Advances in mRNA Cancer Vaccines: Mechanisms, Clinical Progress and Future Outlook

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Abstract. Despite significant advances, cancer continues to be a serious burden to the world and the lack of effectiveness of conventional therapies has encouraged the exploration of new immunotherapeutic strategies. mRNA cancer vaccines are one of these that are an attractive approach due to the speed of their design, their high immunogenicity and the potential of personalized treatment. The present review outlines the biology of mRNA cancer vaccines, such as tumor antigens, mechanisms of immune escape and immune activation of the vaccines. Novel developments in lipid nanoparticle (LNP) delivery systems, lymph node targeting strategies, and preclinical development are discussed. In addition, existing clinical data from melanoma, lung cancer, breast cancer, pancreatic cancer, and other cancers are explored, including the exciting results from the KEYNOTE-942 trial. Lastly, key challenges related to tumor heterogeneity, delivery efficiency, manufacturing complexity, and regulatory considerations are analyzed together with future directions involving personalized neoantigen vaccines, AI-driven vaccine design, and next-generation delivery technologies. In conclusion, mRNA cancer vaccines are a rapidly developing field and hold great promise in reshaping the future of precision cancer immunotherapies.

Keywords: mRNA cancer vaccines; cancer immunotherapy; personalized neoantigen vaccines; lipid nanoparticle delivery.

1. Introduction

Cancer continues to be one of the most important issues in health across the world and is placing a heavy burden on healthcare systems in all countries. The latest estimates from GLOBOCAN (2022) indicate that there were about 20 million new cases of cancer and 9.7 million cancer-related deaths worldwide in 2022, and that cancer is one of the top causes of death worldwide [1]. The global burden of cancer is projected to grow more in the upcoming decades, particularly with the urgent population growth and aging, and thus, there is an urgent need for developing more effective therapeutic strategies [1,2].

With the present traditional cancer treatment, including surgery, chemotherapy and radiotherapy, the outcome and survival rates have been effectively improved. However, these methods are still linked to significant drawbacks. Surgical therapy is usually most effective in localized disease but becomes less effective after metastasis has occurred. Healthy tissues are also often damaged by chemotherapy and radiotherapy, which have unpleasant side effects and a negative impact on quality of life. Moreover, in many types of cancer, especially in advanced-stage disease, the occurrence of treatment resistance and tumor recurrence is a major challenge [2].

To overcome these shortcomings, cancer immunotherapy has become one of the most significant advances in the field of oncology today. Immunotherapy does not directly attack the tumor cells but aims to stimulate and boost the immune system in the host to recognize and destroy the malignant cells. In the last decade, there has been some positive clinical activity with immune checkpoint inhibitors, adoptive cell therapy and therapeutic cancer vaccines in several different types of cancer [3,4]. But tumors can evolve complex mechanisms for immune evasion, such as the loss of antigens, activation of immune checkpoints, and the creation of immunosuppressive tumor microenvironments (TME). These challenges have spurred the quest for new, more effective and sustained ways to induce antitumor immune responses through immunotherapeutic approaches.

mRNA cancer vaccines have garnered significant interest among the emerging immunotherapies because of their special biological and technological features. Unlike traditional vaccine platforms,

mRNA vaccines transfer the vaccine information that codes for tumor antigens to host cells. After being synthesized in the cell, these antigens are processed and presented to immune cells, which triggers immune reactions against the antigens that can be directed against malignant tissues [5,6]. The unprecedented success of mRNA vaccines in the COVID-19 pandemic highlighted the potential of mRNA vaccines for fast vaccine development, scalable production and efficient immune activation, which spurred interest in the application of mRNA vaccines to cancer treatment [3,5]. This makes mRNA cancer vaccines especially appealing for oncology applications, as they have several characteristics. First, the sequence of mRNA can be easily designed and adapted to the molecular features of every single tumor, allowing for a very personalized therapeutic strategy. Second, LNP delivery systems have been significantly improved in terms of the stability of the mRNA, the efficiency of intracellular delivery, and antigen expression. Third, mRNA vaccines can induce cellular and humoral immune responses, involving activation of CD4+ helper T cells and CD8+ cytotoxic T cells, which are essential for an effective antitumor immune response [5-7].

There has been significant advancement in preclinical and clinical studies of mRNA vaccines for cancer. These vaccines have been shown to elicit strong antigen-specific immune responses, to activate CD8+ T-cells and to inhibit tumor growth in several animal models [8]. The pace of clinical development has also been quick, and many different vaccine candidates are now under investigation for melanoma, lung cancer, breast cancer, pancreatic cancer and other types of cancer [9,10]. The most recent breakthrough was the phase IIb KEYNOTE-942 trial, which found that the personalized neoantigen vaccine mRNA-4157/V940 plus pembrolizumab halved the risk of recurrence or death in high-risk melanoma by around 49% [4]. The results offer valuable insights into the therapeutic potential of a personalized mRNA cancer vaccine.

Despite these promising advances, several challenges continue to influence clinical translation. Tumor heterogeneity, immune evasion and other factors constitute major bottlenecks limiting broad clinical application [7,10,11]. Addressing these limitations is essential for maximizing therapeutic efficacy and facilitating broader clinical adoption.

2. Biological Basis of mRNA Cancer Vaccines

Tumors and the immune system are the main protagonists in the development of cancer. Immune surveillance is the normal process by which the immune system's ability to recognize and gets rid of abnormal cells. Antigens on malignant cells that become targets of immune recognition are important. These antigens can be broadly classified as tumor-associated antigens (TAAs), tumor-specific antigens (TSAs), and neoantigens [10,11]. TAAs are proteins that are overexpressed in cancer cells which can also be expressed at lower levels in normal cells. They include HER2, MUC1 and carcinoembryonic antigen. These antigens are common to several patients and thus have been extensively studied as vaccine targets. Immune tolerance can, however, restrain the immune responses against these antigens. TSAs are only present in malignant cells and not in normal cells. A large number of TSAs are the consequence of mutations that produce new protein sequences. These antigens are more specific and would be less likely to cause off-target toxicity and therefore are attractive candidates for immunotherapeutic intervention [10]. Neoantigens are one of the most intriguing targets of personalized cancer vaccines among all other antigen classes. Neoantigens are formed from somatic mutations that are specific to each individual tumor and thus not centrally immune-tolerized. As a result, they are able to generate very specific and strong T-cell reactions. The development of next-generation sequencing techniques has contributed to the identification of neoantigens, specific to each tumor and patient, and thus to the development of personalized vaccine strategies [4,10].

Even though the immune system is able to recognize malignant cells, successful tumors often evolve ways to evade immune evasion. The most well-studied pathway is programmed cell death protein 1 (PD-1) and its ligand, PD-L1. Over-expression of PD-L1, which binds to PD-1 receptors on T cells and inhibits T cell activation, is seen in many tumors. This pathway allows cancer cells to

escape from being destroyed by the immune system and helps the cancer grow. Checkpoint inhibitors targeting PD-1 and PD-L1 have proven to be successful, highlighting the need to overcome immune suppression in the current treatment of cancer. Tumors have multiple ways of escaping the immune system, beyond checkpoint activation. These involve downregulation of major histocompatibility complex (MHC) molecules, production of immunosuppressive cytokines, recruitment of regulatory immune cells and metabolic changes in the TME. All of these are mechanisms that collectively work to impair effective antitumor immunity and decrease the efficacy of therapy [3,11].

The TME itself has become a major focus of cancer immunology research. Accordingly, the effectiveness of cancer vaccines depends not only on antigen selection but also on the ability to overcome the immunosuppressive conditions present within the TME [10,11].

3. Mechanisms and Delivery Systems of mRNA Cancer Vaccines

For mRNA cancer vaccines to have therapeutic efficacy, they need to be capable of delivering genetic information encoding tumor antigens to host cells and of triggering strong immune responses. The difference between conventional vaccines and mRNA vaccines is that the latter do not contain any protein or pathogens; instead, the mRNA vaccines are designed with a sequence of code that triggers the host's cellular machinery to produce target antigens. This special mechanism affords a great deal of flexibility and is one of the key factors that have been making mRNA-based cancer immunotherapy so popular.

Typical mRNA vaccines are synthetic molecules of mRNA (derived from a cell's genetic material) that contain the code for one or more tumor antigens. The mRNA is composed of 5 caps, untranslated regions on both ends, an open reading frame that codes the target antigen and a poly(A) tail. Recent improvements in molecular engineering have allowed the optimization of such structural elements, leading to an improvement in antigen expression and vaccine performance. After administration, the vaccine must be able to get into the host cell. The mRNA sequence is translated into proteins corresponding to the encoded tumor antigens by cellular ribosomes once it is in the cytoplasm. mRNA does not cross into the nucleus and directly acts in the cytoplasm, thus circumventing the problem of genomic integration that is associated with some gene therapy methods. The transient expression of mRNA is another advantage in terms of safety [12-14].

Post-translation, antigenic peptides are presented on MHC molecules, initiating adaptive immune responses. Antigens presented through MHC class I pathways activate CD8+ cytotoxic T lymphocytes, whereas MHC class II pathways stimulate CD4+ helper T cells. Together, these immune responses contribute to tumor elimination [5-7].

CD4+ helper T cells have a role in the anti-tumoral immune response through the secretion of cytokines that stimulate immune cell activation, proliferation and coordination. These cells help in the maturation of dendritic cells, increase the activity of cytotoxic T-cells and help in developing long-term immune memory. CD8+ cytotoxic T cells, in contrast, are able to directly recognize and eliminate tumor cells that express the target antigen. Favorable tumor control and therapeutic activity have been shown in numerous studies to be associated with robust CD8+ T-cell responses.

The efficient delivery of mRNA vaccines is one of the most critical challenges for their development. The naked mRNA molecules are very sensitive to extracellular ribonucleases and have low cellular uptake. Therefore, clinically applicable delivery systems must be developed that are able to protect mRNA and deliver it into the cell. LNPs have proven to be the most successful and most used delivery technology among the range of delivery technologies studied so far. Most current LNP formulations include four key components: ionizable lipids, cholesterol, phospholipids, and polyethylene glycol (PEG)-modified lipids. The role of each component is the stability of the structure and its functioning in the nanoparticles [15,16]. The most important part of modern LNPs is the ionizable lipids. These molecules are relatively neutral at physiological pH, but bear positive charges at acidic pH, inside the cell, such as in endosomes. This unique property allows the interaction with endosomal membranes and facilitates the release of mRNA into the cytoplasm [17,18]. Cholesterol

adds to the stability of the membrane and to the integrity of nanoparticles; phospholipids act as an additional structural support. PEG-modified lipids can improve the colloidal properties and decrease aggregation, leading to an increase in circulation time and biodistribution. In vivo, the main mechanism of internalization of LNPs is endocytosis. Dendritic cells and macrophages have been shown to readily uptake nanoparticles and process the delivered mRNA. Ionizable lipids promote endosomal escape after they enter endosomal compartments by destabilizing the endosomal membrane. The ability to escape from endosomes is important since mRNA confined in these compartments can be degraded prior to being transported into the cytoplasm.

While the efficiency of mRNA delivery has greatly improved with the current technologies of LNP, endosomal escape is one of the key bottlenecks that affect vaccine performance. Only a relatively small fraction of mRNA delivered into cells is able to access the cytoplasm, as suggested by studies. Thus, extensive research is being directed to the development of next-generation nanoparticles that will be better able to deliver cargo to cells. Along with the enhancement of cell internalization, targeting of lymph nodes has become an emerging issue. Lymph nodes are the sites of central immune activation where antigen-presenting cells (APCs) meet with naïve T lymphocytes. The efficiency of delivery of vaccine antigen into lymphatic tissues can significantly boost adaptive immune responses. However, recent studies have shown that optimal formulations of LNPs can selectively target lymph nodes, thereby enhancing antigen uptake and T-cell priming [8,15]. Recent progress in genomic sequencing also has made it possible to develop personalized neoantigen vaccines that are specific to each tumor profile [4,10].

mRNA platforms have several advantages over conventional cancer vaccines, such as the short manufacturing time, flexibility in the antigen design, and capacity to potently trigger innate and adaptive immune responses [7,14]. Nevertheless, there are a number of known problems with these, such as delivery efficiency, biodistribution, manufacturing costs and large-scale production. The targeting specificity and intracellular delivery will need to be improved in order to maximize the therapeutic efficacy and facilitate broader clinical application [11,15].

4. Clinical Progress of mRNA Cancer Vaccines

mRNA cancer vaccines have been one of the most significant advances in modern oncology—moving from lab to clinical trials. New technologies such as genome sequencing and antigen discovery, along with bioinformatics and LNP delivery systems, have greatly sped up the transfer of preclinical findings to human clinical trials. Thus, there is ongoing development of various mRNA vaccine candidates in multiple types of cancer. While many are still in the early stages of clinical development, recent discoveries have been encouraging with respect to the feasibility and therapeutic utility of mRNA-based cancer immunotherapy.

The most important advantage of the mRNA cancer vaccines is their flexibility. mRNA vaccines can be quickly adapted to the molecular features of each tumor as opposed to traditional vaccines, which may only target a handful of biomarkers. This flexibility has paved the way for the creation of both shared-antigen vaccines and highly personalized neoantigen vaccines, opening up a wide spectrum of potential clinical applications.

4.1. Personalized Neoantigen Vaccines in Melanoma

Melanoma has become one of the most promising models for developing mRNA vaccines, among all the cancer types that are under investigation. Melanoma is a tumor that carries a relatively high mutational burden that generates a large number of neoantigens, which can be recognized by the immune system. Because of the number of potential targets, melanoma is especially amenable to personalized approaches to immunotherapy [3,4,16].

A major breakthrough in this field was made with the development of mRNA-4157 (V940). This individualized neoantigen vaccine is co-developed by Moderna and Merck and is individualized for each patient. After sequencing the tumor, computational algorithms search for mutations that could

create neoantigens that are immunogenic. Selected neoantigens are then inserted into a personalized mRNA construct, which is then injected to trigger an immune response against the tumor. This is a major step towards precision oncology as every vaccine is patient-specific, based on the molecular profile of the patient's tumor [16].

The phase IIb KEYNOTE-942 trial was particularly telling as to the clinical significance of mRNA-4157/V940. This is a randomized trial with patients with high-risk resected melanoma receiving either pembrolizumab alone or pembrolizumab plus the personalized vaccine. The trial showed that the risk of recurrence or death was about 49% lower in patients who were treated with mRNA-4157/V940 and pembrolizumab than with pembrolizumab alone. These results are some of the most robust clinical data ever indicating the potential clinical benefit of personalized mRNA cancer vaccines [4].

4.2. mRNA Vaccines in Other Solid Tumors

Besides melanoma, lung cancer is another important target for mRNA vaccine development. Lung cancer is the top killer of cancer-related deaths worldwide, and is responsible for a significant share of cancer-related deaths every year. Although the targeted therapies and immunotherapies have made important progress, the outcome for survival is not good for many patients diagnosed with advanced disease. Therefore, novel approaches, which have the potential to enhance long-term disease control, are still being investigated [19,20].

BioNTech's BNT116 is one of the most promising vaccine candidates being studied as a treatment for non-small cell lung cancer (NSCLC). BNT116 is a targeted vaccine against multiple TAAs commonly found in lung cancer cells, as opposed to personalized neoantigen vaccines. The vaccine aims to augment immunity against these antigens, thereby boosting the anti-tumor response and consequently the clinical response. Initial clinical trials have been mainly dedicated to safety, tolerability and immunogenicity. There is still limited effectiveness data at the very long term; however, early results indicate that BNT116 is able to generate immune responses that are measurable and has an acceptable safety profile [20].

Breast cancer is also a key field of study. Breast cancer is one of the most common malignancies among women worldwide and a public health concern. There are several subtypes of breast cancer with properties that could make them good targets for an mRNA vaccine. Especially, the HER2-positive breast cancer has been a focus of interest as HER2 is an established tumor-associated antigen. Several preclinical and clinical trials have focused on vaccines against HER2, and initial results have shown that they can trigger an immune response against the antigen. Triple-negative breast cancer (TNBC) is another disease with potential for immunotherapeutic intervention. TNBC does not have the expression of estrogen receptors, progesterone receptors and HER2, which means that treatments are limited. TNBC is often, however, characterized by a relatively high mutational burden and higher infiltration of immune cells, presenting opportunities for personalized neoantigen vaccine approaches. The ongoing studies are continuing to assess the potential of mRNA vaccines to improve outcomes in these patients with this aggressive disease [9,16].

Pancreatic cancer continues to be one of the most difficult cancers to treat, with five-year survival rates still being one of the lowest for the major cancers. Pancreatic tumors' profound immunosuppression has long hampered immunotherapy efficacy, yet recent advances spark guarded optimism. Post-resection autogene cevumeran, a personalized neoantigen mRNA vaccine, elicits sustained T-cell responses in eligible patients, proving mRNA vaccines can trigger robust antitumor immunity in hard-to-treat malignancies. Ongoing early-phase trials evaluate mRNA vaccines against ovarian, colorectal, glioblastoma and other cancers. Collectively, these studies broaden mRNA vaccine indications, mirroring rising recognition of mRNA technology's versatile therapeutic capacity [3,9,16].

Overall, clinical data highlight key merits of mRNA cancer vaccines: favorable safety, tolerable toxicities and detectable immune activation, with personalized neoantigen platforms yielding promising efficacy in specific cohorts. Still, most programs are at early stages; large phase III trials

with extended follow-up and diverse patient cohorts are required to validate their sustained therapeutic benefits [9,16].

5. Challenges and Future Perspectives

Although mRNA cancer vaccines have made great strides, there are still a number of hurdles to their widespread clinical use. The efficiency of delivery is a significant challenge as only a fraction of the mRNA injected reaches the cytoplasm and weak cytoplasmic delivery results in limited therapeutic effects. Moreover, personalized neoantigen vaccines are also complicated and expensive to produce, and have not yet been extensively adopted. Individualized treatments also require further development to ensure safety and quality control, as do the regulatory regimes for such treatments [16,17].

However, the outlook for mRNA cancer vaccines is still very bright. The development of next-generation sequencing technologies has enhanced the ability to identify patient-specific neoantigens and has the potential to make personalized vaccine development more attainable. Moreover, new delivery formats and combination approaches with immune checkpoint inhibitors will be likely to further increase the effectiveness of therapy. Overall, the continuous development of technology and clinical studies indicates that mRNA cancer vaccines are becoming a more and more significant part of precision oncology and cancer treatment [19].

6. Conclusion

The mRNA vaccine technology has gained new ground in the field of cancer immunotherapy in recent years. mRNA vaccines can induce innate and adaptive immunity and provide very personalized treatments. The clinical translatability of this platform is greatly enhanced by optimized LNP delivery, improved antigen screening, and cutting-edge genomic sequencing. Promising clinical outcomes have been observed, notably in melanoma: the personalized mRNA vaccine mRNA-4157/V940 drastically lowers recurrence risk when co-administered with pembrolizumab. Continual testing in the lung, breast cancer, pancreatic cancer and other cancers further substantiates mRNA-based immunotherapy.

Nevertheless, there are still significant challenges to address, such as delivery efficiency, tumor heterogeneity, manufacturing complexity, and regulatory considerations. Maximizing clinical benefit will require continued advances in the design of personalized vaccines, next-generation vaccine delivery technologies and combination immunotherapies. In total, mRNA cancer vaccines are making swift progress, and they could become a key element of precision oncology.

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