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Viral Missiles: Research Advances in Achieving Efficient Targeted Delivery of Cancer Therapeutics Using Viral Vectors

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Abstract:

Cancer has become one of the main diseases threatening human health. Although traditional methods such as surgery, radiotherapy and chemotherapy have improved the prognosis of patients to some extent, there are still various problems, such as strong side effects, high recurrence rate and insufficient targeting. With the development of the concepts of precision medicine and targeted therapy, viral vectors have become an important tool to construct new targeted drug delivery systems, because they have the ability of cell infection and gene transfer.This study conducted a systematic review of relevant literature, the application strategy and research progress of virus vector in achieving efficient targeted drug delivery in tumors are comprehensively expounded, and its advantages and mechanisms in drug loading, gene regulation and immune activation are emphatically introduced. The results show that after structural modification, promoter improvement and receptor-mediated recognition, viral vectors can significantly improve drug delivery efficiency and targeting characteristics, and achieve this goal on the basis of ensuring safety.This conclusion provides important theoretical basis and technical direction for precision treatment of tumors. During this period, it also faces the problem of controlling immune response and improving drug delivery efficiency in solid tumors, so it is necessary to explore more engineering improvement methods and transformation ways.

Keywords: Virus vector; Targeted drug delivery; Cancer treatment; Gene therapy; Precision medicine.

1. Introduction

As a major public health problem, the incidence and mortality of cancer have been on the rise all over the world, and it has become one of the most important diseases that endanger human life and health. Tradi-

tional tumor treatment methods, including surgical resection, radiotherapy and chemotherapy, have improved the survival of patients to a certain extent, but these methods still have great limitations, such as postoperative recurrence, drug resistance to radiotherapy and chemotherapy, strong side effects and nonspecific damage to normal tissues, which seriously restrict the progress and improvement of cancer treatment effect. The new progress in molecular biology and immunology in recent years makes it possible to target and precisely attack cancer cells. Compared with the traditional way, viral vectors can serve as the core delivery tool of precision medicine, achieving precise delivery of therapeutic molecules to tumor sites through molecular marker mediated targeted modification, which greatly reduces the harm to human health.

In this context, viral vectors-biological tools with natural cell infection and gene transfer ability-have attracted people's attention. Virus vectors can effectively introduce foreign genes, siRNA, mRNA or immunogenic antigens into specific cells by imitating the way viruses enter host cells, thus realizing drug release and expression [1]. Compared with traditional non-viral delivery systems, viral vectors have the advantages of higher cell transduction rate, stronger immunogenicity and easier engineering transformation [2]. Significant progress has been made in tumor vaccine, gene therapy, immune regulation and oncolytic virus infection, which shows that these methods play an important role in achieving efficient, specific and controllable drug delivery to cure cancer [2].

Therefore, the research on the mechanism and application development of virus vector in efficient targeted drug delivery will not only help the clinical application of precision medicine, but also provide a theoretical basis for developing a safe and controllable new generation of tumor treatment strategies.

This study focuses on the application development and basic principles of viral vectors in cancer drug delivery. As a drug delivery platform, viral vectors operate through key steps, including efficient drug or gene loading, targeted delivery, cell influx and gene expression regulation. Different virus vectors, such as adenovirus, adeno-associated virus, lentivirus and vaccinia virus, have obvious differences in drug carrying capacity, cell affinity, immune response capacity and long-term expression level, which makes it possible to customize the design and transformation of these virus vectors for treatment needs.

Therapeutic load can be tumor suppressor genes, RNA interfering molecules, immunomodulators or antigen coding sequences, while targeted delivery strategies often involve capsid protein modification, receptor-mediated recognition, promoter improvement and exogenous ligand binding, etc. These means are helpful for accurate drug delivery and controlled expression in the tumor microenvironment (TME).

The main research method is literature synthesis and inductive analysis, which systematically summarizes the structural characteristics of virus vectors, engineering transformation approaches, drug loading methods and application results in cancer treatment, and also explores the problems and prospects for target delivery rate, safety and industrial scale production.

In this study, we want to systematically review and analyze the latest development of viral vectors as drug delivery tools for tumor treatment, and find out its possible advantages and trends in gene transfer, immune regulation and precise targeting. By comparing the structural characteristics and delivery mechanisms of different types of viral vectors, this study also explains the key scientific problems of how to achieve efficient transduction effect, low immune response and control the expression level. The significance of this work roughly includes two aspects:

Its theoretical significance lies in gaining a deep understanding of the engineering design of viral vectors, cell invasion, and the response mechanism of tumor microenvironment, so as to enrich the theoretical knowledge in the field of tumor biological therapy and gene transfer.

Practical significance: it provides a scientific basis for improving the design and safe application of virus vectors in clinical anti-tumor drug delivery system, and promotes their transformation and application in precise treatment and personalized drugs.

2. Viral vectors as drug delivery tools

Virus vector is an efficient drug delivery tool. Because of its evolved and complicated infection mechanism and adaptability to the host, demonstrating irreplaceable advantages in the fields of tumor therapy and gene delivery. After long-term evolution, producing strong entry ability and extensive host tropism, making it possible to maintain a constant high level of transduction rate when viruses infect different types of cells, thus effectively achieving delivery in vivo or in vitro, breaking through the limitations of traditional non-viral vectors in cell uptake rate and expression stability.

Virus vector can not only be used as an effective tool for gene transduction, but also induce multilevel immune response in vivo. Their delivery system can activate humoral, cellular and innate immune pathways at the same time, which greatly enhances the body's ability to recognize and respond to foreign antigens, and is an ideal carrier platform to improve the immunogenicity of tumor vaccines. As shown in Figure 1, personalized cancer vaccines

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based on virus vectors can effectively activate DCs, promote antigen presentation and stimulate CD8+and CD4+T cell responses, thus identifying and killing tumor cells in the tumor microenvironment. Viral vectors (adenovirus, vaccinia virus, etc.) have been widely used in oncolytic virus and cancer vaccine research because of their strong immune activation. AAV and LV play an important role in the field of gene therapy because of their high safety and long-term expression.

From the engineering point of view, the virus vector has the special ability of foreign gene insertion and expression regulation. Strategies such as capsid protein remodeling, receptor binding site modification or promoter improvement can achieve targeted delivery and controllable performance, which can obviously improve the specificity and safety of treatment. Nowadays, with the development of virus engineering and synthetic biotechnology, people can accurately design these molecules to regulate tissue selectivity, immune evasion and transduction efficiency.

At the production level, the virus vector preparation system has become mature. The construction of large-scale platforms such as fixed-bed bioreactor has enabled industrial scalability and the possibility of clinical transformation to be realized. The improvements in improving the high purity, stable titer and repeatable production process have laid the foundation for the application of virus vectors in clinical drug delivery.

In a word, the virus vector has the characteristics of high transduction rate, strong immunogenicity, easy engineering and industrialization. They not only provide strong technical support for the research and development of tumor vaccines, but also open a new path for precise drug delivery and personalized treatment.

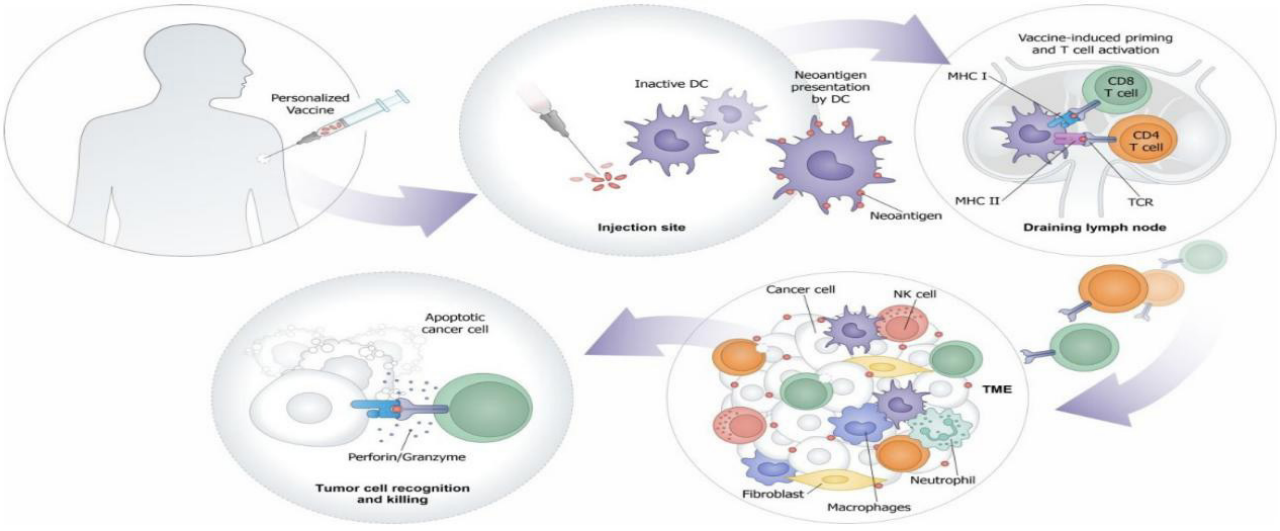

Fig. 1 Schematic Diagram of the Mechanism of Action for Personalized Cancer Vaccines Using Viral Vectors [3]

3. Viral vector types and their distinctions

Viral vectors can be divided into several main types according to the sources of viruses used. Adenovirus (Ad) is an envelope-free, double-stranded DNA virus. The third generation of high-capacity vectors almost eliminated all virus genes, which greatly reduced the immunogenicity. AAV is an envelope-free single-stranded DNA virus. Although its gene payload capacity is limited, it is very safe and non-pathogenic. LV is an enveloped RNA virus, which can infect splinter cell and non-splinter cell, and integrate into the host genome to achieve long-term expression. Non-integrated vectors are usually used to reduce the risk of insertion mutation. Poxviruses, such as modified vaccinia virus (MVA), are double-stranded DNA viruses with large gene capacity and strong immunogenicity, and are often used to construct recombinant vaccines. Vesicular stomatitis virus (VSV), parainfluenza virus (PIV), lymphocytic meningitis virus (LCMV) and measles virus (MV) are also often used in the study of tumor immunology. Recombinant viruses are often designed by reverse genetic system, and foreign genes are integrated by homologous recombination or restriction enzyme insertion, and these virus particles are generated in specific types of packaging cell lines, and purified and standardized by titer such as PFU/mL or vg/mL. Each vector type has obvious advantages in transduction efficiency, immunogenicity, safety and application occasions, thus providing a variety of different platform foundations for tumor vaccines and

gene therapy.

4. Drug design strategies for viral vector delivery

4.1 The rationale for choosing to load the drug inside the virus

The virus surface has specific proteins, such as the fibrin of adenovirus and the G protein of VSV, which can accurately recognize and bind receptors on the host cell surface. Through mechanisms such as receptor-mediated endocytosis, the virus can bypass the cell membrane barrier and deliver the entire particle (including internal cargo) to the cell. This is particularly important for macromolecular drugs that are difficult to penetrate cell membranes, such as nucleic acids and proteins [4].

After the virus enters the cell, it can utilize the cell's transport system, such as endosomes and the microtubule network, to precisely transport itself to the organelles where it needs to, such as near the nucleus. It can also rupture the endosome by changing the endosomal pH and release the internal cargo into the cytoplasm, avoiding degradation by lysosomes. This process is called "endosomal escape", which is a design difficulty for many drug delivery systems, while viruses are naturally equipped with this ability.

Different viruses have their natural tissue tropism. For example, AAV2 has a natural affinity for the liver and neurons, and AAV6 has a high affinity for muscle tissue. By selecting or modifying the viral capsid, targeted delivery of drugs to specific organs, tissues, or even cell types can be achieved, significantly reducing side effects on normal tissues [5].

4.2 Medications loadable within the viral vector

Nucleic acid drugs are a relatively classic application type. DNA can be used for gene therapy, such as replacing defective genes or DNA vaccines expressing antigenic proteins in the body.

MRNA can be used to express therapeutic proteins, antigens, or gene editing tools such as Clustered Regularly Interspaced Short Palindromic Repeats-CRISPR-associated protein 9 (CRISPR-Cas9), and it is safer than DNA because it does not integrate into the genome; siRNA/shRNA can be used for gene silencing to knock down harmful or over expressed genes; Components of the CRISPR-Cas system can be used for gene editing [6]

Protein or polypeptide drugs can also be directly encapsulated in the viral capsid. The virus can protect these fragile biological macromolecules from degradation in the blood circulation and directly deliver them into cells to exert their effects.

The field of traditional chemical drugs in combination with viruses is an emerging frontier direction. Small-molecule chemotherapeutic drugs such as doxorubicin can be loaded into the cavity of virus particles. For example, drug molecules can enter the cavity through the capsid pores by gradient driven passive diffusion, can be electrostatic adsorption combined with the negatively charged viral capsid surface by positively charged doxorubicin, or can be linked to the specific amino acid residues of viral capsid protein by covalent linking technology. A typical adenovirus particle has an icosahedral structure with a diameter of about 90 nm and a large internal volume. Theoretically, it can carry up to 1000 doxorubicin molecules, thus significantly improving the local drug concentration at the tumor site. However, high drug loading, especially through chemical connection or long-term incubation, may destroy the natural conformation and stability of viral capsid protein, leading to capsid rupture or content leakage, which may significantly reduce or even completely eliminate the infectivity of the virus. In this case, the virus acts as a highly targeted "nanodrug capsule", which can precisely deliver highly toxic drugs to tumor cells, achieving a "decapitation operation" and avoiding systemic toxic side effects. For example, "oncolytic virus loaded with SN-38 and carboplatin" is such an application [7][8].

4.3 Targeted Modification of Viral Vectors for Tumor Antigen Recognition

Viral vectors can be engineered to specifically target tumor cells by modifying their surface proteins to recognize tumor-specific antigens. The main strategies include:

Antibody fusion involves binding specific antibodies or antibody fragments like single-chain variable fragments (scFv) to viral surface proteins. These antibodies are highly specific for tumor cell surface antigens, thus achieving targeted delivery of viral vectors. For example, the modified adenoviral vector is designed to express ScFv against human epidermal growth factor receptor (HER2), which can specifically recognize and bind HER2 overexpressing breast cancer cells.

Ligand modification refers to the integration of small molecule ligands or peptides, ranging from growth factors to hormones, onto the viral surface, thereby mediating the targeted binding with cognate receptors on tumor cells. For example, viral vectors modified with epidermal growth factor (EGF) can selectively target tumor cells expressing EGF receptors.

Genetic engineering, taking CRISPR-Cas9 technology as an example, is used to modify viral surface proteins to

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generate new binding sites or domains that can recognize tumor specific antigens. For example, through CRISPR-Cas9-mediated editing, the capsid protein of adeno-associated virus (AAV) has been engineered to have specific binding ability to tumor cell surface receptors.

Glycosylation modification involves the glycosylation of viral surface proteins, enabling the vector to recognize abnormal glycosylation patterns present on tumor cells, including the Lewis y antigen which is overexpressed in some cancers. Therefore, glycosylated viral vectors can achieve targeted delivery to tumor cells expressing the corresponding glycosylated receptors [9].

Multivalent display refers to the presentation of multiple targeting ligands on the virus surface, which is a strategy to improve the binding affinity with tumor antigens and significantly improve the targeting efficiency. For example, adenoviral vectors displaying a variety of anti-HER2 single chain variable fragment (scFv) molecules have been shown to enhance the targeting effect on HER2 positive breast cancer cells.

4.4 Safety Challenges and Optimization Approaches in Viral Vector Applications

There are inherent security risks in the application of viral vectors, which need to be mitigated by strategic measures. Preexisting antibodies, especially those against common serotypes such as adenovirus type 5 (Ad5), may neutralize the vector, thereby reducing the therapeutic effect. In addition, carrier components may activate innate and adaptive immunity, triggering inflammatory cascades or autoimmune pathologies. Retroviral (RV) and lentiviral (LV) vectors are at risk of insertion mutations - as indicated by lentiviral gene events - and random genome integration may activate protooncogenes. Theoretically, recombination with wild-type viruses also carries the risk of restoring virulence.

The challenge of vector specificity further increases the complexity of clinical translation. Adenovirus platforms often cause dose-dependent hepatotoxicity and systemic inflammatory responses. AAV exhibits hepatotoxicity at high doses and is at risk of antibody mediated clearance due to the presence of previous humoral immunity. Lentiviral systems are at risk of integration-related mutations and long-term tumor formation, while poxvirus vectors usually cause febrile reactions (>38.5 ° C, occurring in >30% of subjects) as well as severe local reactions.

Safety optimization applies multifaceted solutions. Rare serotypes, such as chimpanzee-derived ChAdOx1, low-prevalence AAV-GA4 evade pre-existing immunity. Capsid engineering by directed evolution can reduce the immunogenicity of AAV and enhance tissue specificity. Nonintegrated vectors, such as integration deficient lentivirus (idlv), can provide exogenous expression without interfering with the genome. Heterologous prime / boost stimulation scheme, using different vector frameworks alternately, such as adenovirus prime / poxvirus boost, can evade anti vector immunity. Plasma exchange can clear the existing anti AAV antibodies, thus restoring the transduction efficiency of seropositive people [10].

These methods collectively address key safety barriers, although long-term genotoxicity analysis and immunogenicity management still need to be continuously studied.

5. Conclusion

This study is reviewed through a systematic review the status of virus vector used as a means of drug delivery in oncology, and expounds in detail the mechanism of action, design principles and advantages of virus vector in precise treatment of tumors. Through literature analysis, viral vectors demonstrate strong potential as drug delivery tools in oncology due to their ability to efficiently enter cells, maintain gene expression control, and be engineered for improved therapeutic performance, which greatly improves the targeting and effectiveness in the treatment process. Different vector types—such as adenovirus, AAV, lentivirus, and poxvirus—offer distinct advantages that support their broad use in gene therapy, oncolytic applications, and cancer vaccine development.

Compared to traditional non-viral systems, these vectors generally achieve higher delivery efficiency, superior tissue targeting, and more stable expression in the tumor microenvironment. At the same time, advances in capsid redesign, promoter optimization, and receptor-guided targeting have enhanced precision while reducing immune-related limitations, thus providing a new way for personalized cancer treatment and immunotherapy.

Virus vector has considerable plasticity and application prospect in tumor drug delivery system. Their overall performance makes them an important link between basic research and clinical translation.

This study holds three significant implications. First, it systematically categorizes viral vector structures, transmission pathways, and engineering optimization methods, establishing a theoretical foundation for understanding their propagation standards and regulatory mechanisms. Second, it provides technical guidelines for developing viral vector-based drug delivery systems, advancing their applications in gene therapy, tumor immunotherapy, and cancer vaccine development. Finally, it pioneers new pathways for precision cancer treatment and personalized diagnostics, accelerating the clinical translation of viral vector technology while providing robust support for nov-

el drug development and biologic therapies.

Although virus vector has shown great potential in tumor treatment, it still has some important problems. Future research should develop and improve the investigation in the following direction. First of all, strategies such as integrating Arginine-Glycine-Aspartic Acid (RGD) peptides or antibody fragments, refining genome structure, and combining immunotherapy may help enhance effectiveness.

Developing a new virus platform and adopting advanced vector engineering technology are the important research directions in the future. Emerging engineered virus platforms and computationally guided synthetic technologies offer control over delivery kinetics and therapeutic impact. To promote the clinical translation and mass production of virus vectors, it is necessary to form a standardized and scalable production system. Scalable production systems such as fixed-bed bioreactors, along with regulatory safety evaluations, will be critical for clinical translation. Overall, viral vector engineering is rapidly evolving, and future efforts aimed at precision, safety, controllability, and personalization will shape cancer therapy development.

Authors Contribution

All the authors contributed equally and their names were listed in alphabetical order.

References

[1] Zhang Tingran, Tian Hong, Yao Wenbing. Advances in the Application of Viral Vectors in Cancer Vaccines. Pharmaceutical Biotechnology, 2024, 31(06): 705-710.

[2] Zhong Chunlian, Fang Changjian, Zhou Guiyu, et al. Research on Nanographene Oxide as a Clinical Drug Carrier in Tumour Therapy. Bulletin of Chinese Pharmacology, 2024, 40(08): 1413-1418.

[3] Seclì L, Avalle L, Brignone C, et al. Personalized Cancer Vaccines Go Viral: Viral Vectors in Cancer Immunotherapy. International Journal of Molecular Sciences, 2023, 24(23): 16591.

[4] Liu Yongfei. Application of carrier-free nanomedicines in combined chemo-gene therapy for tumours. Fuzhou University, 2022.

[5] Raguz J, Pinto C, Pölzlbauer T, et al. Preclinical evaluation of two phylogenetically distant arenavirus vectors for the development of novel immunotherapeutic combination strategies for cancer treatment. J Immunother Cancer, 2024, 12(4).

[6] Makafui D D, Sandoval E V T, Emmanuel F, et al. Technological advances in the use of viral and non-viral vectors for delivering genetic and non-genetic cargos for cancer therapy. Drug Deliv Transl Res, 2023, 13(11): 2719-2738.

[7] D. I. O., A. V. V., S. D. Z., et al. Development of Oncolytic Vectors Based on Human Adenovirus Type 6 for Cancer Treatment. Viruses, 2023, 15(1): 182.

[8] Ester G, Sarah R. DC-targeting lentivectors for cancer immunotherapy. Immunotherapy Advances, 2023, 3(1): ltad023.

[9] Shrey K, Tanmay K, Suyash D, et al. Non-Viral Vectors for Delivery of Nucleic Acid Therapies for Cancer. BioTech, 2022, 11(1): 6.

[10] Shuang F, Xiaodong X, Yu M, et al. RGD peptide-based non-viral gene delivery vectors targeting integrin αvβ3 for cancer therapy. J Drug Target, 2019, 27(1): 1-11.