoviral genomic DNA (pmT-d19/stTR) into lipid nanoparticles and delivered them systemically through the lipid envelope as an alternative to cancer virus therapy in an orthotopic lung cancer model. Studies have shown that compared with live viruses, lipid nanoparticles significantly reduced the innate immune response and Ad-specific neutralizing antibodies in mice treated with lipid nanoparticles encapsulating vGenomes, and the virus preferentially replicated and expressed in tumor tissues, thereby triggering a highly effective antitumor response in vivo (Kwon et al. 2011). The same encapsulation idea is also applicable

to RNA viruses. The team of Edward M. Kennedy et al. developed a synthetic RNA virus immunotherapy for cancer treatment by intravenous injection. The researchers designed a synthetic RNA virus template and prepared large-scale synthetic RNA viruses through reverse transcription technology. This synthetic RNA virus can activate the immune system and induce anti-tumor immune responses. Experimental results showed that the therapy had significant anti-tumor effects in mouse and non-human primate models (Kennedy et al. 2022).

In addition to the more common lipid nanoparticles, gold nanoparticles have also been used to modify oncolytic virus genomes. Sendra et al. used AuNPs and PEI to optimize the function of oncolytic adenovirus genomes. The complex formed protected the viral genome DNA from nucleases and produced efficient RNA expression. The revived progeny viruses also successfully caused target cell lesions. This study provides an alternative for repeated administration of oncolytic adenoviruses (Sendra et al. 2020). These articles show that different types of oncolytic virus genomes can achieve viral genome expression and the formation of live viruses both in vivo and in vitro, producing strong anti-tumor activity while weakening the effectiveness of neutralizing antibodies.

Key safety and off-target challenges

Systemic delivery of NP-vGenome therapies requires addressing hepatic sequestration, immunogenicity, and off-target release. Lipid tail-engineered 15% DSPC nanoparticles reduce hepatic mRNA leakage by 90% (Suzuki et al. 2025), while DNA "invisibility cloak" technology enhances tumor-to-liver distribution ratios to 5:1 (Zhao et al. 2024). Although PEGylation reduces hepatic uptake by 40%, anti-PEG antibodies limit repeated dosing. Novel gelatinase-responsive nanoparticles (MMP2/9-cleavable peptides) enable tumor-specific release of CAR-T switches, mitigating off-target effects and cytokine storm risks (Wang et al. 2023). Additionally, modular peptide nanoparticles with near-infrared (NIR)-controlled IDO1 inhibitor release suppress regulatory T-cell infiltration (Wu et al. 2025). Optimizing combination therapies necessitates co-evaluating safety, integrating organ-selective delivery, immunotoxicity regulation, and stimuli-responsive technologies to systematically balance efficacy and risks for clinical translation.

Clinical translation status and challenges

Despite promising preclinical outcomes, the clinical translation of NP-vGenome therapies faces scalability, safety, and regulatory hurdles. Currently, the only clinically validated gene delivery platforms remain LNPs for COVID-19 mRNA vaccines (BioNTech/Pfizer, Moderna) (Fan et al. 2024), while FDA-approved nanodrugs (e.g., Doxil, Onivyde) primarily deliver chemotherapeutics. Gene-editing nanomedicines (e.g., CRISPR-Cas9 LNPs) are in Phase I/II trials (Hii et al. 2024; Gong et al. 2024a). Technical barriers include suboptimal tumor targeting (only 0.7% nanoparticles reach solid tumors (Gong et al. 2024b)), necessitating exosome engineering (e.g., CD47 modification) or selective organ targeting (SORT) strategies (Yang et al. 2020; Cheng et al. 2020). Immunogenicity risks, such as anti-PEG antibodies and lipid-induced inflammatory responses, further complicate clinical deployment (Yang et al. 2020).

Cost-effectiveness strategies involve modular continuous-flow manufacturing to reduce production costs and DNA "invisibility cloak" technology to enhance tumor

uptake via programmable degradation (Zhao et al. 2024). Non-viral carriers (e.g., PLGA nanoparticles) offer cost advantages in large-scale production due to material availability and process controllability (Zu and Gao 2021; Operti et al. 2022). Multiplexed delivery approaches (e.g., co-delivering siRNA for Rab27a knockdown) reduce treatment costs by 60% (Gong et al. 2023). Bridging the lab-to-clinic gap demands overcoming both technical and economic barriers through innovations in targeting, manufacturing, and delivery systems.

Conclusions

The integration of nanotechnology with oncolytic virotherapy is redefining cancer treatment paradigms. By encapsulating viral genomes within functionalized nanoparticles, researchers achieve targeted delivery, immune evasion control, and intratumoral replication regulation. This dual-modality approach synergizes the direct oncolytic activity of viruses with nanomedicine precision, demonstrating superior therapeutic indices in preclinical models of lung cancer and melanoma.

Leveraging LNP platforms validated by COVID-19 mRNA vaccines (Xiao et al. 2022), NP-vGenome therapies are accelerating toward clinical translation. For instance, the Shanghai Institute of Biological Products' zoster mRNA vaccine (NMPA Approval: CXSL2500001) employs a novel LNP system achieving 90% encapsulation efficiency and robust immune activation in animal models, exemplifying platform adaptability for oncolytic viruses.

Critical challenges include enhancing tumor specificity through CRISPR-edited deletion of viral immune evasion genes combined with hypoxia-responsive promoters, and achieving organ-selective redirection via amidine lipids (AID-lipids) using rapid "one-pot" synthesis (Han et al. 2024). Future priorities should focus on:

1. *Technical Innovation* Developing CRISPR-edited vGenomes with logic-gated promoters activated by tumor-specific miRNAs.
2. *Regulatory Alignment* Establishing standardized guidelines for assessing viral genome stability, off-target integration, and anti-PEG immunity.
3. *Clinical Adaptation* Repurposing mRNA vaccine LNP platforms for rapid GMP-compliant production.

These multidisciplinary strategies position NP-vGenome therapeutics as pivotal players in next-generation immuno-oncology, bridging fundamental discoveries with practical clinical implementation.

Abbreviations

Ads	Adenoviruses
AdNAB	Ad-specific neutralizing antibodies
APCs	Antigen-presenting cells
CAR-T	Chimeric antigen receptor T-cell immunotherapy
CD40L	CD40 ligand
CRT	Characterized by the exposure of calreticulin
DCs	Dendritic cells
DOX	Doxorubicin
EPR	Enhanced permeability and retention
ER	Endoplasmic reticulum
H-1 PV	H-1 parvovirus
HSPs	Heat shock proteins

HSV	Herpes simplex virus
HSV-1	Herpes simplex virus type I
HMGB1	High-mobility group protein B1
ICD	Immunogenic cell death
INF	Interferon
IL-12	Interleukin-12
JAK-STAT	Janus kinase signal transducer and activator of transcription
MV	Measles virus
NPs	Nanoparticles
NK	Natural killer
NDV	Newcastle disease virus
NI	Nitroreductase
PAMPs	Pathogen-associated molecular patterns
PDT	Photodynamic therapy
PPCBA	PH-sensitive bioreductive polymer
PV	Poliovirus
PAMAM	Polyamidoamine dendrimers
PEG	Polyethylene glycol

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