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Research Progress and Application Mechanism Analysis of mRNA Vaccines

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Abstract. The mRNA vaccine technology, as a groundbreaking advancement in modern medicine, is promoting the innovation of infectious disease prevention and treatment interventions in a rapid and adaptable manner. In recent years, the successful application of mRNA vaccines in the COVID-19 pandemic has further accelerated research and expansion in areas such as tumor treatment, tropical disease control, and individualized immunotherapy. The current research has made significant progress in mRNA sequence design optimization, improvement of lipid nanoparticles (LNPs) delivery systems, and scale-up of production processes. Multiple clinical trials have demonstrated positive prospects in the development of cancer neoantigen vaccines and mRNA vaccines for diseases such as malaria and tuberculosis. However, scientific, logistical, and regulatory obstacles still limit the widespread application and equitable accessibility of such vaccines. This article systematically analyzes the mechanism of action of mRNA vaccines, the current application status in tumors and infectious diseases, the expansion paths of platform technologies, as well as the challenges faced in immunogenicity, storage stability, manufacturing capacity, and intellectual property rights. Through the analysis of typical clinical cases, this article summarizes the advantages and disadvantages of current mRNA vaccine strategies and points out the key directions for future innovation. Research shows that optimization of delivery systems, development of heat-stable formulations, and construction of local production capabilities will be the key to ensuring the global promotion and long-term success of mRNA vaccines.

Keywords: mRNA vaccine, Immunotherapy, Neoantigen cancer vaccine, Global vaccine equity

1. Introduction

mRNA vaccines represent a breakthrough innovation in contemporary immunology that has transformed the core process of vaccine development and administration, particularly during the COVID-19 pandemic. In contrast to conventional vaccines that utilize inactivated viruses or protein subunits, mRNA vaccines provide host cells with instructions to produce certain antigens associated with pathogens, thereby inducing adaptive immunity in a regulated and efficient manner [1]. The pandemic situation resulted in the emergency deployment of two novel mRNA vaccines, Pfizer–

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BioNTech's BNT162b2 and Moderna's mRNA-1273. They were found to be extremely efficacious—over 90% against symptomatic COVID-19 in trials, opening a new era in vaccine science [2].

The platform's distinctive characteristics, including its modularity, production speed, and synthetic origin, differentiate it from traditional vaccine strategies. The mRNA technology can be rapidly modified to combat various pathogens, allowing for a responsive creation in the event of the emergence of new variants or future pandemics. Furthermore, the application of lipid nanoparticle (LNP) technology has been successful in addressing issues of mRNA stability, delivery to cells, as well as immunogenicity [3]. The development of mRNA technology has expanded the potential uses of mRNA vaccines well beyond the confines of COVID-19. Ongoing research activities are aimed at the application of these methods for the prevention of diseases such as influenza, HIV, Zika virus, and tuberculosis, and their potential application in personalized oncology [4].

Prior studies have already determined that the efficacy of mRNA vaccines is not equal in all demographic groups. To be precise, Collier et al. reported reduced immunogenic response in older individuals and the immunocompromised, which suggests the necessity of specifically tailored interventions for these populations in particular [5]. In addition, Andrews et al. reported the natural decline of vaccine immunity with time, which suggests the necessity of booster vaccinations and antigenic evolution in a continuous fashion to maintain herd immunity [6].

This research aims to present a detailed examination of the current state of mRNA vaccines. First, it will demystify the fundamental working principles of these vaccines and compare them to conventional vaccine technologies. Next, the study will assess their contemporary clinical effectiveness and discuss future prospective uses in oncology and infection. Second, the article will address ongoing worldwide access challenges and ethical implications of distribution and fairness. Lastly, it will address innovation opportunities, including the potential union of mRNA and AI-based design platforms and universal vaccine platforms.

2. Mechanism and scientific foundation of mRNA vaccines

2.1. The working principle of mRNA

mRNA vaccines are a new immunization platform that is totally different from traditional vaccines, which induce an immune response by inactivated pathogens or protein subunits. Instead, mRNA will deliver mRNA encoding for viral antigens directly into the host cell to produce target antigens by using the host cell's machinery. When the synthetic mRNA encoding for viral antigens comes into the cytoplasm, the ribosomes in the host cell will translate the mRNA into the corresponding encoded protein antigen. Some antigens will subsequently be presented on the cell surface through major histocompatibility complex (MHC) molecules, thereby activating T cell responses. Other antigens are released extracellularly in a secreted form, which are then recognized by B cells and trigger an antibody response [1].

To enhance the stability and translation efficiency of mRNA, some nucleotide modifications, such as pseudouridine and N1-methylpseudouridine, have been introduced into the molecule by researchers. Modifying nucleosides is able to reduce innate immune recognition and inflammatory responses [3]. In addition, mRNA is usually stored and sealed in Lipid nanoparticles (LNPs) because this structure can not only protect mRNA from enzymatic degradation, but it also helps facilitate cellular uptake and endosomal escape [3].

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2.2. Key differences with traditional vaccines and the advantages and disadvantages of mRNA vaccines

mRNA vaccines have several differences compared with traditional vaccines, and it has become a powerful alternative to traditional vaccines. Its particular features, like safety, high potency, and good efficacy with the ability for quick clinical development, all demonstrate that mRNA is a perfect developing area for future deeper study [7]. Due to its characteristics, such as being easy to produce, low cost, it is an ideal and suitable choice during the pandemic [8]. Moreover, unlike traditional vaccines, the mRNA technology enables precise antigen engineering design: it can express stable "native-like" structural proteins, effectively expose key antigenic epitopes, and even combine multiple pathogen antigens into a single vaccine formulation.

However, mRNA vaccines still have several challenges. Heavily depending on ultra-cold chain logistics makes the durability and breadth of immunity a serious problem. Some studies point out that extensive use of nucleoside-modified mRNA (nms-mRNA) could induce epigenetic or genomic alterations, although there is no direct evidence to support this risk [7]. There are also concerns about ethics and fairness because IP ownership, LNP delivery rights, and manufacturing capacity limit mRNA vaccine distribution in low- and middle-income countries.

3. Clinical applications in infectious diseases

3.1. Case comparison: Pfizer BioNTech (BNT162b2) and Moderna (mRNA 1273)

In the COVID-19 vaccine clinic, Pfizer BioNTech (BNT162b2) and Moderna (mRNA 1273) are the representative examples of mRNA vaccine platforms. They share the same platform technology but differ in dosage, lipid nanoparticle encapsulation formulation, and storage conditions. BNT162b2 contains 30 micrograms of nucleoside-modified mRNA per dose, whereas mRNA-1273 utilizes 100 micrograms. When comparing vaccine efficacy among various subgroups of the population, the discrepancy between Pfizer and Moderna in persistence became more apparent. In a matched cohort study conducted on American veterans, the study indicated that Moderna exhibited greater vaccine efficacy in all age groups, particularly the elderly aged 65 years and older. More than 120 days following the vaccination, Moderna's efficacy in warding off COVID-19 hospitalization was 86%, whereas that of Pfizer was only 75% [9]. The CDC's study also indicated that the neutralizing antibody titers among Moderna recipients were consistently higher compared to Pfizer recipients and that the difference was especially obvious in the elderly and immunocompromised individuals [10].

The occurrence of variant strains of the novel coronavirus demonstrates the impact of viral mutations on the effectiveness of mRNA vaccines. By noting the data, Moderna has superior effectiveness against the variants. During the Delta variant prevalence, Moderna's breakthrough infection rate was 3.5 cases per thousand individuals and that of Pfizer was 6.5 cases per thousand individuals [10]. Collier et al. indicated in a study that serum induced by Moderna has wider neutralizing capacity against the Delta and Beta variant strains [5]

3.2. Effectiveness across population subgroups

The efficacies of mRNA vaccines are different among different age groups, immune statuses, and individuals with underlying diseases. Scientists found that although the overall protection rate is high, the immune responses of elderly people and people with weakened immune functions are

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generally weaker [5]. The reason for this phenomenon is that the functional impairment or suppression of the immune system in these people. Neutralizing antibody titers and CD4+ and CD8+ Tcell responses of patients who are 75 years old or more than that are much lower than in younger adults [5]. This means that as people age, the response capabilities of B cells and T cells decline, which affects the efficacy of vaccines or similar drugs in the elderly population. A large-scale study conducted in the UK shows that individuals who have compromised immune systems (such as organ transplant recipients and cancer patients) have significantly lower protection against severe COVID-19 after receiving two doses of mRNA vaccines compared to the general population. The protective efficacy of vaccines for individuals who have weakened immune systems is approximately 60% against severe cases, which is significantly lower than the protective efficacy of the immunocompetent population (over 90%) [6].

3.3. Impact of viral mutations

Because of the continual evolution of the novel coronavirus and the rapid emergence of multiple variants such as Alpha, Beta, Delta, and Omicron, the mRNA vaccines are facing unprecedented challenges in immune evasion. Some studies pointed out as early as ten years ago that the flexibility of the mRNA platform can cope with mutant viruses, but the variations still may lead to a decrease in antibody affinity [1]. Collier et al. (2021)'s study further confirmed that different variants have different effects on the neutralizing ability of antibodies. For example, the neutralizing ability against the Beta and Delta variants was significantly lower than that of the original strain, especially after a single vaccination [5].

Nevertheless, the feature, which is rapid reprogramming of mRNA vaccines, offers tremendous potential for vaccine updates.

4. Potential applications of mRNA vaccine platforms

4.1. Cancer vaccine progress

Though mRNA vaccine technology was first used in infectious disease prevention and control, its potential application in oncology is also highly anticipated. The mechanism of mRNA cancer vaccines involves delivering synthetic mRNA that encodes tumor-associated antigens into host cells, primarily dendritic cells (DCs). These DCs then present the antigens via MHC I and II molecules, which leads to the activation of $CD8^+$ cytotoxic T lymphocytes and $CD4^+$ helper T cells, thereby facilitating targeted immune responses against tumor cells [11]. The core advantage of using mRNA vaccines to treat cancers lies in their ability to rapidly encode tumor-specific antigens, especially neoantigens, which are unique mutated proteins present in specific patients' tumors, and they can enable personalized cancer treatment [3]. A milestone in this area was the KEYNOTE-942 clinical trial which is an open-label, randomized controlled IIb phase study that included 157 patients with completely resected IIIb-IV stage melanoma. This clinical trial tested the personalized cancer vaccine mRNA-4157/V940 in combination with the checkpoint inhibitor pembrolizumab in melanoma patients. Among all the participating patients, 107 patients received treatment with mRNA-4157 combined with pembrolizumab, while 50 patients received only pembrolizumab monotherapy [12].

The individualized neoantigen cancer vaccine mRNA-4157/V940 can encode up to 34 patient-specific neoantigens. These antigens are determined through algorithmic screening of the exonome and HLA typing of each patient's tumor, and then administered intramuscularly using LNPs

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encapsulation, concurrently with pembrolizumab, with a maximum of 9 injections [3]. The results showed that the combination therapy reduced the risk of tumor recurrence or death by 44% compared with using pembrolizumab alone.

However, there are still challenges using mRNA vaccines to treat cancers. Because of the heterogeneity of tumors, the immune escape mechanisms, and the complex microenvironment, all limit the efficacy of vaccines. Moreover, unlike viral antigens, cancer antigens are mostly "self-antigens", so how to break through immune tolerance remains a key problem [1].

4.2. Other infectious diseases

Apart from cancer, mRNA vaccine technology is also rapidly advancing in the fields of infectious diseases such as malaria, tuberculosis and HIV. This type of vaccine is composed of stable envelope mRNA transcripts, including an optimized 5' cap, 3' poly(A) tail and non-translated regions, to enhance translation efficiency and RNA stability. The expressed antigen can trigger a strong humoral immune response and cellular immune response, which is crucial for combating pathogens that invade cells, such as Mycobacterium tuberculosis and HIV [4]. The latest research on mouse models shows that the LNP-mRNA vaccine has a significant protective effect against tuberculosis and the ability to activate T cells [13]. These research results have laid a solid foundation for advancing mRNA vaccines to clinical trials, demonstrating their extensive potential as a new generation of technologies for combating global infectious diseases.

5. Real-world barriers and ethical issues

5.1. Challenges in the cold chain and manufacturing

One of the main scientific obstacles in the promotion of mRNA vaccines is their reliance on an ultra-low temperature cold chain storage and transportation system. Unmodified mRNA molecules are extremely unstable and are easily degraded by RNase enzymes. Therefore, many mRNA vaccines must be stored at -80°C to maintain their structure and biological activity. However, this is particularly difficult to achieve in areas with limited resources or in tropical regions [3]

Furthermore, the production process of mRNA vaccines encapsulated in LNPs also faces challenges related to large-scale production. The current technology depends on advanced microfluidic mixing systems and accurate regulation of the lipid-to-mRNA ratio. During large-scale manufacturing, maintaining such precision necessitates the use of high-cost equipment and rigorous quality control measures, which collectively result in substantial production issues and impede the rapid scaling of production capacity to meet the demands posed by global epidemics or infectious disease outbreaks [1].

5.2. IP barriers and global inequality in vaccine distribution

The technology property rights system is a major obstacle hindering fair global access to mRNA vaccines. During the COVID-19 period, pharmaceutical companies applied for hundreds of related patents for COVID-19 vaccines, enabling them to control production and exclude competitors, even in middle-income countries [14]. Although several LMICs supported the TRIPS exemption proposal in the WTO, merely relaxing the laws cannot solve the problem of unequal distribution and use of mRNA vaccines worldwide, because the vast majority of vaccine production capacity is concentrated in high-income countries. LMICs lack infrastructure, regulatory capabilities and production technologies, and even if IP restrictions are lifted, it is impossible to effectively produce

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vaccines [14]. These inequalities caused by IP result in severe unfairness in vaccine access: high-income countries prioritize purchasing and even waste a large number of early vaccines, while LMICs can only obtain very small doses of vaccines at critical stages. To bridge this gap, in addition to relaxing IP, LMICs must also enhance local production capacity, train the workforce, and improve the construction of regulatory systems to achieve effective technology transfer and production autonomy.

6. Innovation directions and future prospects

The main innovation directions of mRNA therapy focus on modularization of the platform, optimization of the delivery system, and the use of intelligent design methods. Firstly, the inherent advantages of mRNA synthesis, such as cell-free nature, scalability, and rapid response, provide a highly flexible platform for the development of multi-target vaccines and the response to emerging pathogens [15]. Secondly, the lipid nanoparticle (LNP) delivery system is continuously being optimized. By developing new ionizable lipids and custom lipid combinations, organ-specific delivery can be achieved and endosome release efficiency can be enhanced, thereby improving the safety of the vaccine and expanding the targeting range beyond the liver limitations [16]. Thirdly, the emerging machine learning-assisted optimization technology is being used for mRNA sequences, such as the Linear Design algorithm for optimizing non-translated regions and coding regions, and the intelligent design of LNP formulations, to enhance stability, translation efficiency, and delivery performance [17]. In conclusion, these technological advancements indicate that future mRNA vaccine platforms may be able to achieve computer-assisted customized design, localized rapid manufacturing, and efficient and precise tissue delivery capabilities. This will not only expand the disease coverage of vaccines but also potentially achieve the ideal vision of global fair vaccination through regional production modules. These innovations collectively laid the foundation for the development of the universal mRNA vaccine platform, which can rapidly adapt to various pathogens through modular design, while ensuring consistent performance and manufacturability across different disease targets [3].

7. Conclusion

This article systematically reviews the current status and future prospects of mRNA vaccine technology, covering its basic mechanism of action, clinical applications in tumors and infectious diseases, platform expansion, as well as the key challenges faced in scientific and global applications. Through the case study of mRNA-4157 in cancer immunotherapy and the exploration of cutting-edge vaccines for infectious diseases such as malaria and tuberculosis, we demonstrate the diversity and transformative potential of mRNA vaccines in modern medicine. The research results emphasize the importance of mRNA vaccines in rapidly responding to pandemics and their far-reaching significance in re-constructing long-term disease prevention and treatment strategies. Through an analysis of the advantages and disadvantages of existing platforms, this article provides valuable references for optimizing antigen design, improving delivery systems, and addressing global vaccine accessibility disparities. However, the development of mRNA vaccines is still constrained by factors such as cold chain logistics, limited manufacturing scale, and intellectual property barriers, especially in countries with limited resources, and the promotion of mRNA vaccines is severely restricted. Additionally, the limitations of this article include the lack of clinical research data in some disease areas. For the future developments, research should focus on

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improving the thermal stability of mRNA vaccines, expanding regional production capacity, and promoting fair technology transfer mechanisms.

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