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Lipid Nanoparticle Delivery in COVID-19 mRNA Vaccines: Immune Mechanisms, Manufacturing Processes, and Future Perspectives

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Abstract

The COVID-19 mRNA vaccine is one of the most successful examples of nucleic acid vaccine technology. Rather than directly injecting the viral protein itself, this technology introduces an RNA sequence that encodes the COVID-19 virus's spike protein into human cells. This causes the cells to temporarily produce the antigen, thereby training the immune system to recognize the virus. Since mRNA itself is easily degraded and cannot enter cells on its own, lipid nanoparticles serve as a reliable delivery system for mRNA vaccines. These lipid nanoparticles help to maintain the stability of the mRNA within the body and facilitating its uptake by cells. This article examines the use of lipid nanoparticles for delivery in COVID-19 mRNA vaccines, summarizing their basic composition, the antigen expression process following cellular uptake, the mechanisms of immune activation, large-scale production processes, and their characteristics when compared to conventional inactivated vaccines. Finally, this article discusses the potential for future improvements to this technology in terms of stability, ease of transport, rapid adaptation to viral variants, and broader vaccine development.

Keywords

mRNA vaccine, lipid nanoparticle, COVID-19, immune response, vaccine manufacturing

1. Introduction

The COVID-19 pandemic has spurred rapid development in vaccine technology. Conventional vaccines typically require inactivating the virus or producing viral proteins, which results in relatively long development and manufacturing cycles [1]. In mRNA vaccine, a "blueprint for producing the antigen" is introduced into human cells, enabling the cells to produce the viral antigen on their own within a short period of time. The advantage of this approach lies in the speed of development. Once the genetic sequence of a key viral antigen is identified, it is possible to develop a vaccine candidate in a short period of time [2].

In the case of COVID-19 mRNA vaccines, the most important antigen is the spike protein found on the surface of the coronavirus [3]. The virus uses this spike protein to invade host cells. Therefore, if the immune system recognizes this protein in advance, it can respond rapidly in the event of an actual infection. The greatest challenge facing mRNA vaccines is their delivery method. mRNA is an unstable macromolecule that is easily degraded by enzymes in the body and cannot efficiently penetrate cell membranes [4]. Lipid nanoparticles

(LNPs) have solved this fundamental problem, which transform mRNA from a purely theoretical technology into a vaccine platform capable of large-scale deployment.

The focus of this article is not merely an introductory explanation of the COVID-19 vaccine, but rather the question: "How do LNPs contribute to the effectiveness of mRNA vaccines?" This article provides a step-by-step summary of the structure of LNPs, the process of delivering them into cells, the mechanisms of immune activation, the industrial manufacturing process, differences from inactivated vaccines, and future development directions. The overall process, from manufacturing and delivery to immune activation and future development, is summarized in Figure 1.

2. Basic Design of COVID-19 mRNA Vaccines

2.1 What mRNA Does in the Vaccine

mRNA is a temporary messenger molecule within cells. While DNA stores genetic information, mRNA carries specific information into the cytoplasm and instructs ribosomes to synthesize proteins. The mRNA contained in COVID-19 mRNA vaccines encodes an artificially developed spike protein. After vaccination, this mRNA does not enter the cell nucleus or alter human DNA; instead, it is translated into protein within the cytoplasm and is gradually broken down by the cell.

To make the mRNA more stable and easier for cells to read, the mRNA contained in vaccines typically includes several key structures: the 5'-cap structure helps ribosomes recognize the mRNA; the untranslated regions regulate translation efficiency; the coding region determines which antigen is produced; and the poly(A) tail enhances the mRNA's stability [3]. These structures are not intended to keep the mRNA in the body for a long time, but rather to produce a sufficient amount of antigen in a short period to train the immune system.

2.2 Why the Spike Protein Was Chosen

The spike protein is located on the surface of the virus and plays a crucial role in enabling the virus to infect human cells. When the immune system produces antibodies against the spike protein, it prevents the virus from binding to cell receptors, thereby reducing the risk of infection. Furthermore, the spike protein is processed by antigen-presenting cells and presented to T cells, contributing to the development of a more comprehensive immune response. For this reason, the spike protein has become a primary target in the development of mRNA vaccines against COVID-19.

3. Lipid Nanoparticles as the Delivery System

Lipid nanoparticles are not merely "droplets"; they are small particles composed of various lipids, typically in nano scale. Their primary functions are to encapsulate and protect mRNA, facilitate cellular uptake, and release the mRNA once inside the cell. Typical LNPs usually contain four types of components: ionizable lipids, cholesterol, auxiliary phospholipids, and PEG-conjugated lipids [5]. Each lipid class has a distinct function, and it is only through their combination that a stable and effective delivery system is formed.

Since the cell membrane itself is composed of lipids, which facilitates contact between the LNP and the cell surface. After administration, the LNP is taken up by local tissue cells and immune cells. Typically, cells encapsulate the LNP in small vesicles called "endosomes" [6]. The LNP must then facilitate the release of the mRNA from the endosome into the cytoplasm. Otherwise, the mRNA will be degraded and will be unable to exert its effects. This process is called "endosome escape" and is a major limiting factor in the efficiency of mRNA vaccine administration.

Maintaining the right balance is essential in LNP development. If the lipid particles are too stable, they may hinder the release of mRNA. Conversely, if they are too unstable, the mRNA risks being destroyed before it reaches the cells. High-quality LNPs must strike the right balance between production in vitro, transport, injection, and release within the cell.

4. Immune Mechanisms of COVID-19 mRNA Vaccines

4.1 Antigen Expression and Presentation

When mRNA enters the cytoplasm, the cell synthesizes the spike protein based on the information contained in that mRNA. Some of the spike protein is broken down by the cell into smaller fragments and presented on the cell surface via the major histocompatibility complex (MHC) [7]. This process can be thought of as the cell presenting "characteristic fragments of the virus" to the immune system.

Antigen presentation occurs primarily through two pathways. The first is the MHC-I pathway, in which antigens produced within the cell are presented to CD8+ T cells, enabling them to recognize and eliminate abnormal cells. The second is the MHC-II pathway, which is primarily carried out by antigen-presenting cells such as dendritic cells and helps activate CD4+ helper T cells, which coordinate the entire defense by sending chemical signals (cytokines) to manage other immune cells, including macrophage, B cells and CD8+ T cells Together, these two pathways help the immune system mount both cellular and humoral immune responses against the virus [7].

5. Manufacturing Processes of mRNA-LNP Vaccines

One of advantages of mRNA vaccine is that mRNA templates can be rapidly exchanged than traditional virus culture [2]. Therefore, manufacturing process for mRNA vaccines is more akin to a molecular-level manufacturing. The main steps include preparation of the DNA template, in vitro transcription, mRNA purification, LNP encapsulation, sterile filtration, filling, and cold-chain storage. Since the vaccine is ultimately administered to humans, quality control is essential at every stage to ensure safety, stability, and consistency between batches.

5.1 From DNA Template to mRNA

To manufacture the vaccine, it is first to create a DNA template containing the sequence of the target antigen. In the case of the COVID-19 vaccine, this template contains the genetic information encoding the spike protein. Subsequently, mRNA is synthesized via an in vitro transcription reaction using the DNA template. Since this process can be carried out in a cell-free system that does not require large-scale viral culture, it allows for rapid adaptation to new viral variants.

The mRNA produced by transcription must then be purified to remove unreacted starting materials, short RNA fragments, and other impurities. The quality of this purification affects the vaccine's stability and the immune response. Subsequently, the length, integrity, concentration, and purity of the mRNA must be verified to ensure that the target antigen is being expressed correctly [8].

5.2 LNP Encapsulation and Formulation

After purification, the mRNA must be mixed with lipid components to form LNPs. In industrial production, high-speed mixing methods are typically used; this allows the mRNA and lipids to self-assemble quickly, forming particles of uniform size. Subsequently, the buffer needs to be adjusted, and solvent residues must be removed, after which the particle size, encapsulation efficiency, pH, sterility, and endotoxin content must be tested [5].

The encapsulation efficiency of an LNP refers to the proportion of mRNA successfully encapsulated within the particles. Particle size affects cellular uptake and distribution within the body. If particles are too large, they may become unstable; if they are too small or have an inappropriate composition, the efficacy of the administration may be compromised [6]. Therefore, the manufacture of LNPs goes beyond simply "encapsulating mRNA" and requires precise control of both the formulation and the process.

5.3 Storage, and Distribution

The vaccine must be packaged in vials under sterile conditions and stored at an appropriate temperature. The mRNA vaccines had strict requirements for low-temperature transport, which limited their global distribution [9]. While low temperatures can certainly slow the degradation of mRNA and structural changes

in the LNP, they also increase transportation costs. In the future, if the stability of vaccines could be improved at normal refrigeration temperatures, or even at higher temperatures, it would help increase vaccine availability in various regions.

6. Comparison With Traditional Inactivated Vaccines

Both inactivated vaccines and mRNA vaccines train the immune system, but their design principles differ. For inactivated vaccines, the entire virus is typically cultured and then rendered non-infectious through chemical or physical processes [1]. In the case of mRNA vaccines, however, only the genetic information for the target antigen instead of whole virus is needed. This difference gives mRNA vaccines the advantage of being able to be developed and updated quickly when new infectious diseases emerge.

mRNA vaccines also present their own challenges, such as a high degree of dependence on the delivery system, strict storage conditions, and the need to monitor RNA quality and the consistency of lipid particles during manufacturing [9]. The technological approach for inactivated vaccines is more traditional and is generally better accepted by the general public; however, the production cycle and the speed at which antigens can be updated may be slower. It is therefore not possible to establish a simple "best-worst" hierarchy between these two types of vaccines, as each has its own specific characteristics depending on the circumstances.

The key differences between mRNA vaccines and traditional inactivated vaccines are shown in Table 1.

Table 1: Comparison Between mRNA Vaccines and Traditional Inactivated Vaccines

Aspect	mRNA vaccines	Traditional inactivated vaccines
Basic idea	Give cells mRNA instructions to make viral antigen.	Use killed whole virus as antigen.
Main material	mRNA and lipid nanoparticles.	Inactivated virus and adjuvant.
Antigen source	Antigen is made inside host cells.	Antigen is provided directly by the vaccine.
Delivery system	Lipid nanoparticles help mRNA enter cells.	No special intracellular carrier is usually needed.
Immune response	Activates antibodies and T cells.	Mainly activates antibody responses.
Production speed	Fast after the viral sequence is known.	Slower because virus culture is needed.
Variant update	mRNA sequence can be changed quickly.	New virus strains may need new production steps.
Storage	Often needs low-temperature storage.	Usually easier to store.
Main advantage	Fast design and strong immune activation.	Mature technology and stable production.
Main limitation	mRNA is unstable without protection.	Updating the vaccine is less flexible.
Safety focus	Control inflammation and mRNA stability.	Ensure complete virus inactivation.

7. Future Perspectives

One of the key challenges in future mRNA vaccine research is improving their stability. The introduction of more stable mRNA sequences, optimized LNP formulations, and freeze-drying processes could reduce reliance on the cold chain. This is particularly important for regions with limited medical resources. If vaccines can be stored for longer periods under normal refrigeration conditions, transportation, storage, and administration will become easier.

COVID-19 has demonstrated that the mRNA-LNP platform can be deployed on a large scale in real-world public health emergency. In the future, this platform may continue to be utilized in the development of vaccines against other infectious diseases, as well as personalized vaccines for cancer [10]. mRNA provides information about the antigen, while LNP plays the role of reliably delivering that information to target cells. Although the specific information used varies depending on the disease, the principles of administration and manufacturing remain the same.

In future vaccine development, vaccination experience and safety must also be taken into account [10]. For example, researchers may optimize lipid composition to suppress unnecessary inflammatory responses or explore more comfortable routes of administration, such as intranasal spray vaccines and other mucosal immunization strategies. The nasal cavity and airways serve as entry points for many viruses into the human

body. Establishing stronger local defenses in these areas could further enhance vaccine efficacy. However, the effectiveness of such approaches must be demonstrated through further research.

8. Conclusion

The success of mRNA vaccines against COVID-19 is not only based on mRNA itself but also on the development of the lipid nanoparticle (LNP) delivery system. After vaccination, cells express the spike protein, and the immune system builds defenses through antigen presentation, T-cell activation, B-cell maturation, and the formation of memory cells.

From a manufacturing technology perspective, mRNA-LNP vaccines offer advantages such as rapid development, modular processes, and adaptability to rapid updates; however, they also face challenges related to stability, the cold chain, quality control, and ensuring a global supply. In the future, through improvements in mRNA sequences, optimization of LNP formulations, enhanced storage stability, and the development of more practical administration methods, mRNA vaccines are likely to become a critical platform in the fight against emerging infectious diseases and other illnesses. Overall, LNP delivery technology is key to understanding COVID-19 mRNA vaccines and represents one of the central directions for the future development of nucleic acid vaccines.

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Conflicts of Interest

The authors declare no conflict of interest.

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