Transactions on Materials, Biotechnology and Life Sciences
ISSN: 2960-1932, eISSN: 2960-2319 | Volume 3
BLSME 2024

mRNA Vaccines in Treatment Tumor: Advancement and Challenges

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Abstract. Immunotherapy has become a well-known cancer treatment method recently. The expeditious development of COVID-19 vaccines has made the extensive use of messenger RNA (mRNA) vaccines possible, and strikingly increased research data have been devoted to exploiting the potential of mRNA vaccines as preclinical and clinical treatments for cancer. mRNA cancer vaccines can stimulate durable and targeted immune responses against tumor antigens (TAs). Despite the promising future of mRNA vaccines, some challenges remain, including mRNA instability and safety concerns. It is possible to improve mRNA's stability, translation efficiency, and immune-stimulating qualities by changing its components. Another main challenge facing the field of mRNA therapy is to improve the effectiveness delivery systems. This review begins with an introduction to the immunological mechanism underlying mRNA cancer vaccines. It then focuses on discussing the subject of improving the efficacy of mRNA cancer vaccines via two main approaches: optimization of mRNA structural and improvement of delivery system.

Keywords: mRNA; cancer vaccine; non-virus delivery; nanoparticles.

1. Introduction

Cancer is among the top causes of death worldwide, leading to almost 10 million deaths each year. In recent times, immunotherapy has emerged as a prominent technique for treating cancer. The field of cancer vaccines has great potential as an immunotherapy approach for stimulating durable and targeted immune responses against TAs. The utilization of genomic methodologies, like as next-generation sequencing and high-throughput single-cell sequencing, has facilitated the identification and validation of an increasing number of TAs.

The global attention has been shifted towards mRNA-based vaccinations due of the COVID-19 pandemic. The quick creation and manufacture of anti-virus vaccines can be attributed to extensive research conducted over several years, which focused on investigating the potential of mRNA vaccines for treating cancer in both diseases' animal model experiments and clinical trial settings.

To begin with, it is noteworthy to mention that mRNA vaccines demonstrate a considerable degree of tolerability, have a tendency to degrade rapidly, and do not undergo integration into the host organism's genome. Additionally, it should be noted that mRNA molecules possess a non-infectious nature, and the utilization of mRNA vaccines has promise in stimulating both immune reactions that are humoral as well as cell-mediated. Finally, it should be noted that the manufacturing process of mRNA vaccines is characterized by its rapidity and cost-effectiveness [1].

Nevertheless, the advancement of cancer vaccines has presented significant challenges, as the encouraging results observed in pre-clinical studies have not been successfully replicated in clinical applications. There are several potential causes that could contribute to these failures, such as a limited comprehension of tumor biology, mRNA structure, and adjuvants [2]. While delivery materials like LNPs have been shown to enhance the effectiveness of mRNA administration, there remain some obstacles that need to be addressed. One such difficulty involves the need to enhance medication safety without compromising stable pharmacokinetics. Additionally, the utilization of LNPs as a delivery platform may potentially result in hepatocyte injury and provoke an inflammatory response.

This review initially presents an overview of the immunological mechanism underlying mRNA cancer vaccines. It then delves into the topic of enhancing the efficacy of mRNA cancer vaccines through two primary avenues: optimizing the structure of mRNA and refining the delivery systems employed.

2. Immune Mechanisms of mRNA Vaccine

mRNA is a macromolecule composed of a single strand including a cap flanked by 5′- UTR, 3′-UTRs, an ORF, and a poly(A) tail. The utilization of mRNA as a cancer vaccine format has gained considerable attention due to its ability to transport antigens and induce co-stimulation through activation of immune response. mRNA, serving as cancer vaccines, possess the ability to encode one or more TAs within the ORF. mRNA does not access the nucleus and is not incorporated within the genome to produce proteins. It enters the cell directly crossing the plasma membrane, or by endocytosis, then translates in the cytoplasm and undergoes a series of protein modifications, degradation, etc., before finally being presented in the major histocompatibility complexes (MHCs) in the form of peptides. The mRNA vaccine possesses the capacity to induce both humoral responses via B cells and cytotoxic T cell responses especially CD8+ T cells, which can contribute to the effective elimination of malignant cells (figure 1).

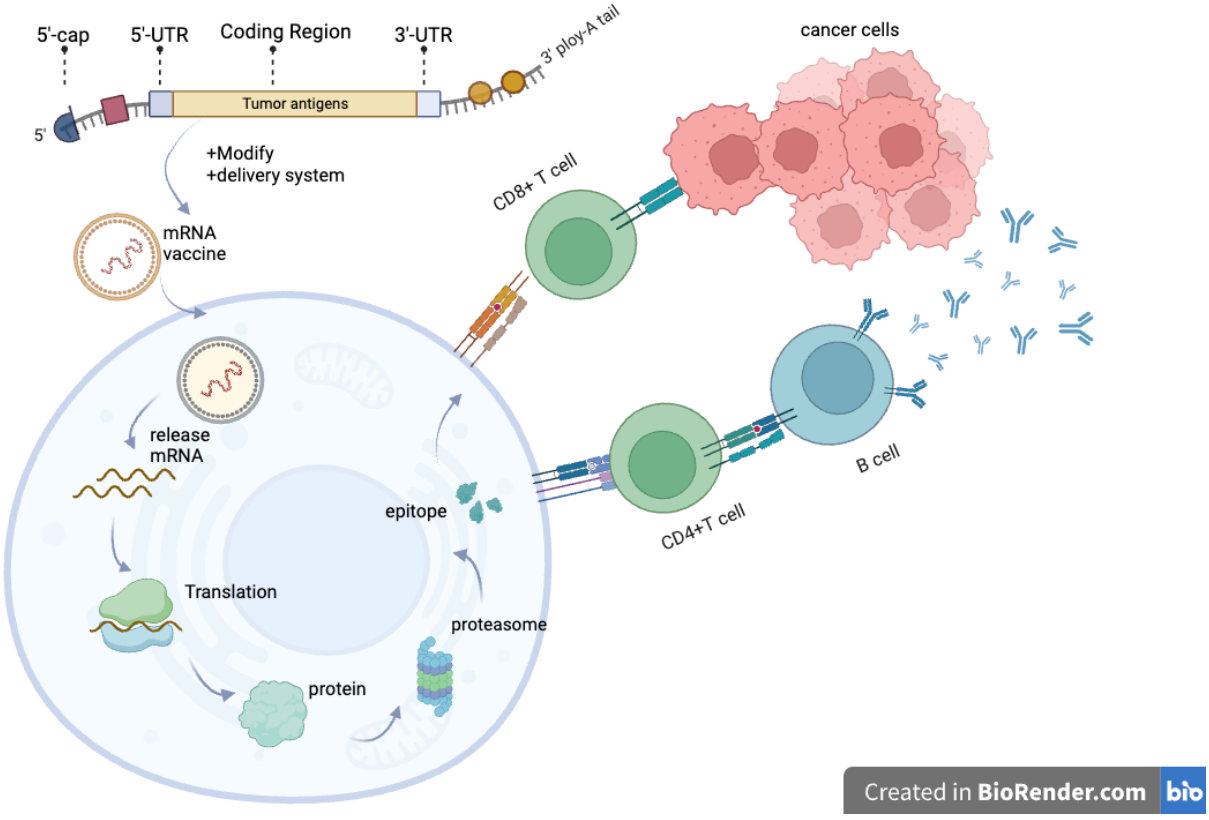

Figure 1. Immune mechanisms of mRNA vaccine

3. mRNA Cancer Vaccines: Rational Design and Optimizing

3.1. Designation of mRNA Cancer Vaccines

Modifying the components of mRNA can enhance its stability, translation efficiency, and immune stimulating properties. The optimizing methods involve design and improvement of the coding and noncoding region, as well as delivery formats [3]. The composition of coding sequence affects translation effciency. One method of optimizing sequences involves enhancing the GC content [3]. Grzegorz Kudla and colleagues designed a HSP70 recombinant gene with or without GC-rich sequences to transefected mammalian cells with green fluorescent protein, showed that the transfected

ratio in high GC sequence is 100-folds of low GC group, demonstrating an increase in steady-state mRNA levels using high GC content [4].

In addition, the noncode sequences are also critical for stability of mRNA in the cytosol. The optimization of the 5'-UTR sequence is capable of achieving through the avoidance of start codons that interfere with the translation of ORF, the avoidance of extremely stable secondary structures, and the utilization of shorter 5'-UTRs [3]. The 3'-UTRs can be introduced α-and β-globin to boost mRNA translation and stability [5].

According to Karikó et al., mRNA with nucleoside modifications had better translational stability and efficiency than unmodified mRNA because they were less susceptible to ribonuclease L breakdown [6]. In contrast, Thess et al. observed that unmodified mRNA that had been codon-optimized exhibited greater translational efficiency and lower immunogenicity when compared to modified mRNA [7]. To gain a deeper comprehension of the impact of varying levels of nucleoside modification on the immune response against tumors induced by mRNA-LNP tumor vaccines, Researchers Chutamath et al. investigated the immunogenicity and therapeutic effects for cancer using alternative mRNA vaccine with N1-methylpseudouridine (m1) in melanoma mice model of B6. The findings of their study revealed that the utilization of lipid nanoparticles to deliver ovalbumin (OVA) encoding mRNA, referred to as OVA-LNP, resulted in significant production of interferon and induced dendritic cells mature. Interestingly, these effects were found to have a negative connection with rising percentages of m1Ψ alteration. The investigators reached the determination that a translational stability mRNA vaccination activated signal pathways due to upreagulation of interferon, which plays a pivotal function in inhibition of tumor progression and metastasisi through restart T cell function to kill cancer cells [8].

Ramos da Silva et al. conducted a comparative analysis of three distinct mRNA platforms in the context of a therapeutic vaccination for malignancies associated with human papillomavirus. The three vaccinations utilized a common antigen, specifically protein hybrid formed by joining the E7 oncoprotein from HPV-16 and the glycoprotein D from herpes simplex virus type 1 (gDE7). Therefore, variations in the effectiveness of the vaccines can be attributed to variances in the underlying platform employed. The study evaluated three different types of vaccines: with or without a modified non-replicating mRNA vaccine (referred to as gDE7 recombinant protein or DNA vaccine), and a self-amplifying mRNA vaccine (referred to as gDE7 mRNA-LNP vaccine). The researchers provided evidence that administering a single low-dose immunization of these three kinds of vaccines resulted in the specific CD8+ T cells activation. Additionally, this immunization strategy elicited memory T cell responses that were effective in preventing the recurrence of tumors and successfully eliminated subcutaneous tumors at various stages of growth. Comparative investigations have shown that the efficacy of all three gDE7 vaccines showed that of gDE7-LNPs mRNA vaccine is better than DNA or recombinant protein vaccines. These findings emphasize the applicability of mRNA cancer vaccines in clinical practice [9].

3.2. Delivery Format Optimization

Another primary difficulty encountered pertains to the requirement for efficacious delivery mechanisms. The passage of naked mRNA across the cell membrane is hindered by its substantial negative charge and considerable bulk. Furthermore, because of its instability, mRNA degrades quickly. Hence, the development of suitable delivery systems is imperative.

3.2.1. Challenges and improvements regarding nanomaterial delivery systems

The main delivery methods currently include: LNPs, self assembled polymer micelles, nano hydrogel, metal nanoparticles(NPs), etc. In recent times, notable advancements have been achieved in the field of nanobiotechnology, which have facilitated the creation of mRNA nanocarriers. The nano-drug delivery system is employed for the direct loading, safeguarding, and release of mRNA within the biological milieu. LNPs are the most advanced mRNA delivery vectors, with a limited number of options available. There are four main parts to a conventional LNP including an ionizable lipid that

forms an electrostatic complex with the mRNA, a phospholipid that aids in the formation of structures, cholesterol which controls membrane fluidity, and a polyethylene glycol (PEG)-lipid which improves colloidal stability and lengthens circulation duration. LNPs possess the ability to stabilize mRNA molecules, and enhance intracellular transportation. Rein Verbeke et al. successfully developed a liposomal formulation using 1,2-dioleoyl-3-trimethylammonium-propane (DOTAP) and cholesterol for the purpose of delivering mRNA. This formulation demonstrated effective targeting of DCs after an intravenous injection. The researchers achieved efficient co-delivery antigens of nucleoside-modified mRNA and the glycolipid and immunopotentiator α-galactosylceramide (α-GC) to APCs by employing DOTAP−cholesterol liposomes as a delivery system, referred to as mRNA Galsomes. mRNA Galsomes co-formulate modest dosages of α-GC to stimulate a robust innate as well as adaptive immune system reaction against tumors in mice., with the enhancement the kill ability of natural killer T cells (iNKT) for tumor cells. In comparison to the control group, there was a robust activation observed in iNKT cells and NK cells. Additionally, there was a notable increase in tumor-infiltrating cytotoxic T cells that were specific to antigens. The suppressive myeloid cells decreased significantly in TME. Further findings showed that tumor expansion minimized and median survival of B16-OVA melanoma mice became longer, suggesting that therapeutic immunization with mRNA Galsomes boosted the response to PD-L1 checkpoint inhibitor [10]. However, LNPs have been found to cause severe inflammatory reactions, most of which are produced from ionizable lipids. [11].

The expeditious progress in the field of LNPs technology has yielded significant breakthroughs in the transport of mRNA. However, a considerable proportion of the documented instances involving the intravenous (IV) or intramuscular (IM) administration of LNPs demonstrate a pronounced liver mRNA expression. This heightened expression in hepatic tissue has been associated with potential adverse effects, including reversible damage to the liver. The mRNA vaccines targeting to the lymph node (LN) are benefit to mitigate adverse effects and enhance the immune responses. In their study, Chen et al. investigated the use of a lipid nanoparticle (LNP113-O12B) that selectively targets LNs without the addition of any active targeting ligands. The purpose of this investigation was to produce an mRNA cancer vaccine in providing protection and therapeutic benefits in the melanoma mice model. Consequently, the precise administration of mRNA to the LN resulted in an enhanced immune reaction of CD8+ T cells towards the whole ovalbumin (OVA) antigen that was encoded inside the mRNA. The shown superior anticancer efficacy of the LN-targeting mRNA vaccine with LNP delivery system exhibits significant promise for the future development [12].

In recent years, researchers have initiated investigations and refinements of polymer-based mRNA delivery systems, leading to notable outcomes. Despite encountering certain obstacles, it is important to acknowledge that the exact engineering design, predictable chemical structure, and consistent repeatability across different batches of polymers are crucial characteristics that enable the conversion of polymer-based mRNA delivery systems into effective therapeutic drugs [13]. Pei Huang has developed highly effective mRNA cancer vaccine vectors that exhibit low levels of inflammation. These vectors consist of a sequence of alternating copolymers known as "PHTA," which are characterized by the presence of ortho-hydroxy tertiary amine (HTA) repeating units. The synthesis of these copolymers enables them to fulfill three important functions: condensing mRNA, enhancing the stability of polymeric nanoparticles (PNPs), and prolonging the duration of circulation within the body. PNPs based on PHTA demonstrate minimal inflammatory side effects when administered in living organisms. Moreover, these PNPs effectively transport mRNA cancer vaccines in vivo, resulting in robust immune responses characterized by CD8+ T cell-mediated anti-tumor cell immunity [11].

Xiyu Ke et al. synthesized a series of NPs featuring a PEG corona (named PEI-g-PEG), wherein the grafting ratios varied and PEG terminal functional groups were incorporated. The nanoparticles with 0.5% grafting ratio and corona that were PEGylated, exhibited the most significant upregulation expression of transgene in the lung when administered systemically. Analysis of cell profiling revealed that pulmonary immune cells were primarily responsible for the observed expression. Additionally, the researchers demonstrated that the synthesis of these nanoparticles may be achieved

using the flash nanocomplexation technique. This method is not only scalable and reproducible but also produces lyophilizable nanoparticles that exhibit stability for a minimum of four months when stored at a temperature of -20 °C. Their findings indicate that the utilization of surface-functionalized PEGylated nanoparticles could be a favorable approach for delivering mRNA to the lung, specifically for the purpose of pulmonary immunomodulation [14]. Additionally, the results highlight the significant influence of PEG coatings on the overall performance of polymers.

3.2.2. Self-amplifying mRNA (SAM) Vaccines

The accelerated advancement of materials science has facilitated the rapid launch of non-viral mRNA delivery systems. SAM vaccines is another type of mRNA vaccine, which different from conventional mRNA-based vaccines. In comparison of conventional mRNA-based vaccines encoding both the antigen gene and RNA virus's modified genome, the novel SAM vaccines only replicate high level of the target antigen gene because they delete the gene of the structural protein of the virus with the enveloped positive-strand RNA virus SFV as vector, which contains four non-structural genes (nsP1-4). Certain SFV vectors exhibit diminished cytotoxicity [10]. A study shows the best ways to make, transfect, and measure the amount of replication-deficient SFV-PD particles that can be delivery of SAM-based vaccines. The study is to address the shortcomings of conventional and contemporary approaches and offer novel methodological assistance for the advancement of preventative and therapeutic vaccination platforms utilizing recombinant SFV particles [15].

4. Summary

Diverse delivery methods make up for mRNA's drawbacks in a number of preclinical investigations on viruses and cancer. Developing a systematic strategy, which is also the initial stage in the creation of tumor antigen vaccines, might be aided by optimizing the screening and identification processes of TAs, particularly neoantigens. Investigating the molecular structure and optimizing the design of mRNA vaccines is conducive to improving its stability. The rapid development of nanotechnology, polymers and other materials has made great contributions to the optimization of mRNA delivery systems, which has brought revolutionary development to the treatment of cancer. Currently, there are various tumor vaccines undergoing clinical trials, mainly focusing on melanoma, glioblastoma, prostate cancer, and leukemia. In summary, via extensive investigation into the properties of mRNA, study of tumor immunological processes, and ongoing advancements in materials science, the potential for the effective production of mRNA tumor vaccines for many types of cancer is steadily growing. Notwithstanding the enormous potential of mRNA tumor vaccines, further study and interdisciplinary collaboration are necessary to enhance their efficacy and establish them as universally successful therapeutic modalities.

References

[1] Lorentzen C L, Haanen J B, Met Ö, et al. Clinical advances and ongoing trials on mRNA vaccines for cancer treatment. Lancet Oncol, 2022, 23 (10): e450 - e458.

[2] Gupta M, Wahi A, Sharma P, et al. Recent Advances in Cancer Vaccines: Challenges, Achievements, and Futuristic Prospects. Vaccines (Basel), 2022, 10 (12).

[3] Vishweshwaraiah Y L, Dokholyan N V. mRNA vaccines for cancer immunotherapy. Front Immunol, 2022, 13: 1029069.

[4] Kudla G, Lipinski L, Caffin F, et al. High guanine and cytosine content increases mRNA levels in mammalian cells. PLoS Biol, 2006, 4 (6): e180.

[5] Sahin U, Karikó K, Türeci Ö. mRNA-based therapeutics--developing a new class of drugs. Nat Rev Drug Discov, 2014, 13 (10): 759 - 80.

[6] Karikó K, Muramatsu H, Welsh F A, et al. Incorporation of pseudo uridine into mRNA yields superior nonimmunogenic vector with increased translational capacity and biological stability. Mol Ther, 2008, 16 (11): 1833 - 40.

[7] Thess A, Grund S, Mui B L, et al. Sequence-engineered mRNA Without Chemical Nucleoside Modifications Enables an Effective Protein Therapy in Large Animals. Mol Ther, 2015, 23 (9): 1456 - 64.

[8] Sittplangkoon C, Alameh M G, Weissman D, et al. mRNA vaccine with unmodified uridine induces robust type I interferon-dependent anti-tumor immunity in a melanoma model. Front Immunol, 2022, 13: 983000.

[9] Ramos Da Silva J, Bitencourt Rodrigues K, Formoso Pelegrin G, et al. Single immunizations of self-amplifying or non-replicating mRNA-LNP vaccines control HPV-associated tumors in mice. Sci Transl Med, 2023, 15 (686): eabn3464.

[10] Verbeke R, Lentacker I, Breckpot K, et al. Broadening the Message: A Nanovaccine Co-loaded with Messenger RNA and α-GalCer Induces Antitumor Immunity through Conventional and Natural Killer T Cells. ACS Nano, 2019, 13 (2): 1655 - 1669.

[11] Huang P, Jiang L, Pan H, et al. An Integrated Polymeric mRNA Vaccine without Inflammation Side Effects for Cellular Immunity Mediated Cancer Therapy. Adv Mater, 2023, 35 (3): e2207471.

[12] Chen J, Ye Z, Huang C, et al. Lipid nanoparticle-mediated lymph node-targeting delivery of mRNA cancer vaccine elicits robust CD8(+) T cell response. Proc Natl Acad Sci U S A, 2022, 119 (34): e2207841119.

[13] Yang W, Mixich L, Boonstra E, et al. Polymer-Based mRNA Delivery Strategies for Advanced Therapies. Adv Healthc Mater, 2023, 12 (15): e2202688.

[14] Ke X, Shelton L, Hu Y, et al. Surface-Functionalized PEGylated Nanoparticles Deliver Messenger RNA to Pulmonary Immune Cells. ACS Appl Mater Interfaces, 2020, 12 (32): 35835 - 35844.

[15] Savar N S, Vallet T, Arashkia A, et al. Packaging, Purification, and Titration of Replication-Deficient Semliki Forest Virus-Derived Particles as a Self-Amplifying mRNA Vaccine Vector. Iran Biomed J, 2022, 26 (4): 269 - 78.