Proceedings of the 3rd International Conference on Biological Engineering and Medical Science
DOI: 10.54254/2753-8818/21/20230839

Revolutionizing vaccinology: The rise of mRNA vaccine

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Abstract. The public health sector has been greatly affected by the COVID-19 pandemic, and vaccines have become a crucial means of managing the virus. mRNA vaccines have gained prominence among the available vaccines due to their effectiveness and safety, marking a significant advancement in the field of biotechnology. Traditional vaccines have often resulted in severe symptoms and partial protection, while newer recombinant vaccines have significant drawbacks. In contrast, mRNA vaccines offer unprecedented cost-effectiveness, safety, and high efficacy per dose. The mRNA vaccines transport bioengineered mRNA to the human body, which translates into proteins that stimulate the immune response. However, there are some challenges associated with the development and production of mRNA vaccines, such as efficient delivery and maintaining the integrity of the mRNA molecule during storage and delivery. Despite these challenges, mRNA vaccines represent the future of vaccinology and the first line of defense against major infectious diseases. This paper explores the structure, mechanisms, immunology, and related areas of study concerning mRNA vaccines. The paper emphasizes the challenges in developing and producing mRNA vaccines and potential solutions to overcome these challenges.

Keywords: mRNA, vaccines, COVID-19 pandemic.

1. Introduction

As the COVID-19 pandemic swept across the globe, healthcare professionals and medical experts increasingly relied on vaccines to contain the spread of the virus. Notably, the pandemic witnessed the development and licensure of the first mRNA vaccines, heralding a new era in immunology. It is worth noting that the first conventional vaccine was developed by Dr. Edward Jenner in 1796. Dr. Jenner discovered that individuals with cowpox did not contract smallpox and subsequently inoculated an eight-year-old boy named James Phipps with a crude vaccine. This event marked the first successful human vaccination, resulting in Phipps' immunity to smallpox [1]. Since the development of the first vaccine, vaccination technology has evolved considerably, with enhanced efficacy and fewer side effects. Conventional vaccines, including live, live-attenuated, or killed vaccines, have often resulted in severe symptoms while only providing partial protection. In contrast, newer recombinant vaccines, such as DNA, subunit, and virus-like particle vaccines, have demonstrated improved efficacy but have significant drawbacks, such as the need for complementary adjuvants to maintain efficacy and the potential for adverse effects. During the COVID-19 pandemic, mRNA vaccines demonstrated their revolutionary potential in biotechnology, offering unprecedented cost-effectiveness and safety. Among the key benefits of mRNA vaccines are their excellent safety profile, ease of production, high efficacy

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per dose, flexibility in adjuvant usage, and rapid response time to emerging variants. mRNA vaccines transport bioengineered mRNA to the human body via various transportation vessels or as a naked vaccine. Once inside the body's cells, the mRNA translates into proteins, which express themselves on extracellular major histocompatibility complex (MHC) complexes and stimulate the human immune response [2]. However, there are some challenges associated with the development and production of mRNA vaccines. One of the main challenges is the requirement for an efficient delivery system, which can be achieved by using lipid nanoparticles. Besides, the lipid nanoparticles used for mRNA vaccine delivery may result in potential side effects. Another challenge is the need to maintain the integrity of the mRNA molecule during production, storage, and delivery, which can be influenced by factors such as temperature, pH, and enzymatic degradation. Despite these challenges, mRNA vaccines represent a major breakthrough in the field of vaccinology. Overall, mRNA vaccines represent the future of vaccinology and the first line of defense against major infectious diseases. This paper will explore the structure, mechanisms, immunology, and related areas of study concerning mRNA.

2. Different types of mRNA vaccines

mRNA vaccines are a new type of vaccine technology that has gained significant attention during the COVID-19 pandemic. They have demonstrated high efficacy and safety profiles and have quickly become the cornerstone of vaccination efforts worldwide. There are three main types of mRNA vaccines: non-replicating mRNA, self-amplifying mRNA (saRNA), and circular RNA (circRNA). (Figure 1)

Non-replicating mRNA is the most widespread and maturely developed type of mRNA present in mRNA vaccines. Similar to natural mRNA, non-replicating mRNA encodes the target antigen and has 5 prime and 3 prime untranslated regions (5’ and 3’ UTRs). These regions help in the stability and translation of the mRNA molecule. Non-replicating mRNA is translated into the target protein antigen by host cell ribosomes and is then presented on the extracellular membrane via MHC I and II complexes, leading to an immune response [3-4].

saRNA is an alternative to non-replicating RNA that contains not only the genetic information for the virus’ antigen but also the information for replication. This genetic code allows saRNA to replicate within the cytoplasm of the host cell. Intracellular replication comes the benefit of increased mRNA translation efficiency and extensive protein expression, resulting in higher efficacy compared to non-replicating RNA. Compared to traditional non-replicating RNA vaccines, the ability of saRNA to self-amplify gives it the advantage of producing higher levels of viral antigen of vaccine origin, allowing for a lower dose, and looser requirements for delivery system efficiency [5].

In terms of safety, both saRNA and non-replicating RNA vaccines have risks for excessive inflammation, but of different causes. Lasting saRNA and continued production of antigen could imbalance the normal function of host cells. Comparatively, unmodified non-replicating mRNA may elicit a type-I interferon response, resulting in critical inflammation. Due to the requirement for an efficient delivery system, components built by lipids and nucleosides of foreign origin may result in potential symptoms [5].

Circular RNA (circRNA) is a newly discovered type of mRNA that requires additional study and refinement. This form of non-coding RNA has a unique looped structure that provides increased structural durability and greater resilience against degradation when compared to other types of mRNA. The intricate secondary structure of circRNA may impact the efficiency of the vaccine. Advantages of circRNA over any linear RNA vaccine include a more relaxed requirement on transportation, storage, and production environments due to the closed-loop structure of circRNA. This allows the vaccine to be transported and stored in a wider variety of locations, potentially lowering the cost of production. SARS-Cov-2-targeting circRNA vaccines have demonstrated the capability to produce potent and functional viral antigens, making it a promising vaccine technology against infectious diseases [6-7].

mRNA vaccines have revolutionized the field of vaccinology and have significant advantages over traditional vaccines. They provide high efficacy per dose, a desirable safety profile, ease of production,

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and high flexibility with regard to adjuvant usage. mRNA vaccines are the future of vaccinology and will serve as the first layer of armor in the defense of major infectious diseases.

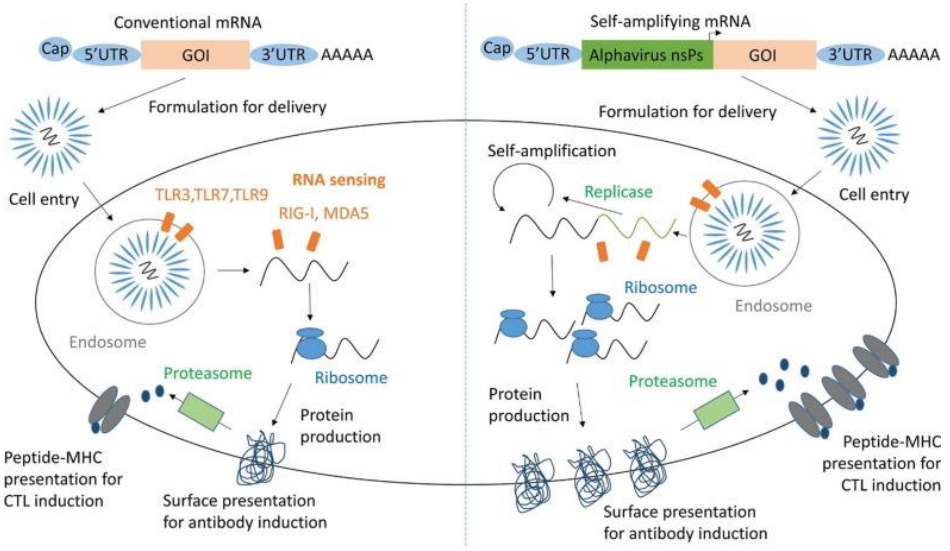

Figure 1. Structure of different types of mRNA [4].

3. mRNA vaccines macunfacturing

mRNA vaccines have become a critical tool in the fight against infectious diseases, and their production process has been the subject of intense research and optimization. The mRNA manufacturing process involves two main steps: upstream processing and downstream processing, followed by a final packaging process. The upstream processing step involves the production of mRNA utilizing RNA polymerase and subsequent enzymes, while the downstream processing step involves the purification and quality control of the produced mRNA. A final packaging process follows, where mRNA is packaged into lipid nanoparticles or alternative delivery vessels.

The manufacturing process plays into the superior safety profile of mRNA vaccines. As the production process excludes cell cultures and any unprocessed materials of animal origin, mRNA vaccines do not include lipopolysaccharides, cellular or foreign impurities, making it safer. Compared to other complex biologicals, the short manufacturing period further lowers risks of contamination.

Upstream processing constructs the mRNA of interest with in vitro transcription (IVT). IVT depends on a series of reactions between RNA polymerases, a linear DNA template, and nucleotide triphosphate substrates. T3, T7, or SP6 RNA polymerases are utilized to catalyze the manufacturing of intended mRNA strands from the previously produced complementary linear-DNA template in IVT.

There are two distinct ways of approaching mRNA capping: The first capping process is executed at the time of IVT, replacing a fraction of the guanosine triphosphate with a cap analog. An alternative capping process involves establishing an independent enzymatic reaction, employing the vaccinia capping enzyme (VCC) and a methyl-donor substrate to cap the mRNA. This alternative capping method guarantees a successful cap with higher efficiency.

The purification process is vital for the mRNA vaccine to meet clinical-grade purity standards. Enzymatic compounds, nucleotides, nucleosides, and DNA templates must be excluded from the final product to avoid triggering acute host immune responses. The purification process has a significant impact on the economy of the entire production process, as the downstream process is a delicate balance between mRNA quality and cost.

The cost of manufacturing mRNA vaccines is largely dependent on the production strategies. Further research and optimization are needed for a more cost-efficient production system. The costs of five prime cap analogs and modified nucleotides also play a role. Essentially, expenditure concerning

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mRNA production has significant correlations with the quantity of RNA per dose of vaccine, production scale, and production titers.

In conclusion, the optimized manufacturing process has played a significant role in the success of mRNA vaccines, with the process being safe and highly specific. Further research and optimization of the production process will likely lead to more cost-effective and widely accessible vaccines [8].

4. Mechanism of mRNA vaccines

The mRNA vaccine has indeed shown remarkable efficacy in combating the COVID-19 pandemic. However, as the virus continues to mutate, it is important to understand the underlying mechanisms of the mRNA vaccine in order to further develop and modify it.

The mRNA component of the vaccine is crucial in inducing an immune response, and selecting the appropriate antigen is key to producing effective antibodies against the targeted virus. In the case of the SARS-CoV-2 vaccine, the mRNA contains the full sequence of the spike (S) protein, which is found protruding from the surface of the virus and is responsible for recognizing and fusing with host cells. The genetic sequence of the antigen is modified with prolines to increase its stability [8].

Once the mRNA vaccine enters the host cell, it is released from the lipid nanoparticles and is translated by ribosomes to form proteins. As showing in Figure 2, these proteins can take two different paths: they can either be fragmented by proteasomes and expressed as the antigens that delivery to the rough endoplasmic reticulum and are captured by MHC class I peptide, presenting to $CD8^+$ T lymphocytes; or they can be expressed as exogenous proteins which will be carried by maturing antigen-presenting dendritic cells and travel to lymph nodes.

B cells will be further stimulated to produce antibodies that target the antigen encoded in the mRNA strand. These free-moving antibodies are the key to achieving immunity against antigenic infections. The $CD8^+$ T cell immune response is instantaneous, while the B cell response takes longer to develop and provides long-term protection [9-10].

Understanding the underlying mechanisms of the mRNA vaccine is crucial for further development and modification to combat evolving viruses. The selection of antigens, optimization of the manufacturing process, and exploration of new delivery systems are all areas of ongoing research in the development of mRNA vaccines.

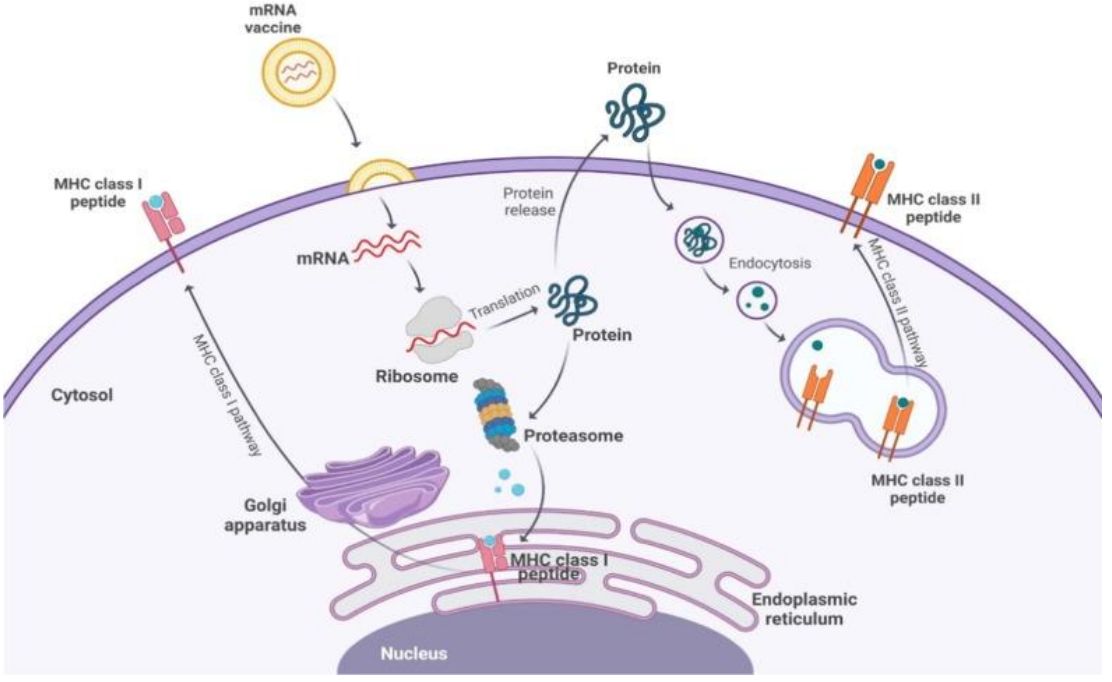

Figure 2. Schematics of mRNA vaccines stimulating immune response path [2].

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5. Conclusion

mRNA vaccines have proven to be highly effective in combating the COVID-19 pandemic. However, there are several limitations that are hindering their widespread use. One major setback is the instability of the mRNA molecule, which is highly fragile and prone to rapid degradation if exposed to temperatures outside of its preferred storage conditions. This limits the real-world applications of mRNA vaccines, as maintaining the necessary storage conditions is economically unachievable in many regions around the globe.

Another critical weakness of mRNA vaccines is the relatively high dosage volume and the need for several doses to achieve bodily immunity. This places a high demand for patient compliance, which can be challenging to achieve in various political areas globally. Patients often have to pay out-of-pocket for vaccines, and market pricing plays a significant role in limiting accessibility. The cost of production, facility, research and development funding, transportation, storage, commercial, marketing, and profit margins all contribute to the final price. Estimates put the cost of the Pfizer vaccine at $38 per patient, while the Moderna vaccine ranges from $30 to $50. These costs can be prohibitive for many individuals, particularly in regions where public sector assistance is limited.

Furthermore, compared to other vaccines, the out-of-pocket cost for patients is still somewhat higher, limiting accessibility to the vaccine. As these vaccines travel further from their manufacturing plants, their prices only increase. This places additional burdens on individuals who are left out of insurance or government care, making it more difficult for them to attain doses of the vaccine.

The limitations placed on mRNA vaccines are preventing them from becoming an accessible pharmaceutical that is highly capable of immunizing patients. Research on stabilizing mRNA structures and superstructures that can help mRNA molecules obtain higher structural integrity can solve many of the issues listed above. Maturing the production pipeline can also help reduce the manufacturing costs of mRNA vaccines, making them more accessible to a wider population.

Overall, mRNA vaccines represent a revolutionary idea of what a vaccine can achieve. They bring innovation to biotechnology, and there are high hopes for their potential in treating and preventing other diseases. However, until the limitations discussed above are addressed, their widespread use will remain limited. It is crucial to focus on finding solutions to these limitations to ensure that mRNA vaccines can reach a broader population and have a significant impact on global public health.

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