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Enhancing Immunogenicity on COVID-19 mRNA Vaccine with Lipid Nanoparticles and Innovation of Nanotechnology

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Abstract: The review highlights recent advancements in mRNA vaccine technology, focusing on the key mechanism of increasing vaccine immunogenicity through lipid nanoparticle (LNP) and its successful application to a COVID-19 vaccine. Optimized mRNA design, coupled with chemical modifications, such as pseudouridine substitution, have enhanced mRNA stability, translational efficiency, and minimized immune-related adverse reactions. Moreover, LNP optimization, through adjusting the ratio of ionized lipid, phospholipid, and cholesterol and regulating the nanoparticle size and surface charge, has proven critical for efficient vaccine delivery and robust immune responses. The review also discusses different administration routes and dosing regimens, emphasizing intramuscular injection as the most effective for systemic immune activation. The successful development of COVID-19 vaccines, as represented by Pfizer and Modena vaccines, supports the importance of those technologies and provides a new paradigm for future vaccine development. Continued optimization of LNP technology and the exploration of novel delivery systems are essential for extending the scope of mRNA vaccines to combat a broader range of diseases, ultimately providing innovative solutions to global health challenges.

Keywords: mRNA vaccine, lipid nanoparticle, immunogenicity, COVID-19

1. Introduction

The emergence of novel coronaviruses continues to challenge global healthcare systems, emphasizing the urgent need for rapid and effective vaccine development to combat the spread of infectious diseases. Traditional vaccines are usually developed using live attenuated vaccines, inactivated viruses, or fake viruses. Although these have proved effective, their development is highly complicated and time-consuming, thus making it hard to deal with the threat of the rapid spread of emerging viruses. These limitations became particularly apparent during the COVID-19 pandemic, underscoring the necessity for innovative vaccine technologies. There is every reason to drive up the need for innovative vaccine technologies to make mRNA vaccines stand out. Compared with traditional vaccines, mRNA vaccines have characteristics such as rapid design, flexibility in production, and fast adaptation to viral mutations. During the COVID-19 pandemic, the rapid introduction of vaccines like mRNA-1273 and BNT162b2 demonstrated not only the potential of mRNA vaccines but also their remarkable protective efficacy of approximately 95%, which significantly exceeds the 70% efficacy achieved by some traditional vaccines[1]. These developments mark a paradigm shift in vaccine technology.

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Various studies have well summarized the potential problems with mRNA vaccine technology and the current regulatory demands. However, some obstacles are observed due to the instability of the mRNA itself. The inherent instability of mRNA, susceptibility to enzymatic degradation, and the risk of host immune activation pose significant obstacles[1]. Currently, this delivery strategy is generally the LNP technology in use; encapsulation and delivery of mRNA from enzymatic degradation may interact with cellular uptake and intracellular release by targeting increased transfection efficiency through LNPs[1]. mRNA formulations show reduced dosing but highly improved vaccine safety profiles with less reactogenicity than most carriers. mRNA vaccines combined with LNP avoid these naturally innate hurdles and represent newer vaccine-oriented technology for rapid responses in public outbreak scenarios. This review will briefly explain the revolutionary perspective toward mRNA vaccines, mainly focusing on lipid nanotechnology's key role in achieving idealized mRNA vaccine delivery platforms aimed at improved vaccine efficacy.

2. Mechanisms for Enhancing Immunogenicity

2.1. mRNA Design and Modifications

Two strategies can be used to increase the immunogenicity of lipid nanoparticles (LNP) mRNA vaccines and induce a stronger immune response to many pathogens. One strategy is to improve ionizable lipids through chemical modifications. These modifications enhance lipid efficiency in delivering mRNA to dendritic cells, thereby activating robust immune responses[2]. Another strategy is to modify the mRNA by adding elements that stimulate the immune system to stimulate the immune system and further enhance activation[2], [3]. For example, it has been demonstrated that manipulating mRNA to express proteins that activate the innate immune system can enhance the immunogenicity of T cells and antibodies[2]. One of the critical advancements in mRNA vaccine technology lies in the use of modified nucleosides, such as pseudouridine and N1-methyl pseudouridine. These modifications address the issues of mRNA instability and innate immune activation by reducing recognition by pattern recognition receptors (PRRs), including toll-like receptors (TLRs)[2]. This enhancement substantially minimizes potential adverse effects of the innate immune system that may, in any other case, activate an inflammatory response and interfere with the process of protein synthesis. These modifications make the mRNA vaccines safer and more efficient and define the new guidelines for developing mRNA vaccines for other diseases. Similarly, the epithelial splicing regulatory protein 2(ESRP2) regulates splicing procedures to ensure stability and efficient translation of proteins required for liver development after birth[2]. For therapeutic mRNAs, modified nucleosides mimic a similar natural stabilization mechanism, helping to increase the expression of therapeutic proteins in liver cells while reducing immune activation[4]. The characteristics of these modified nucleosides make them particularly suitable for liver-targeted mRNA therapy, in which continuous and controlled protein expression is indispensable.

2.2. Lipid Composition and Formulation

Ionizable lipids are essential to encapsulate mRNA. The design of mRNA affects cellular uptake and endosomal release. Lipids with longer alkyl chains improve delivery and enhance immune responses by increasing antigen translation efficiency[5]. Phospholipids stabilize LNP structures, facilitate membrane fusion, and support mRNA release, with natural phospholipids minimizing adverse immune reactions[5]. Cholesterol enhances membrane fluidity and stability, aiding antigen presentation and absorption, while PEG lipids extend LNP circulation by reducing immune clearance[5], [6]. However, excessive pegylation may inhibit cellular uptake, necessitating optimized PEG concentrations for effective immune activation. Key physicochemical properties, such as particle size, surface charge, and lipid ratios, regulate immune responses. LNPs sized 50–200 nm

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penetrate tissues efficiently, with 70–100 nm balancing transport efficiency and immune clearance[6]. Positively charged nanoparticles improve cellular uptake but risk aggregation and cytotoxicity, while neutral or negatively charged LNPs prolong circulation and maintain immune efficacy. Adjusting lipid ratios can bias immune responses toward Th1 or Th2 pathways, emphasizing the importance of fine-tuning these properties to maximize mRNA vaccine efficacy[6], [7].

2.3. Delivery Methods and Dosing Strategies

2.3.1. Effect of Administration Routes on Immune Response

The most common route of administration is the intramural (IM) injection, which effectively delivers it into the muscular tissue and promotes the absorption of lipid nanoparticles by muscle cells and dendritic cells[8], [9]. This route typically exhibits a potent systemic immune response, providing high titers of neutralizing antibodies and T-cell activation, both critical for longer-term resistance against infection. Intradermal (ID) administration directly targets dendritic cells in the skin, which are abundant immune cells. This method enhances antigen presentation and accelerates T-cell activation, promoting a rapid cellular immune response. However, ID delivery may result in reduced antibody titers compared to the IM pathway[9]. Subcutaneous (SC) administration is seldom utilized in the case of mRNA vaccines but gives rise to the induction of an adequate immune response[9]. It delays absorption and prolongs the period during which mRNA is presented to immune cells, although this route usually leads to generally lower overall immune activation than intramuscular injection. In general, IM management is the most effective in eliciting a comprehensive immune response.

2.3.2. Optimization of Dosing Schedules and Concentrations

The time interval between doses can make all the difference in the robustness and sustainability of the subsequent immune response. Prolonging the interval between the first and second doses enhances antibody affinity maturation and increases memory B-cell formation, contributing to stronger long-term immunity[8], [10]. A longer gap between the doses correlated with more solid long-term immunity—a finding observed in some COVID-19 vaccines. Another important aspect is the concentration of mRNA in the vaccine formulation; higher concentrations of mRNA can deliver more antigens into the body, thereby influencing the initial immune response[8], [10]. However, high doses might have unpleasant side effects, creating toxicity or more inflammation without corresponding benefits of immunogenicity[8], [10]. Therefore, the optimization strategy in developing mRNA vaccine-related mRNA concentrations should aim at a proper balance to trigger an optimal immune response with the lowest possible risk.

3. Case Studies and Practical Applications

3.1. Existing mRNA Vaccines

The significant efficacy of Pfizer-BioNTech (BNT162b2) and Moderna (mRNA-1273) COVID-19 vaccines relies on advanced mRNA and LNP technology. Both vaccines use nucleoside-modified mRNA, where the pseudouracil binding further reduces immune recognition and inflammation, enhancing the mRNA's stability and translation efficiency[11]. The encoded mRNA expresses a pre-fusion stabilized SARS-CoV-2 spike protein, essential for inducing strong immune responses. Pfizer-BioNTech uses a 30 μg dose per injection, significantly lower than Moderna’s 100 μg dose, contributing to differences in immune response durability[10]. Both vaccines employ LNPs with ionizable lipids, which protonate in the acidic environment of the endosome to release mRNA into

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the cytoplasm for protein translation[11]. However, specific compositions have some variation in their formulation, which may secondarily impact immune response and the profile of side effects. Both vaccines involve a two-dose administration to maximize the immune response. Pfizer-BioNTech administers its vaccine 21 days apart, whereas Moderna schedules its doses 28 days apart[11], [12]. Moderna's higher dose and longer interval result in slightly higher antibody titers, although both vaccines exceed 94% efficacy in preventing symptomatic COVID-19[13]. Real-world studies have subsequently further cemented the efficacy of both vaccines. Among 1.2 million people in Israel, Pfizer-Biontech was 94% effective against symptomatic COVID-19[11]. In the large cohort in the United States, Moderna's vaccine was 93% effective in preventing hospitalization[13]. Though different in dosage and formulation, both vaccines have played a significant role in bringing down the morbidity and mortality due to COVID-19 globally, thus showcasing the flexibility and potential that mRNA-based approaches come with.

3.2. Experimental Approaches

3.2.1. Innovation of Nanotechnology

Self-assembled protein-based nanoparticles represent a new mRNA vaccine delivery system. These nanoparticles leverage proteins' natural self-assembling properties to form stable nanostructures, protecting mRNA from degradation while enhancing cellular uptake and immune response[14]. Through hydrophobic and electrostatic interactions, these nanoparticles efficiently deliver mRNA into immune cells, boosting vaccine immunogenicity[14]. Their biocompatibility also supports precise targeting, improving the safety and efficacy of vaccines[14]. Beyond vaccines, protein-based nanoparticles show promise in therapeutic applications, including delivering therapeutic proteins and genes, marking a significant breakthrough in mRNA technology[14]. Exosome-based vaccines represent another transformative advancement. Exosomes, which are small extracellular vesicles secreted by cells, serve as natural vehicles for delivering antigens to the immune system[15]. Their lipid-protein-nucleic acid structures can carry tumor antigens, viral proteins, or other immunogenic materials. After their administration, exosome-based vaccines stimulate the engulfment of antigens that they carry through dendritic cells, macrophages, and B cells, further activating T cells and inducing an adaptive immune response[15]. Therefore, it enhances the recognition and specific immunity against selected pathogens or tumor-associated antigens. Applications for exosome-based vaccines have already been extended to a significant number of fields, especially in the areas of cancer immunotherapy and infectious diseases.

3.2.2. Preclinical and Clinical Studies Showcasing Innovative Methods

Emerging nanotechnology constructs, such as virus-like particles (VLPs), ferritin-based complexes, and engineered proteins, are reshaping vaccine design[14]. Spike proteins in NVX-CoV2373 of Novavax induce natural trimer conformation and elicit potent immunogenicity in preclinical models and Phase III trials (NCT04368988, NCT04611802)[14], [16]. Ferritin is a spherical protein complex that presents antigens for improving immune responses. The SARS-CoV-2 RBD-ferritin vaccine showed highly affine interaction with the ACE2 receptor and elicited neutralizing antibodies; ferritin-based influenza vaccines demonstrated potent immunogenicity in clinical trials[14], [16]. Computational design platforms like I53-50 extend these possibilities by instructing viruses such as HIV and Lassa to present antigens rapidly[14], [16]. Exosome-based delivery systems also show immense promise. Preclinical studies on exosomes loaded with SARS-CoV-2 RBD induced effective humoral and mucosal immunity, outperforming conventional LNP-based vaccines in stability and storage[15], [16], [17]. Oral mRNA vaccines utilizing milk-derived exosomes showed neutralizing antibody production in mice, while the multivalent COVID-19 exosome vaccine elicited long-lasting

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IgG and IgA responses with strong t-cell activation[15], [16]. These emerging technologies represent promising strategies for improving vaccine design, targeting, and immune response, offering great potential to combat multiple infectious diseases[17].

4. Challenges and Future Directions

4.1. Potential Risks and Side Effects of BNT162b2 and mRNA-1273

The clinical trials demonstrated that both the BNT162b2 and mRNA-1273 vaccines are very effective, providing approximately 95% protection against symptomatic COVID-19 and severe disease[18]. However, protection against newer variants, such as Delta, is somewhat reduced, though both vaccines still substantially prevent severe outcomes like hospitalization and death. Over time, immunity wanes, necessitating booster doses to maintain protection, particularly in high-risk groups. Both vaccines demonstrate a good safety profile, though each carries certain risks and has some side effects. The most frequently reported adverse reactions after administering both vaccines were pain at the injection site, fatigue, headache, myalgia, fever, and chills. The intensity of side effects in most cases was mild to moderate and faded within several days. These effects are more frequent after the second dose. Rare severe side effects, such as anaphylaxis, occur at a rate of about 5 per million doses for BNT162b2 and 2.8 per million for mRNA-127318[18]. Most cases develop within 30 minutes after vaccination. Increased immunogenicity may result in a greater immune response, therefore increasing the frequency of these side effects[18]. There is also a small but not negligible risk of infrequent side effects such as myocarditis and pericarditis, most often in young males within the first week following the second dose. Other side effects, also infrequently seen, are autoimmune-like reactions and neurological effects, including Bell's palsy[18]. Despite all these possible risks, the benefit of vaccination, specifically protection against severe COVID-19 infection, outweighs the risks of vaccination. Vaccination with booster doses is accordingly highly recommended to protect public health further.

4.2. Challenges of COVID-19 vaccines

mRNA-LNP vaccines represent a significant advancement in vaccine technology, yet several challenges limit their widespread effectiveness. One key challenge is the limited predictive value of animal models, which often fail to replicate human immune responses, especially in the presence of pre-existing immunity that could compromise vaccine efficacy[8], [17]. Adverse events, while typically mild, such as fever and muscle pain, and rarer but concerning events like myocarditis and allergic reactions, remain difficult to predict in preclinical studies.

Furthermore, while mRNA vaccines potentiate systemic immunity, there are various limitations in building up robust mucosal immunity, which is essential in protecting against respiratory infections like COVID-19. Lastly, with time, the immune response weakens and needs boosting. Furthermore, the use of lipid nanoparticles, especially with PEG components, can induce an antibody response against subsequent administration of vaccine doses or other therapies[8], [17], [18]. Other challenges arise with the achievement of multivalent vaccines, such as the fact that the antigen mixture can result in a reduced dosage of antigens and, hence, reduced immune response in mRNA vaccines[8], [17].

4.3. Future Opportunities

The future directions in mRNA vaccine development are to address these challenges in terms of safety, efficacy, and stability. Preclinical models need to be refined to better mimic human immune responses, particularly in the context of pre-existing immunity, allowing for more accurate assessments of vaccine efficacy[8], [17]. Other vaccination routes, such as intranasal or oral vaccines, should be

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further explored to enhance mucosal immunity and thereby achieve greater protection against respiratory infections[8], [17]. To counteract the weakening of the immune response, prolonging immunity-in order not to need frequent boosts-is an imperative; another promising direction in that respect can be the use of nonpolyglycated LNP to avoid interference with vaccine efficacy and immune response to further treatments[8], [17]. Finally, work must be done to optimize multivariate vaccines to ensure that several antigens combined do not impair the immune response. It is also crucial that further research on improving global vaccine distribution- including thermal stability and intellectual property rights- ensures that vaccines reach the farthest corners, mostly low-income countries[8], [17]. By addressing such challenges and pursuing such lines of research, the full potential of mRNA vaccines can be brought into play to extend their use in preventing infectious diseases.

5. Conclusion

mRNA-LNP vaccine development has been one of the milestones in modern vaccinology and the cornerstone in the fight against infectious diseases, serving also as the basis for developing novel immunotherapies. Various ways of enhancing mRNA vaccine immunogenicity are discussed here, including improved mRNA design through chemical modification, optimization of the composition and structure of lipid nanoparticles, innovative delivery methods, and dosing regimens. These approaches have significantly improved vaccine stability and enhanced vaccine delivery to induce robust immune responses. In addition to using several common nanotechnology types, deeper analysis was made in the context of the potentials of self-assembled protein nanoparticles and exosome vaccines-technologies emerging and very important for better targeting ability and immune response and further widening their adaptability. mRNA vaccines face many challenges, such as the low predictability of animal models, possible adverse reactions, poor mucosal immunity, or design complexities regarding multivalent vaccine formulation. More effort should be put into solving the problems mentioned above, especially in developing more predictive preclinical models to enable the more appropriate assessment of vaccine effects in humans; exploring new vaccination routes, such as nasal or oral vaccination, which would result in enhanced mucosal immune responses; and enhancing the stability of vaccines and their conditions of distribution, even more, to make them accessible for low-resource settings. Lastly, to surmount this attenuated immune response, there needs to be a continued optimization of strategies directed at amplifying immunity, increasing protection duration, and studying modes of application of nanoparticles with no PEGylation, thereby reducing probable interferences. Despite several shortcomings in today's mRNA vaccine development, thanks to its flexible design, efficient delivery, and excellent immunogenicity, mRNA vaccines are found to have great promise for preventing and controlling COVID-19. Overcoming these current hurdles and promoting technological innovation is indeed an all-important part of mRNA vaccine endeavors; hence, these mRNA vaccines may become significant means for the prevention and cure of a range of diseases while opening a new page for biomedical research.

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