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mRNA Vaccine for Infectious Disease Prevention and Cancer Immunotherapy

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Abstract. The recent rapid advance in biotechnology has enabled the therapeutic use of messenger RNA (mRNA) to fight against a wide range of viral diseases and cancers. The development of mRNA vaccine and mRNA therapeutic agent showed extraordinary potential in safety, efficacy, and industrial production. One of the most effective preventive measures against unexpected, widespread outbreaks of infectious illnesses, like the pandemic coronavirus sickness that is presently raging, is the use of mRNA vaccines (COVID-19). It took decades for scientists to make the mRNA vaccine an applicable approach for medical use due to the stability and delivery of mRNA. Although the previous challenges were overcome, scientists still intended to further improve the stability, immunogenicity, delivery systems, and translation efficiency of mRNA into the body to make mRNA technology even more powerful in both preventative and therapeutic use. Encouraging results showed that the mRNA vaccine is a tremendous platform against infectious diseases and cancers, which is a new era in vaccinology and oncology. This study concentrated on a thorough overview of mRNA vaccine development, including a basic explanation of the mechanism of action of mRNA vaccines, various delivery techniques, present obstacles, and future prospects of mRNA vaccines for both preventive and therapeutic purposes.

Keywords: mRNA, Vaccine

1. Introduction

One sort of vaccination that uses mRNA to start the immune response is the mRNA vaccine. The adaptive immune response that targets the particular proteins to eradicate the pathogen or cancer cells is stimulated by the mRNA, which can code for proteins generated by a pathogen like a virus, or by a cancer cell [1].

Vaccinations prevent millions of people from becoming sick and save countless lives every year. As a result of widespread vaccination, the smallpox virus has been completely eliminated, and the frequency of polio, measles and other pediatric infections has greatly dropped internationally [2]. Despite the fact that conventional vaccinations are efficient at preventing illnesses, the necessity for more rapid and widespread deployment presents a more difficult challenge. Additionally, the traditional vaccination might not be effective in treating non-infectious disorders like cancer [3]. The key difference between the traditional vaccine and mRNA vaccine is the way of introducing antigens into the body. Traditional vaccines use live-attenuated pathogens, killed pathogens, subunits of pathogens, or using viral vectors to deliver instructions to the cells. These processes are time-consuming as the pathogens should be made

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weakened enough to trigger an immune response without causing disease. Instead, the mRNA vaccine uses the receivers' cells to make the viral antigens by themselves, which is safer and more efficient than the traditional vaccines. People can make new mRNA vaccines without a sample of the pathogen, but only the sequence of antigen instead. Furthermore, the mRNA vaccine does not require adjuvants which enhance the immune system's response and attract the right immune cells [4]. Consequently, mRNA vaccines have several benefits over conventional immunizations, which mainly include the simplified design process and improved speed of production. The promise of mRNA vaccines, which provide strong protection against COVID-19 induced by infection with severe acute respiratory syndrome coronavirus 2, was revealed during the coronavirus pandemic (SARS-CoV-2). The two mRNA vaccines for COVID-19 prevention authorized by the FDA are from Pfizer-BioNTech and Moderna. Starting July 2022, more than 12 billion vaccine doses had been given out globally, acting as a significant barrier to the virus's spread [5].

Apart from prophylactic treatment, the mRNA vaccine has been shown to be capable of treating cancer as a type of immunotherapy. Cancer immunotherapies have become a hotspot in cancer treatment research. The U.S. Food and Drug Administration (FDA) has approved many types of cancer immunotherapies, including checkpoint blockade modulators and chimeric antigen receptor (CAR)-T cell immunotherapies, and the mRNA vaccine immunotherapy is considered the next surge of approval according to its promising efficacy and safety shown by recent clinical trials [6]. The specificity, safety, and tolerability of cancer vaccines are higher than those of other immunotherapies as their targets, tumor-associated antigens (TAAs) or tumor-specific antigens (TSAs) are specifically attacked by the overexpress of the antigens and form immunologic memory which triggers the chronic therapeutic response. The cancer vaccines can be divided into two classes, prophylactic cancer vaccines which are given to healthy people to prevent future disease, and therapeutic cancer vaccines which are given to treat existing malignancy [7]. Recently, the FDA authorized two cancer vaccines for preventative use, the one targeting the hepatitis B virus which accounts for liver cancer, and another one targeting the human papillomavirus (HPV) which causes 70% of cervical cancers [8]. As for therapeutic cancer vaccines, the Sipuleucel-T (PROVENGE; Dendreon) is the first one approved by FDA in 2010 [9]. In addition to these early accomplishments in prophylactic and therapeutic cancer vaccines, a variety of customized cancer vaccines were created in combination with cytokine therapies or checkpoint blockade modulators, which also showed encouraging clinical outcomes [10]. However, the delivery of mRNA into cells remains a problem, and Several methods to increase mRNA translation efficiency and reduce innate immunogenicity through modifications of the synthesized mRNA strands have been established via ongoing research [11].

This review introduced the development of mRNA vaccine from its discovery to entering the market, demonstrates the basic pharmacology of mRNA vaccine including the general mechanism and its efficacy and safety evaluations, and summarizes the current clinical applications and existing challenges of mRNA cancer vaccines, as well as the potential benefits of using an mRNA vaccine in the future to reduce the burdens of cancer immunotherapies.

2. Development of mrna vaccine

After the discovery of mRNA in 1961 by Brenner et al., it took decades of research to make the mRNA vaccine work [12]. In 1971, lane et al. pioneered the transfer of mRNA into eukaryotic cells. During their study of hemoglobin synthesis, they successfully put hemoglobin mRNA from rabbit reticulocytes (9S RNA) into Xenopus laevis oocytes egg cells through microinjection [13]. They found that the oocytes produced the rabbit version of hemoglobin because of the injection of mRNA [14]. This success led to a series of similar experiments which ultimately allowed scientists to insert mRNA into more complex types of cells, even including plant protoplasts [15].

In the meantime, finding an efficient way to deliver mRNA into a cell was an upcoming problem. After the discovery of the 5' Cap modification of mRNA in 1975, this finding in mRNA translation mechanism led to the first use of lipid materials for mRNA delivery in 1978. While the previous transfer of mRNA into oocytes was successful, due of the oocyte's unspecialized nature, this conclusion could

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not be applied to the translational machinery of more specialized cells. Using rabbit reticulocyte 9S mRNA transfected into mouse spleen lymphocytes, researchers from the UK showed that the trapping of ribonucleic acids in liposomes protects the mRNA against ribonucleases and may be extracted both intact and physiologically active [16]. Furthermore, an efficient and reproducible method for RNA transfection was initiated using a synthetic cationic lipid, leading to the concept proposal of mRNA-based drugs. The method of introducing foreign mRNAs into differentiated cells through liposomes solved the delivery issue and permitted research on the production and degradation of mRNA in the host cell, which contributed to the subsequent step of incorporating mRNA into vaccine development.

The first experiments in using mRNA as an actual vaccine started taking place in the early 1990s. After the successful direct gene transfer into mouse muscle, researchers initiated the concept proposal of mRNA vaccines [17]. However, a huge problem came up in the meantime. When the mRNA is introduced into the body, the mRNA strands are hard to keep in one piece as they are rapidly degraded by the immune system. Experiments of injecting liposomes containing mRNA encoding the influenza virus nucleoprotein (NP) to mice showed that the injected mRNA was responsible for the induction of anti-influenza cytotoxic T lymphocytes (CTL), indicating that cellular immunity is inducible by mRNA [18]. Later studies revealed that tumour cells frequently employ free-floating RNA to migrate over normal tissue or act as a remnant of an infected cell by the virus, so ribonucleases break up free-floating RNA to avoid any potential danger. Researchers tried to find ways to make mRNA more stable and one solution was adding specific gene sequences to cap the mRNA strand's beginning and end with 5'cap and 3' poly-A tail, but the problem remained until 2005 when researchers discovered a way to avoid immune destruction of mRNA. The researchers found that the activation of Toll-like receptors (TLRs) attributes to the destruction of unmodified nucleotide strands, while DNA contains methylated CpG motifs and naturally methylated nucleotides in RNA are not stimulatory. They concluded that nucleoside modifications are capable of suppressing RNA's capacity to stimulate immunological cells, such as dendritic cells, thus preventing the destruction of RNA strands by the innate immune system [19]. Through in vivo mouse trials, a different team of researchers later shown that nucleoside modification is a successful strategy for improving the stability and translation capability of mRNA. They discovered that changed mRNAs translate more quickly than unaltered ones when they include pseudouridines, thus concluding that the enhanced stability given by pseudouridines makes the mRNA a promising tool for vaccination [20].

After this breakthrough, the development of the mRNA vaccine gained a massive application in clinical investigations. Since the researchers can customize the percentage of modified bases in the mRNA, the first utilization of direct injection of mRNA as a human cancer treatment took place. In a clinical experiment including 21 patients with malignant melanoma, injection of mRNA coding for TAAs elicited antitumor immune responses, demonstrating the viability and safety of direct injection of mRNA protected by protamine. This study significantly accelerated further clinical investigations of the protamine-mRNA vaccine as an applicable immunotherapy approach. 23 Following this study, several studies took place, including the first preclinical trial delivering DCs-targeted mRNA intranodally, a preclinical study of influenza and RSV-specific mRNAs protective vaccines, and the first human test of conceptual personalized mRNA cancer vaccines for melanoma [21]. Then researchers encountered the final challenge for making the mRNA vaccine, the effective way to deliver the massive mRNA strand into the cell by passing through cell membranes. The solution came up as similar to the liposomal nanoparticle developed in the 1990s, but instead of using naked mRNA, a lipid-based nanoparticle (LNP) containing chemically modified mRNA was used. In comparison with the delivery of naked mRNA, the LNP particles substantially enhance the endocytosis efficiency and allow the release of mRNA inside the cell by protecting it against enzymatic degradation conditions. Different compositions of the LNP were studied later and the strategy of LNP production was also studied, and it was also combined with checkpoints therapies in order to activate sufficient immune responses against cancer and maintain immune homeostasis.

After the discovery of LNP, the main burdens were ultimately overcome and the mRNA vaccine is about ready to hit the market. There are various mRNA vaccines available when the technology first

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came out, and the mRNA vaccines for COVID-19 are typical examples. Pfizer BioNTech and Moderna received approval for their mRNA-based COVID-19 vaccines in December 2020. The mRNA vaccine was initially approved by the UK's Medicines and Healthcare products Regulatory Agency (MHRA), and this makes it possible for the Pfizer-BioNTech vaccine to be widely used. The Pfizer-BioNTech vaccine was later given emergency use permission by the FDA, while the Moderna vaccine was authorized about a week later [22].

The three primary forms of RNA vaccines available today are the non-replicating mRNA vaccine, the in vivo self-replicating mRNA vaccine, and the non-replicating mRNA vaccine produced in vitro using dendritic cells. The simplest sort of RNA vaccination among them is the non-replicating mRNA vaccine. To create the antigen, cells in the body accept an mRNA strand that has been packaged and sent there. The pathogen-mRNA strand is packed with an extra RNA strand for the in vivo-self-replicating mRNA vaccination to ensure that copies are present within the cells. This reaction suggests that more antigens can be produced from a lower quantity of vaccination, leading to a stronger immune response. Based on the action of dendritic cells, the in vitro dendritic cell non-replicating mRNA vaccine is successful. The dendritic cells are in charge of displaying antigens on their cell surfaces so that other cell types can assist in activating an immune response. Notably, the patient's blood sample is taken out and used to transfect dendritic cells with the mRNA vaccine. The patient is then given the cells again in order to trigger the immunological response. In 2022, Moderna plotted the mRNA vaccine against 15 pathogens, such as HIV, malaria, and tuberculosis. It is obvious that this development is intended to make use of the new technology and has provided preparation against possible future pandemics [23].

The anti-virus, anti-tumor mechanisms, and efficacy of mRNA vaccines (Fig.1) are still under research. There are still challenges in both prophylactic and therapeutic mRNA vaccines and the ongoing clinical research is trying to prove the safety and efficacy of the new technology [24].

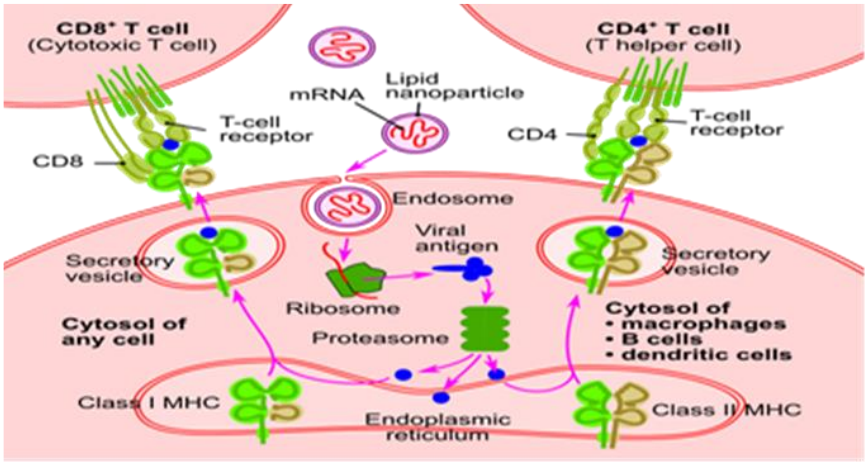


Figure 1. The general mechanism of mRNA vaccines and how it triggers the immune response [11].

Human angiotensin-converting enzyme 2 (ACE2) is the corresponding target receptor of SARS-CoV-2 in order to start its infection, where all SARS-CoV-2 variants followed the same infection mechanism---binding of the RBD site in its C-terminus to the host ACE2 receptor for virus entry and followed fusion into the host cell membrane through endocytosis [10].

3. Pharmacology of mrna vaccine

mRNA vaccines, like conventional vaccinations, aim to stimulate the adaptive immune system to produce antibodies by focusing on the particular pathogen. mRNA vaccines provide a synthetic segment of the RNA sequence of a particular virus, whereas conventional vaccinations trigger the immune response by injecting various types of proteins made in the body, such as antigens, attenuated viruses, and inactivated viruses, or recombinant viral vectors.

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In general, mRNA-based medications employ disease-specific antigen targeting methodologies and primarily go through three steps, including mRNA production, intracellular processing, and the start of immune defence [25].

During mRNA synthesis, when capsuled mRNA sequences, such as nanoparticles, enter the body through injection, they are endocytosed by mostly dendritic cells, one type of antigen-presenting cells (APC). Once taken up, particles undergo intracellular processing to synthesize antigens. Most mRNA is read by the ribosomes in the dendritic cells, which then translate it into viruses. Immune cells may theoretically uptake mRNA and display the antigens on the surface. Since the mRNA is translated in the cytoplasm, the genomic DNA in the nucleus is intact, which lowers the potential threat of induced DNA mutations. The adaptive immune system is activated once the host cells manufacture and deliver the antigens, and proteasomes break them down into polypeptides. The class I and class II MHC molecules bind to the antigens and present them, activating the dendritic cells in the process. By exposing the antigens to T cells and B cells in lymph nodes, the activated dendritic cells contribute to the formation of antibodies that are directed against the particular antigen. Specifically, MHC class II molecules provide antigens to helper T cells (CD4 T cells) and stimulate B cells to make antibodies. MHC class I molecules present antigens to activate cytotoxic T cells (CD8 T cells).

The principle of mRNA technology for vaccination includes mRNA construct, delivery into the host cells, expression of proteins, and presentation of specific antigens. Non-replicating mRNA (NRM) and self-amplifying mRNA (SAM) constructs are the two primary forms of mRNA constructs (Fig. 2).

A cap structure, 5' and 3' untranslated regions (UTRs), an open reading frame (ORF), and a 3' poly-A tail may be found in both NRM and SAM. Then the mRNA strand is created and sealed inside of LNPs to prevent destruction. The LNPs are uptaken by membrane-derived endocytic pathways and the mRNA is released from the endosomal escape pathway. Then NRM and SAM undergo slightly different pathways. The key difference between NRM and SAM is that SAM includes also contains extra genetic replication machinery generated from the mRNA virus. This machinery allows the production of replicase used for mRNA self-amplification. While ribosomes quickly translate NRM structures in the cytoplasm to make proteins and enable post-translational modifications, SAM constructs produce the replicase machinery to amplify the mRNA. The amplified mRNA is then translated by the ribosomes to produce proteins and secreted as transmembrane or intracellular protein after post-translational modification. Finally, the presented antigens stimulate the innate and adaptive immune systems.

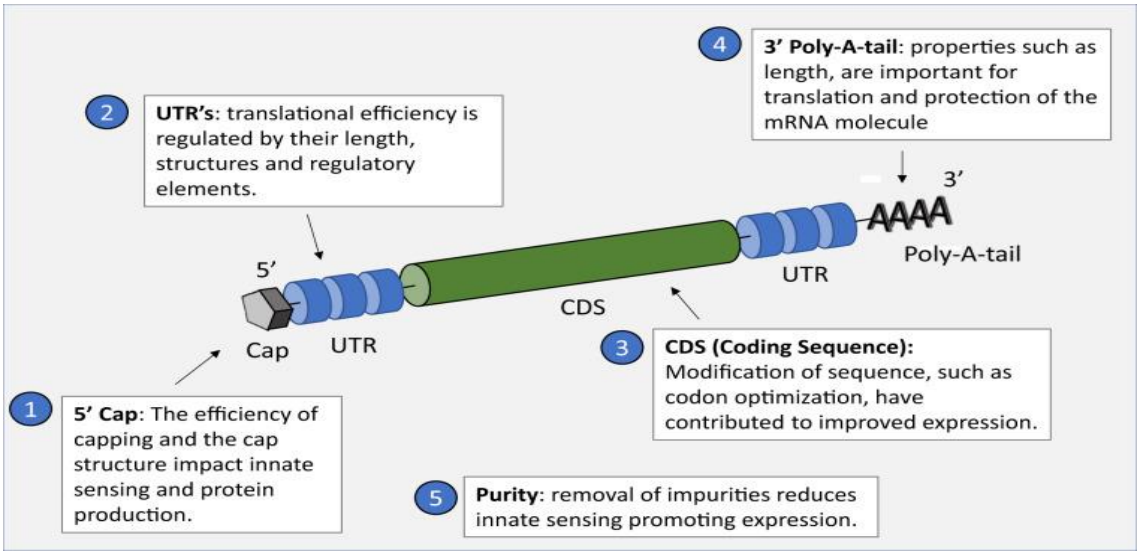


Figure 2. The critical quality attributes (CQAs) for the mRNA construct [26].

For the mRNA construction process, the design of the mRNA construct is crucial. In order to maximize the translational efficiency, the primary goal of the mRNA sequence is to effectively use the host

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cells' constructed translational machinery. Based on critical quality attributes (CQAs), the expression efficiency of the constructed mRNA is dependent on five principles, including 5'caps, characteristics of UTRs, modifications of the coding sequence, 3' poly-A tails, and mRNA purity. More specifically, immunogenicity and protein synthesis are influenced by capping efficiency and capping structure. Translation initiation is prevented by some capping structures, such as incomplete capping with tetratricopeptide repeats (IFIT1). The elimination of contaminants from the mRNA synthesis process decreased the innate immune response, according to research, since less innate sensing allowed for the release of interferons and inflammatory cytokines [28]. The modification of coding sequence, such as optimization, contributes to the improvement of expression. For instance, A study revealed that mammalian cells produce more mRNA when there is a high concentration of guanine and cytosine (GC). By deactivating the intracellular signalling cascade for non-self mRNA degradation, modified nucleosides, such as pseudouridine or N-1-methylpseudouridine, promote increased antigen expression and levels of adaptive immune system responses. The 5' and 3' UTR regions are capable to regulate the translational efficiency by their length, structures, and regulatory elements. RNA structure and function in regulating translation efficiency are demonstrated by internal ribosome entry sites (IRESs) in viral genomes. The viruses use IRESs to predominant the host translation machinery for efficient replication and translation. The viral mRNAs rely on the specific 5' UTR RNA sequence, which directly recruits the host ribosomes for translation [29]. The translational efficiency and stability of mRNA are significantly influenced by the length of the 3' UTR, according to a study that found that lengthening the 3' UTR improves expression. The translation and protection of mRNA depend on the 3' poly-A tail's features, such as length. The TAIL-seq methodology was used in a study to assess poly-A tails. The results revealed that transcripts with high levels of expression typically have short, distinct tails. This implies that efficient protection and translational activities concentrate in mRNAs with deleted tails, which have a smaller number of poly-A binding proteins [30].

To synthesize the mRNA product, the plasmid DNA (pDNA) is generated as a vector, which contains a DNA-dependent RNA polymerase promoter and corresponding mRNA construct sequence. T7 phage RNA polymerase is used together with the pDNA template to produce the mRNA in vitro. The 5' cap and 3' poly-A tail are also constructed in the transcription step of enzymatically modified after transcription via transferases and poly-A polymerase. Then the modified mRNA strands are purified using high-pressure liquid chromatography (HPLC) and formulated for industrial production using the same reaction materials and vessels [32].

Besides mRNA construction, it is also essential to find an efficient way of mRNA delivery to overcome the hurdles of large size and negative charge, allowing it to pass through the injection site and negatively charged plasma membranes. Studies showed that different sites and injection methods, such as into the muscles or blood, lead to a significant difference in levels of mRNA uptake and level of immune responses. According to a comparison among various routes of injection from a study, the lymph node injection results in the greatest T-cell response, with effective antigen-specific CD8 cell and CD4 T cell growth.

A suitable method of protection is essential for a successful delivery procedure since mRNA molecules have low stability and are vulnerable to many mechanisms of destruction by RNases [33]. There are two categories of delivery methods: in vitro and in vivo. The method for in vitro conditions is more complicated and less efficient than its counterpart as it requires the extraction of dendritic cells from the patients and the endocytosis for the cells to take up mRNA molecules is an inefficient pathway in the laboratory setting. For the in vivo settings, there are various ways available and they are generally less expensive because they avoid the harvesting and adapting steps of dendritic cells [34].

Currently, different kinds of delivery strategies are proposed and studied, and lipid nanoparticle (LNP) formulations are a preferred strategy. Before getting into details of LNP, other strategies are worth mentioning as well. Naked mRNA injection is the first developed mode of delivery, and it was studied in clinical trials using intradermal injections of naked mRNA. However, later studies demonstrated that the naked mRNA delivery causes relatively weak immune responses and often gets degraded after the injection [35]. Other methods, such as polymer and peptide vectors, were discovered and well

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developed. This method uses the polyplex, a type of protective coating, as a vector to transport mRNA by mixing mRNA with cationic polymers, such as protamine, a natural cationic peptide. This type of delivery method enhances the stability of mRNA during transporting and has been tested in a clinical trial of metastatic melanoma, which showed an increased immune response.

The LNP delivery system has a more diverse application as it has advantages other than just stability. Additionally, the organ selectivity and endosomal escape properties of this delivery mechanism make it easier to release certain cargos at the target cytoplasmic site of action and transport the mRNA cargo successfully [36]. Massive number has shown effective mRNA transport with LNPs for both vaccine development and therapeutic applications. For example, the mRNA liver depot system has been tested to treat Fabry disease using LNPs and showed higher protein expressions, indicating the improved efficacy of mRNA delivery. Another example is the delivery of customized mRNA vaccines for the influenza A virus and the Zika virus (ZIKV) using this technique, which both showed improved efficacy with rapid and durable protective immunity. Currently, the primary focus of this delivery strategy is the optimization of the ionizable lipid components as they play essential roles in efficient cytoplasmic entry, cargo release, and endosome escape.

4. Developing and testing personalized mrna cancer vaccine

Not only for infectious diseases, the mRNA vaccine has also been used to develop cancer-specific vaccines. Due to its high efficacy, safe administration, quick development potential, and affordable manufacture, the mRNA cancer vaccine surpasses other traditional vaccination platforms. Nevertheless, the mRNA vaccine's applicability has been constrained by its instability, inherent immunogenicity, and ineffective in vivo administration [37].

Many specific advantages of mRNA vaccines as cancer vaccines have been demonstrated unique in comparison to traditional vaccinations. First of all, Theoretically, mRNA may fulfill all genetic information needs for protein encoding and expression. In comparison to other methods of vaccine modification, mRNA sequence alteration is a more practical method for vaccine optimization. Additionally, although having distinct encoded antigens, the majority of the mRNA vaccine manufacturing and purification techniques are fairly similar, making it possible to maintain or even standardize them when creating new mRNA vaccines with a comparable structure [38]. Thus, mRNA vaccines can evidently save both time and financial expenses. Tumor necrosis factor (TNF), interferon (IFN), and other cytokines are secreted as a result of the self-adjuvanting capabilities of mRNA, which promote powerful and protracted adaptive immune responses, while additional adjuvants are required for the response from polypeptide and protein-based vaccinations. Effectively controlling mRNA expression and in vivo half-life requires changing the mRNA sequence and delivery method. In addition, Because the expression of proteins in the cytoplasm does not need to penetrate the nucleus, mRNA vaccines can produce target proteins more effectively than DNA vaccines. The likelihood of mRNA integrating into the host DNA genome is reduced because of the chemical makeup of the mRNA sequence, which differs from that of DNA, preventing the induction of an immune rejection response. Additionally, because mRNA is only temporarily active, it is easy for it to be entirely broken down by physiological metabolic pathways, making it unlikely to disturb the equilibrium [39].

However, the situation for cancer is more complex for a number of reasons, so creating vaccines for either cancer therapy or prevention is more challenging. Specifically, cancer cells are more physiologically and physically comparable to our regular cells than germs and viruses are to the immune system, which makes them more difficult to target. Furthermore, since the tumor cells in each patient are unique in some way with their specific antigens, customizing is necessary for effective cancer vaccines.

For preventative cancer vaccines, the basic principle is to prevent people from being infected by viruses as viral infections are the cause of several cancers. Hepatitis B virus (HBV), which causes liver cancer, and the human papillomavirus (HPV), which causes cervical cancer and neck cancer, are common examples. There are vaccines developed to prevent HBV and HPV infections, thus preventing HBV- and HPV-related cancers. For therapeutic cancer vaccines, Targets may be found on the individual tumors of patients, and cancer cells can be distinguished from healthy ones. Cancer targets may be

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common proteins that cancer cells generate in unusually large amounts, such as prostate cancer cells' overexpression of prostatic acid phosphatase (PAP). The sipuleucel-T vaccine was invented using this target and received FDA approval in 2010 as a treatment for prostate cancer. Bacillus Calmette-Guerin (BCG), a TB vaccine that functions as a general immune stimulant, is another FDA-approved immunotherapy that is continuing in use today for early-stage cancer [40].

In comparison to the general cancer vaccines, personalized neoantigen vaccines are another promising category of cancer vaccine due to the variance between individuals having the same type of cancer. The neoantigens, which are only produced by tumor cells and not by other healthy cells, are cancer's main target. Based on this target, the customized neoantigen vaccination is a method that shows promise for inducing immune responses by being directed precisely against tumor cells without negatively affecting the healthy cells, which prevents possible side effects theoretically. The neoantigen vaccine is the key focus in the field of cancer vaccine research and There are various different neoantigen vaccines being tested currently, either on their own or in conjunction with other medicines such as checkpoint inhibition immunotherapies.

To summarize, approaches include using appropriate mRNA structure modifications, such as optimization and nucleotide modification, formulating methods, such as LNPs and polymers, and co-delivery routes with other immune therapeutic agents, such as checkpoint inhibitors. These innovations have further boosted the development of the mRNA cancer vaccine and progressed toward eradicating tumor cells.

5. Conclusion

In the past few decades, mRNA stability, function, and synthesis have improved noticeably thanks to mRNA-based treatments. It's worth noting that many mRNA vaccinations frequently trigger an adaptive immune response via interferon signals. Antigen proteins are translated through the delivery of mRNA into the cytoplasm, where they are primarily processed on MHC molecules and trigger the T cell response. Numerous mRNA therapeutic applications are now the subject of extensive study and ongoing clinical studies. Although problems such as better delivery methods and regulation of the triggered immune response still exist, the effectiveness of mRNA vaccines in preventing infectious illnesses has shown promise, and further research on cellular immunity is required. Overall, researchers are in a positive attitude to accelerate the page in mRNA vaccine development, especially for treating cancer and combating the currently incurable diseases.

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