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REVIEW ARTICLE

Innovations in Nanoparticle-Mediated mRNA Delivery

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Abstract: A safe and efficient delivery system and enhanced mRNA stability can lead to successful mRNA treatment. The mRNA vaccine is a ground-breaking immunology discovery that has gained international recognition after winning the prestigious Nobel Prize. It has emerged as a promising prophylactic and therapeutic modality for a variety of diseases, particularly cancer, rare diseases, and infectious diseases like COVID-19. A plethora of nanoscale platforms, including lipid nanoparticles, lipoplexes, polyplexes, and lipid-polymer hybrid nanoparticles, have emerged as frontrunners in mRNA delivery research. These platforms serve to safeguard mRNA from extracellular degradation and facilitate endosome escape, thereby augmenting therapeutic efficacy. The efficacy can be increased by using nanoscale platforms to shield mRNA from extracellular degradation and to encourage endosome egress following endocytosis. This article offers a summary of the many nanoplatforms used in preclinical and clinical research to deliver mRNA phases of preclinical and clinical development, encompassing formulation, method of production, effectiveness of transfection, and mode of administration. Additionally, this article discusses the state of the mRNA vaccine market and its future possibilities.

Keywords: Lipoplex; Solid Lipid Nanoparticles; Gene therapy; Vaccination; mRNA.

1. Introduction

The "blueprint" of human cells is found in naturally occurring molecules called RNA (mRNA). It can manufacture immunogens that trigger immune responses in vivo to combat different infections, or target proteins for therapeutic purposes. When it comes to therapeutic applications, mRNA presents a number of benefits over DNA-based gene therapy. 1 and 2.First off, mRNA's transient action offers great flexibility, timing management, and a variety of therapeutic effects. Second, mRNA is capable of carrying out essential tasks in the cytoplasm without going into the nuclei of the cells [1,2]. Thirdly, because antigen translation takes place in the cytoplasm, there is a lesser chance of insertional mutation and carcinogenesis, which increases the protein's safety and therapeutic usefulness [3-5]. With little success, researchers have attempted to address these problems by chemically altering mRNAs [6,7]. In order to facilitate mRNA cell entrance and accomplish lysosomal escape, it is crucial to use an effective delivery method. Viral vectors have been characterized as an effective mRNA delivery technique in a number of delivery vector papers. However, the main barriers to its continued development are toxicity, vector size, and unwanted immunological reactions. [8].

Numerous non-viral nanovehicles, including lipid-based nanoparticles, polymeric nanoparticles, lipid-polymer hybrid nanoparticles, and others, have drawn a lot of attention for mRNA delivery, which is a significant advancement[9–11]. Non-viral nanocarriers have a number of benefits over viral vectors.a) Effectively condensing mRNA prevents it from being broken down by enzymes [12] b) efficiently targeting and delivering mRNA to lymphatic organs like lymph nodes or antigen-presenting cells promotes the uptake and presentation of antigens, increasing the effectiveness of vaccinations [13]; c) Nano-delivery methods lead to endosome escape following endocytosis and enhance transfection effectiveness. Because of these benefits, mRNA vaccines and treatments are currently the focus of a lot of research on nano-delivery technologies. The endosome escape process can be explained by the proton sponge effect. Following mRNA-loaded nanoparticle uptake by endocytosis, the ATP-dependent pump causes the pH of the endosomal compartment to acidify, going from roughly 7.2 to 6.3 in the early endosomes to about 5.5 in the late endosomes[14, 15]. In order to give endosomes buffering capability and cause a significant influx of protons (H+) and chloride (Cl-) counterions, nanoparticles are usually constructed with a pKa within the pH change window range of the endosomes. The endosomes then enlarge, rupture, and eventually release the cargo into the cytosol as a result of a significant volume of water flowing into them to maintain osmotic pressure [16–18]. Depending on the material's characteristics, such as pH sensitivity or bioreducible linkages, nanoparticles may collapse in the cytosol or during endosome escape [19, 20] promoting transfection and mRNA release even further. [22-24]

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2. Nanoplatforms for the transport of mRNA

2.1. Lipoplexes

Cationic liposomes, owing to their amphiphilic nature, are composed of cationic lipids featuring positively charged head groups, such as DOTMA or DOTAP, combined with stabilizers like cholesterol. These components assemble spontaneously to form cationic liposomes, which adopt a vesicular structure [25]. Various techniques, including reverse evaporation, solvent injection, and thin film dispersion, are commonly employed for the preparation of liposomes [26, 27].

Upon binding to cationic liposomes, mRNA becomes embedded within the lipid bilayer, resulting in the formation of lipoplexes (LPX). This molecular complex serves to protect mRNA from nuclease hydrolysis and facilitates efficient cellular uptake. Researchers have observed that during the transfection of murine bone marrow-derived dendritic cells (BMDCs), lipoplexes composed of DOTAP/cholesterol in a 1:1 molar ratio exhibit superior performance compared to those composed of DOTAP/DOPE in a 2:3 molar ratio. [28-30]

2.2. Lipid Nanoparticles (LNPs)

Since the introduction of Onpattro® (patisiran), a siRNA-LNP for the treatment of polyneuropathy, LNPs have been the most extensively explored non-viral vectors for mRNA delivery [30, 31].Ionizable lipid, phospholipid, cholesterol, and PEG-lipid[32] are the four main components of LNPs. The efficacy of transfection and mRNA distribution are largely dependent on the ionizable lipid component. With several hydrophobic tails and an ionizable head group, it is an amphiphilic molecule. Ionizable head groups, which attach to negatively charged mRNA[33], are uncharged at neutral pH but protonated at lower pH levels. Examples of these head groups are tertiary amines. Endosome escape and cell uptake can be facilitated by DOPE or DSPC) by increasing the permeability of the cell membrane [35]. By regulating membrane stiffness and integrity, cholesterol is a key factor in improving particle stability[36]. Additionally, the biodistribution and delivery efficiency of LNPs might be further impacted by its derivatives [37]. In a research conducted by Sahay et al., it was discovered that substituting cholesterol with β-sitosterol might enhance endosome escape, boost transfection effectiveness, and boost LNP stability during nebulization[38]. PEG-lipids significantly influence the adjustment of particle size and zeta potential; they also help stabilize particles by decreasing particle aggregation; they extend the time that nanoparticles spend in circulation in the bloodstream by lowering renal and monocyte phagocyte system (MPS)-mediated clearance; and they facilitate the coupling of particular ligands to particles for targeted delivery. [39-43]

2.3. Lipid Nanocrystal (LNC)

Calcium (Ca^{2+}) ions and naturally occurring phospholipids (phosphatidylserine, PS), a component of the cell membrane, are used to make lipid nano-crystals (LNCs). PS spontaneously self-assembles into multilayered, stable crystalline spiral structures with no internal aqueous space when Ca2+ interacts with them . LNC will therefore be a promising mRNA delivery technology in the future. LNC is especially well-suited for oral administration and offers mRNA stability for a prolonged amount of time at room temperature because mRNA can be contained between the layers, where it is shielded from water and hazardous exterior factors. LNC uses both fusion and phagocytosis to efficiently deliver its cargo inside cells. Endogenous PS migrates toward the cytosol from its usual location in the inner layer of the membrane. when there is an infection or inflammation of the cell, the outer layer (cell membrane)[44]. This process serves as a prelude to the fusion of cells and LNC, which makes it easier for cells to phagocytose LNC. LNC progressively collapses to release mRNA once it is inside the low-calcium cytoplasm. Matinas Biopharma has used the LNC platform to create two interesting therapeutic candidates, and in partnership with BioNTech, the same LNC technology will be employed to create oral mRNA vaccines. While early in vitro research demonstrated the effectiveness of LNC-based oral mRNA vaccines, more recent in vivo investigations in mice revealed little effect. As a result, there was no more cooperation between the two parties. [45, 46]

2.4. Lipid nanoparticle with selective organ targeting (SORT-LNPS)

LNPs are mostly absorbed by the liver after being injected into the blood, which restricts their potential for use in a variety of therapeutic contexts. As a result, developing extrahepatic targeting for LNPs has emerged as a crucial field of study. In this context, Daniel Siegwart's group has suggested SORT-LNPs, which allow for the introduction of a fifth component: SORT lipids [47], to accomplish specific organ targeting. The results of the study showed that the lungs can be efficiently targeted by SORT-LNPs when the cationic lipid DOTAP is used as the SORT molecule. However, the SORT-LNPs can target the spleen by using the negatively charged 1,2-dioleoyl-sn-glycero-3-phosphate (18PA) as the SORT molecule[48]

2.5. Nanoparticles supported by cationic lipids (CLANs)

Wang's group investigated the CLANs system for the first time in 2009. Major CLANs made of a cationic lipid shell and PLGA core were created using the double-emulsion technique. Because PLGA is uncharged, it is commonly employed in conjunction with cationic lipids to load mRNA by electrostatic interactions. For example, PEG-b-PLGA-based nanoparticles with cationic lipid

assistance After BHEM-Chol was created to create CLAN nanoparticles, these were tested to ensure that Cas9 mRNA and NLRP3 gRNA could be effectively delivered to mouse macrophages [49]. By deleting the NLRP3 gene and inhibiting the NLRP3 inflammasome's activation, sepsis, peritonitis, and type II diabetes were successfully prevented or treated in mice. [50]

3. Need for development of mRNA vaccines

Development of mRNA vaccines holds significant promise in clinical practice, particularly in combating infectious diseases, such as SARS-CoV-2, influenza, rabies, HIV, and cancer

Infectious diseases pose a substantial risk to human health, driving the urgent need for effective vaccination strategies. mRNA vaccines have emerged as a promising solution due to their ease of production, immunogenicity, and safety profile [51]. The approval of mRNA-based COVID-19 vaccines, including Pfizer-BioNTech's BNT162b2 and Moderna's mRNA-1273, by the US Food and Drug Administration marked a pivotal moment in mRNA vaccine technology [52]. These vaccines demonstrated remarkable efficacy, with BNT162b2 achieving a 95% overall efficacy in preventing COVID-19 infection. Influenza, a common respiratory infection, poses a persistent threat to public health. The evolving nature of influenza viruses necessitates continuous updates to vaccination strategies to provide adequate protection against emerging strains. mRNA-based influenza vaccines have shown promise in eliciting strong and durable immune responses against the virus [53].

Rabies, a fatal brain illness, has been targeted for vaccination using mRNA technology. CureVac's mRNA vaccine candidate, CV7201, utilizes a cationic polypeptide protamine as a delivery vehicle. Preclinical studies have demonstrated the vaccine's ability to induce robust immune responses in animal models, with phase I clinical trials showing safety and efficacy [49, 50]. HIV remains a global health concern, highlighting the need for effective preventative vaccines. Despite past setbacks in HIV vaccine development, Moderna's experimental mRNA HIV vaccine has shown considerable potential, leveraging the same platform technology as their successful COVID-19 vaccine. Cancer vaccines, offering both therapeutic and preventative benefits, represent a promising approach in cancer immunotherapy. mRNA vaccines targeting tumor-associated antigens (TAAs) or tumor-specific antigens (TSAs) have shown potential in precisely targeting and eliminating cancer cells while inducing immunological memory for long-lasting therapeutic effects [53]

4. Conclusion

In conclusion, mRNA-based therapy holds significant promise for the treatment of cancer, hereditary illnesses, and infectious diseases. The rapid progress in nanotechnology and biomaterials offers valuable solutions to challenges such as transfection efficiency, cell targeting, stability, and distribution. Non-viral vectors, particularly lipid nanoparticles (LNPs), have shown efficacy in loading mRNA, enhancing antibody titers, increasing transfection efficiency, and eliciting immunological responses, as exemplified by the success of COVID-19 mRNA vaccines. Further development of mRNA-based therapies can be achieved through the utilization of lipoplexes, polyplexes, lipid-polymer hybrids, and other delivery tools, necessitating rigorous evaluation of functionality, safety, and efficacy. Biodegradable lipid-based nanoparticles offer advantages over conventional lipid-based vectors due to their rapid clearance from tissues and plasma. The efficacy and toxicity of lipid nanoparticle-mRNA formulations are influenced by the structure of cationic lipids, with ionizable lipids offering low toxicity and stealth properties. Optimization of lipid structures can enhance cellular absorption and endosomal escape, while modifications enable targeted delivery to specific cells and organs. Natural membrane lipids, such as exosomes and cell membranes, present additional avenues for mRNA distribution.

Polymeric nanoparticles, with their flexibility, scalability, and tunability, offer diverse delivery techniques for mRNA, both in vitro and in vivo. However, clinical vaccination candidates utilizing polymeric nanoparticle-mRNA formulations require thorough safety assessments and quality controls. Hybrid nanoparticles, such as lipid-polymer hybrids (LPPs) or core-shell lipid-polymer nanoparticles (CLANs), hold promise for enhancing mRNA delivery potency, but considerations regarding biodegradability and breakdown products are essential. While injectable administration remains prevalent for mRNA vaccines, opportunities exist for the development of novel delivery systems and dosage formulations. Future research efforts should focus on discovering new nanoplatforms and improved formulations that enhance drug delivery efficacy in vivo while minimizing toxicity and maximizing potency. The ongoing pursuit of enhanced mRNA delivery vehicles represents a critical step towards addressing a wide range of disorders and realizing the full therapeutic potential of mRNA-based therapies.

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