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mRNA Vaccine Delivery Techniques

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Abstract

mRNA vaccines offer streamlined manufacturing, rapid development during health crises, and a safe profile with strong immune responses. The main advantage of mRNA vaccines is that it can be developed more quickly than traditional vaccines and unlike traditional vaccines which uses weakened or inactivated viruses, mRNA vaccines do not introduce the virus itself into the body. Also, mRNA vaccines represent a transformative advancement in immunization strategies, offering a faster and safer path to tackle emerging health crises and infectious diseases. Here we emphasize on the various delivery techniques for mRNA vaccines.

1. Introduction

Messenger RNA/mRNA has emerged as a promising therapeutic tool for immunotherapies, viral vaccines, genome editing, and cellular reprogramming. However, the effective application of mRNA-based therapies faces significant challenges, particularly in intracellular delivery. The larger size of mRNA compared to smaller molecules like small interfering RNA (siRNA) and antisense oligonucleotide (ASO) makes it difficult to efficiently deliver it to the cytoplasm of target cells. Additionally, the negatively charged nature of mRNA molecules and the composition of the cell membrane, featuring a zwitterionic lipid bilayer and negatively charged phospholipids, create further barriers, impeding cellular uptake. Furthermore, mRNA is vulnerable to degradation by

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ribonucleases in the extracellular environment, emphasizing the need for protective measures to preserve its integrity and function. Despite these formidable obstacles, researchers continue to explore various delivery methods, such as lipid-based carriers, polymers, and protein derivatives, to optimize mRNA delivery and harness its full therapeutic potential in combating diseases and advancing medical treatments. The development of efficient intracellular methods for delivering mRNA holds the key to unlocking a new era of targeted and personalized medicine, offering hope for a wide array of medical conditions and bringing mRNA-based therapies closer to clinical reality.

1.1 mRNA vaccine delivery methods

Injection of Naked mRNA

Naked mRNA injection, without carrier molecules, offers advantages like easy preparation, storage, and cost-effectiveness. Freeze-dried naked mRNA remains stable for 10 months at 4°C in a suitable buffer like 10% trehalose. Before administration, reconstitution and dilution in Ringer's or Lactated Ringer's solution are sufficient. However, ribonucleases (RNases) can degrade naked mRNA that has been injected and so its intracellular delivery remains debated. Intramuscular injection in mice demonstrated the feasibility of delivering naked mRNA *in vivo* in the 1990s.

Dendritic-Cell-Based mRNA Vaccine Electroporation

Antigen-presenting cells (APCs), especially dendritic cells (DCs), play a crucial role in presenting antigens to T cells, initiating the immune response. DCs are desirable for vaccination due to its ability to migrate to T cells and high expression of MHC molecules, co-stimulatory molecules, and cytokines. Electroporation, applying electric shock to disrupt cell membranes, enhances mRNA vaccine delivery in DC-based clinical trials. In summary, DCs are essential for presenting antigens to T cells, making them attractive targets for vaccination, and electroporation improves mRNA vaccine delivery to DCs.

Lipid Nanoparticles (LNPs) for mRNA Delivery

Lipid nanoparticles (LNPs) serve as intelligent nano-sized lipid-based carriers for delivering mRNA into the cytosol. In addition to protecting mRNA from ribonucleases in systemic circulation, LNPs aids in efficient delivery of mRNA intracellularly by union with the lipid bilayer of early endosomes and facilitating the mRNA's entry into the cytosol.

The components of LNPs include:

i. Cationic ionizable lipids - It is essential for encapsulating mRNA with the help of electrostatic interactions. They become positively charged below a certain pH (pKa) for efficient endosomal release while remaining neutral and safe during systemic circulation at pH 7.4.

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ii. Polyethylene glycol (PEG) lipids provide colloidal stability to LNPs, preventing protein binding and increasing systemic circulation. However, they can hinder endosomal release of mRNA, which can be addressed using cleavable PEGylation. PEG lipids also enhance storage stability of LNPs.

iii. Phospholipids like DSPC (DiStearoylPhosphatidylCholine) and DPPC (DiPalmitoylPhosphatidylCholine) add structural stability to LNPs and influence the release profile of mRNA. DPPC, a natural lung surfactant, is commonly used in pulmonary drug delivery.

iv. Cholesterol, a neutral lipid, improves lipid bilayer stability, prevents leakage, and aids in membrane fusion for LNPs and gene transfer at optimal concentrations.

Peptide-Based Delivery Protamine

Peptides are used as carriers for mRNA vaccines, for which it should include strings of positively charged amino acids, such as lysine and arginine. This allows for the formation of electrostatic between peptides with positive charges and negatively charged mRNA, thus enabling spontaneous complex formation. The advantage of using protamines as delivery systems is, it protects the mRNA from being degraded by RNases. And the protamine-mRNA complex is having high adjuvant activity and is immunogenic due to its structural similarity to viral RNA genomes. The feasibility of the mRNA protamine complex was tested with β-galactosidase mRNA-protamine, which was injected into a glioblastoma tumour. However, it was observed that the mRNA complexed with protamine was poorly translated.[**Error! Reference source not found.**]

Polymer-Based Delivery

Polymer-based delivery systems show promise for mRNA vaccines, protecting against RNase degradation like protamines. To enhance stability, researchers are incorporating lipid chains, hyperbranched groups, and biodegradable units, despite facing challenges like high polydispersity. Cationic polymers like polyethyleneimine (PEI), polyamidoamine (PAMAM) dendrimers, and polysaccharides have shown potential for mRNA delivery. PEI formulations demonstrated efficacy for HIV and influenza vaccines, generating T-cell responses and viral protection. Self-amplifying mRNA vaccines against different infectious pathogens are made using PAMAM dendrimers. Chitosan, a polysaccharide, has been employed for influenza vaccination. Chitosan is biocompatible, biodegradable, and non-toxic, making it a favourable choice it also has immunostimulatory properties. While preclinical studies show promise, further research is needed to develop functional polymers with improved biodegradability and delivery efficacy before clinical translation.

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Virus-Like Replicon Particle (VRP)

Adenoviruses, lentiviruses, and adeno-associated viruses (AAV) are examples of viruses used as delivery systems for gene therapies and vaccines. Viral particles can deliver self-amplifying mRNA encoding antigens, replicating and expressing the designated antigens efficiently. VRPs, like alphaviruses, flaviviruses, rhabdoviruses, and measles virus, are effective in delivering RNA payloads to the cytoplasm via different pathways. VRP vaccines were injected intradermally in non-human primates to produce immunity against the Venezuelan equine encephalitis virus (VEEV) [5]. Similar to this, animals with colon cancer were intravenously administered a Kunjin virus-derived VRP expressing GM-CSF, which resulted in the total eradication of the main tumour and a decrease in lung metastases. [6].

2. Conclusion

mRNA vaccines revolutionize immunization with streamlined manufacturing, safety, and cost-effectiveness. They prompt cells to produce antigens, triggering immune responses without live viruses. COVID-19 approval showcases speed and adaptability. Future delivery systems offer targeted, efficient, and personalized treatments, transforming medical interventions for various health conditions. Combining therapies, immune modulation, and cost-effectiveness enhance medical treatments.

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