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Viral and Non-viral Delivery Systems for Gene Therapy: Clinical Applications

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Description

Gene therapy holds the promise of revolutionizing the treatment of various genetic and acquired diseases by introducing, correcting, or silencing specific genes within a patient's cells. Effective delivery of therapeutic genes to target cells is critical to the success of gene therapy. There are two main categories of delivery systems: viral and non-viral vectors. Each system has its own set of advantages and challenges, and the choice of vector depends on the specific clinical application. Viral vectors are highly efficient in delivering genetic material into cells due to their natural ability to infect host cells. The most commonly used viral vectors include adenoviruses, adeno-associated viruses, lentiviruses, and retroviruses [1].

Adenoviruses are non-enveloped, double-stranded DNA viruses that can infect a wide range of cell types, both dividing and non-dividing. They are highly efficient in gene delivery and can accommodate large inserts of genetic material (up to 36 kb). Adenoviral vectors are often used for gene therapy applications requiring high levels of transgene expression. Adenoviruses have been used in clinical trials for cancer therapy, such as oncolytic adenoviruses engineered to selectively replicate in and kill cancer cells. Additionally, adenoviral vectors have been employed in cardiovascular diseases and monogenic disorders like cystic fibrosis. A major limitation of adenoviral vectors is their high immunogenicity, which can lead to an immune response against the vector, reducing its efficacy and causing potential adverse effects. Moreover, transgene expression is often transient due to the lack of integration into the host genome [2].

AAVs are small, non-enveloped, single-stranded DNA viruses that are not pathogenic and elicit a mild immune response. They can infect both dividing and non-dividing cells and integrate into a specific site in the human genome with low risk of insertional mutagenesis. AAV vectors can carry a limited genetic payload (up to 4.7 kb). AAV vectors have shown promise in treating a variety of genetic disorders, including retinal diseases (e.g., Luxturna for Leber's congenital amaurosis), hemophilia, and spinal muscular atrophy. AAVs are also being explored for neurodegenerative diseases and cardiovascular disorders. The small packaging capacity of AAV limits its use for delivering large genes. Additionally, pre-existing immunity to AAVs in the human population can reduce the effectiveness of AAV-based therapies [3].

Lentiviruses are a subclass of retroviruses capable of infecting both dividing and non-dividing cells. They integrate their genetic material into the host genome, providing long-term expression of the transgene. Lentiviral vectors can carry relatively large genetic payloads (up to 8 kb). Lentiviral vectors are widely used in gene therapy for hematopoietic stem cell disorders, such as β-thalassemia and sickle cell disease. They are also being investigated for use in CAR-T cell therapies for cancer and in treating neurodegenerative diseases. Integration into the host genome raises concerns about insertional mutagenesis and oncogenesis. Advances in vector design, such as self-inactivating lentiviral vectors, have been made to reduce these risks. Retroviruses are RNA viruses that reverse transcribe their RNA into DNA, which then integrates into the host genome. They are primarily used for gene therapy in dividing cells, as they require cell division for integration.

Retroviral vectors have been used in clinical trials for treating severe combined immunodeficiency, X-linked adrenoleukodystrophy and certain cancers. Similar to lentiviruses, retroviruses pose risks of insertional mutagenesis. Additionally, their inability to infect non-dividing cells limits their use in certain applications. Non-viral delivery systems offer several advantages over viral vectors, including lower immunogenicity, ease of production, and the ability to carry larger genetic payloads. Common non-viral delivery methods include lipid nanoparticles, polymers, electroporation, and physical methods such as gene guns and ultrasound. Lipid nanoparticles are composed of lipids that encapsulate genetic material, facilitating its delivery into cells. LNPs are particularly effective for delivering RNA-based therapeutics, such as mRNA and small interfering RNA [4].

LNPs gained significant attention during the COVID-19 pandemic for their role in delivering mRNA vaccines (e.g., Pfizer-BioNTech and Moderna COVID-19 vaccines). They are also being investigated for cancer immunotherapy, liver diseases, and rare genetic disorders. Ensuring targeted delivery and avoiding off-target effects are major challenges for LNPs. Additionally, stability and efficient endosomal escape of the encapsulated genetic material are critical factors influencing their effectiveness. Polymers, such as polyethylenimine and poly(lactic-co-glycolic acid), can form complexes with nucleic acids, facilitating their cellular uptake. These polymer-based systems can be engineered to enhance stability, biocompatibility, and targeted delivery. Polymer-based delivery systems are being explored for cancer therapy, cardiovascular diseases, and genetic disorders. For example, polymer nanoparticles have been used to deliver siRNA targeting oncogenes in cancer cells.

Toxicity and immunogenicity of certain polymers can limit their clinical use. Designing polymers with optimal properties for specific applications remains a critical area of research. Electroporation involves applying an electric field to cells, creating transient pores in the cell membrane through which genetic material can enter. This method is highly efficient and can be used for in vivo and ex vivo gene delivery. Electroporation has been used in clinical trials for cancer immunotherapy, such as delivering DNA vaccines encoding tumor antigens. It is also employed for genetic modification of T cells in CAR-T cell therapy. The technique can cause cell damage and is less effective for delivering large genetic payloads. Optimizing the electric field parameters to balance efficiency and cell viability is crucial.

Physical methods, including gene guns and ultrasound, physically force genetic material into cells. Gene guns use high-pressure gas to propel DNA-coated particles into tissues, while ultrasound uses sound waves to enhance cellular uptake of genetic material. Gene guns have been used for DNA vaccination and delivering therapeutic genes to skin and muscle tissues. Ultrasound-mediated gene delivery is being explored for cancer therapy and cardiovascular diseases. Physical methods can cause tissue damage and have limited control over the delivery process. Ensuring efficient and targeted delivery remains a significant challenge. Both viral and non-viral delivery systems have made significant contributions to the field of gene therapy, each with its own strengths and limitations. Viral vectors, with their high efficiency and ability to integrate into the host genome [5].

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Conflict of Interest

None.

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