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mRNA Vaccines: a Powerful Tool in Cancer Treatment

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Abstract:

Cancer has always been one of the difficult objects for people to conquer. It's killed a lot of people over a long period of time. As time goes on, technology becomes more and more advanced, and people are not limited to previous cancer treatments, but continue to research and try to find more treatments. In recent years, mRNA vaccines have gradually entered our field of vision. Compared with conventional vaccines, it often has a more flexible structure that can be modified, safer delivery methods, and higher efficiency. Although functional beyond imagination, the lack of knowledge in this area has prevented the use of mRNA vaccines in the treatment of many cancers. Once the many limitations and problems of mRNA are successfully solved, it can not only greatly promote the development of cancer treatment, but also make modern medicine get a milestone. This review introduces the current research and development progress of mRNA vaccines, and discusses the structure, delivery and application of mRNA vaccines.

Keywords: mRNA vaccine; cancer immunotherapy; mRNA delivery; LNP; personalized vaccine.

1. Introduction

For a long time in the past, cancer was always regarded as an incurable disease. People have been fighting them for years and they haven't been able to conquer them. In recent years, with the development of science and technology, more and more treatments for cancer have been developed and put into use. Among them, immunotherapy is highly expected by people, including microbial therapy, car T cell therapy and so on [1]. Among these therapeutic means, mRNA vaccine is one of the focus objects in recent years.

mRNA was first discovered as a form of genetic material in 1961 [2]. The concept of it as a drug was not mentioned until about 30 years later. Its main mechanism is based on the mechanism of immunotherapy: by activating the own immune system to effectively kill cancer cells [1]. In contrast, mRNA vaccines encode cancer antigens by using mRNA's own characteristics, so that the immune system can recognize cancer tissue more efficiently [3]. In fact, mRNA vaccine, as a type of immunotherapy, has many advantages that traditional therapies do not have. For example, the mechanism of mRNA vaccines is based on genetic material, which makes them safe and free of contamination during use [4]. In addition, the process of converting genes into proteins is relatively simple, which is helpful for large-scale use [4]. Then it is easier to overcome traditional vaccine resistance due to the unique mechanisms of mRNA vaccines themselves. Although mRNA vaccine has many advantages in the field of cancer treatment, it still has many defects, the main ones are: low stability, poor transportation efficiency and so on[4]. And these are the main breakthrough directions that people want to take at present. Once the major shortcomings of mRNA vaccines are successfully reduced or even completely solved, this will have a huge impact on vaccines and the entire field of cancer treatment. Deaths from cancer may also be greatly reduced.

This review provides an overview of the current status of mRNA, including the structure and improvement of mRNA vaccines, their delivery methods, and some currently available applications.

2. Sequence Optimization of mRNA Vaccine

With the continuous development of science and technology, immunotherapy has become a promising cancer treatment. The main mechanism is to activate immune system through full-time antigen-presenting cells and try to amplify the anti-tumor immune response, so as to achieve the effect of killing diseased cells [1]. At the same time, immunotherapy also has fewer side effects than conventional cancer treatments, which can also help patients recover in the future.

At present, mRNA vaccines are mainly divided into two categories: non-replicating mRNA and self-amplifying RNA. The non-replicating mRNA consists of a 7-methylguanosine (m7G) 5′ cap, a 5′-untranslated region (5'-

UTR), an open reading frame (OFR), a 3'-untranslated region (3'-UTR), and a 3'poly(A) tail [5]. Self-amplifying RNA, on the other hand, has two OFRs. One encodes objective antigen, and another encodes viral replication component [6]. These features enable durable RNA amplification and induce a more durable and robust immune response. However, the research of SAM vaccines is still in the preclinical stage, and its feasibility needs to be further verified, so the current focus of mRNA vaccines is mainly on non-replicating mRNA [6].

mRNA vaccines are mainly introduced into the body through adoptive transfer of dendritic cells (DCs) in vitro and direct injection [7]. The basic principle of an mRNA vaccine is that it can encode some tumor-specific antigens (TAA and TSA), deliver them to the cytoplasm of the host and express them as epiantigens [7]. Through the main histocompatibility complex, TAA and TSA are presented on the surface of the APC. When they come near the T cells, the T cells are activated. The antigenic activity of T cells is substantially enhanced to enhance host anti-tumor activity. Subsequently, the tumor cells are targeted and destroyed by the body's immune system.

Compared with other vaccine platforms, mRNA vaccines often have many advantages. First of all, compared with other immunotherapies such as DNA vaccines, mRNA vaccines are usually more efficient and safer because they do not need to enter the nucleus to translate into the desired genes, which makes them not integrate with the host genome and avoid the possibility of mutations [4]. Second, the production of mRNA vaccines tends to be low-cost and simple, which allows them to be used on a large scale [4]. Then, it was also found that mRNA also has great potential to promote memory immunity and activate innate immunity [4]. This may mean that fewer doses of the mRNA vaccine may be enough to activate the immune system.

Although there has been a great breakthrough in the development of mRNA, there are still many problems that need to be solved. The main problem is the instability of RNA itself, mainly due to the presence of a hydroxyl group at the 2' position on the ribose [7]. This makes mRNA vaccines more sensitive to the environment. Second, mRNA activates innate immunity by expressing different pattern recognition receptors on the surface of APCs[7]. However, in fact, this immune activation may inhibit mRNA translation to a certain extent, thus affecting the antigen expression ability of mRNA to a large extent [6]. Finally, there are some problems with the clinical performance of mRNA. The safety of mRNA vaccines has been verified before clinical trials [7]. However, in clinical trials, it has been found that mRNA vaccines may be related to some rarer thrombosis times [7]. So far, little is known about the sector.

At present, there are a number of optimization strategies for mRNA vaccines. The main attempts were to tweak the skeletal and non-translated regions. Often, these structures are modified to improve their stability and translation efficiency. Poly(A)-binding proteins can also interact with the 5′ cap-binding complex eIF4G under human manipulation, which also improves the stability of mRNA itself [8]. Other optimization methods that can play a role in the same type of improvement also include ORF codon optimization and shortening of poly(A) sequences [8].

As mentioned earlier, one of the main factors limiting the development of mRNA is the activation of innate immunity. People choose to modify mRNA transcripts with alternative nucleotides, such as 5-methylcytidine (m5C) for cytidine, and pseudouridine (Ψ) or 1-methylpseudouridine (m1Ψ) for uridine [7]. In addition, high-purity mRNA has been found to contribute to minimal innate immune activation [7]. In response to this discovery, some new purification methods have also begun to be studied.

In recent years, major studies have been conducted on the effectiveness and immunogenicity of mRNA. By using genetic engineering, the synthesized mRNA tends to become easier to translate. In addition, there are a number of mRNA vaccines in development, each with its own unique mechanism of action, advantages and disadvantages. Adjuvants, immune checkpoint inhibitors, gene-editing tools, or novel delivery systems are also being tried in combination with mRNA vaccines, which may enhance the immune system's immune response to cancer cells. The abundance of possibilities has led to the prospect of mRNA research, and it is believed that these innovative therapies have great potential in the fight against cancer.

3. Delivery of mRNA Vaccines

mRNA vaccine molecules are generally larger, which is why they are generally difficult to pass directly through the lipid bilayer of cell membranes [2]. At the same time, exposed mRNA is easily degraded by nucleases in the blood, making it lose its original role [2]. Therefore, a suitable delivery method becomes very important.

Currently, LNPS are the most promising means of delivery because they can efficiently transport most hydrophilic or hydrophobic molecules [4]. At the same time, it is the only delivery method that has shown clinical effectiveness and is approved for use. The composition of LNP is mainly composed of cations, auxiliary lipids, cholesterol and polyethylene glycol [2]. The lipid double shell formed by LNP can effectively stabilize the internal molecules, so that it can not be affected by the blood environment. In fact, every component within the LNP plays a signifi-

cant role in mRNA vaccine delivery. The first is ionizable cationic lipids. It plays an important role in determining the ability of RNA to be released and functionalized: it can encapsulate and isolate mRNA so that it is no longer affected by nucleases [9]. The second is phosphoric acid, which can mainly optimize the structure and targeted delivery of LNP to a certain extent [9]. And finally, cholesterol. At first, researchers thought it played only a small role in keeping the LNP structure stable [10]. However, in further investigation, it was found that the structural instability caused by the lack of cholesterol would greatly affect the efficacy of cell absorption and intercellular transport [10]. Recent studies have shown that the transport efficiency of LNP can be further improved by chemical modification of cholesterol [10]. Interestingly, the transport performance of LNP is easily affected by changes in some physical and chemical properties. First of all, the size of LNP can directly affect the interaction between LNP and biological system, and the reduction in size can make LNP particles more sensitive and reactive to their surrounding environment [2]. Secondly, charge also has a non-negligible effect on LNP. Negatively charged mRNA interacts electrostatic with positively charged cationic lipids [2]. As the ability of cationic lipids to gain positive charge increases, the force of this interaction becomes stronger, resulting in a better sealing effect of mRNA [2]. Shape is directly related to LNP performance. It has been investigated that the proliferation of kernel cells of spherical nanoparticles is relatively easy, but the reason behind this is not yet clear [9].

In addition to LNP delivery, there are many promising delivery methods, but they are still in the research stage and have not been put into practical use. One promising comparison is between peptide-based transport and the use of viruses as vectors [5].

Peptide-based transport is also possible. The important mechanism is to allow mRNA to form a tight bond with protein amines and allow peptides to provide protection for mRNA, separating it from nucleases and avoiding degradation [5]. At the same time, various immune cells are induced to mount a powerful immune response. In this research direction, cellular osmotic peptides have achieved great success. Cytosolic peptides can prompt endosome to release mRNA and induce an immune response, while enhancing protein expression in dendritic cells and cancer cells, which can make mRNA expression in dendritic cells easier [5].

Virus-like particles use the virus as their carrier and then present the antigen [5]. Many viruses can act as this sample, but there are many security risks. After conducting research, it was decided to use only replication-deficient or attenuated viruses. Their delivery mechanism is usually to encapsulate the required rna and deliver it directly to the desired location [5]. Since the carrier used has been screened, the process does not cause damage to the body. In addition, it has many advantages: its simple and rapid preparation makes it potentially useful in large quantities, and the carrier can be introduced into the body by subcutaneous injection, reducing the risk of internal particles leaking into normal organs [5].

4. Application of mRNA Vaccines in Cancer Treatment

mRNA-based therapeutic vaccines have made many breakthroughs in the past period, and the infection of mRNA into dendritic cells for adoption and transfer is the first project to enter clinical trials. Although dendritic cell-based mRNA vaccines still account for the majority of mRNA vaccines, a large number of collected anti-tumor data prove that more mRNA-based therapeutics have a promising future. The first is the mRNA that encodes an immunostimulant. By injecting this stimulator within the tumor, the inhibitory tumor environment can be effectively altered [5]. This therapy is not considered a cancer vaccine, but it is usually used in conjunction with a cancer vaccine or other immunotherapy agents to achieve better results. In addition, more mRNA-based cancer vaccines are also being tested in clinical trials, and they can either encode personalized neoantigens, TAA antigens, or have other coding methods [5].

The first to be mentioned are the immunostimulants encoded by mRNA. Immunostimulants are usually composed of cytokines or chemokines that induce the maturation of APCs to activate T cells and trigger corresponding immune responses [5]. At present, a certain breakthrough has been made in an adjuvant based on TriMix mRNA, which is mainly composed of three bare mRNA molecules [11]. The therapy can stimulate CD70 molecules to induce activation of CD8+ T cells, activate CD40 ligands to activate CD4+ T cells, or constitute active TLR4 to promote direct current antigen presentation [11]. In clinical trials, the TriMix mRNA loaded with this therapy is immunogenic and well tolerated. In the treatment of melanoma patients, TriMix mRNA can elicit a strong immune response and effectively increase the survival rate of patients when used in combination with the CTCA-blocking monoclonal antibody ipilimumab checkpoint inhibitor or alone [11].

In addition, two other mRNA products encapsulated in the LNP platform have also entered clinical testing, which are mainly used for immunostimulatory activities within tumors [5]. One is mRNA-2416, which can be used to treat lymphoma or metastatic ovarian cancer. Often, it can be given alone or in combination with some PD-L1 to

good effect. The other product is mRNA-2752, which is mainly composed of OX40L/IL-23/IL-36Y mRNA [5]. It is mainly used to treat lymphoma. During the treatment, OX40L composed of 40L positive and secondary signals, which can effectively enhance the function of T cell effectors, and IL-36Y further enhances the body's anti-cancer response. IL-23 compensates for innate and adaptive immunity[5] .

In addition to immunosuppressants, mRNA can also be used to encode tumor antigens and trigger immune responses [5]. The development of TAAs expressed by malignant cells can be effectively inhibited, but locating and countering these TAAs is always the most difficult part of vaccine development [5]. For example, TAA in melanoma includes tyrosinase, gp100, MAGE-A3, and MAGE-C2. An mRNA vaccine that encodes all TAAs has already been used.

The more well-known of this mRNA vaccine platform is Lipo-MERIT [5]. It is formed by mRNA binding to cationic lipids. Lipo-MERIT has been tested and proven to effectively target spleen dendritic cells in mice and activate a large number of immune cells [5]. In clinical trials, four patients with advanced melanoma received the BNT111 vaccine, which can encode four TAAs at the same time, and the results showed that three patients successfully elicited a large number of T-cell responses in their bodies, confirming the feasibility of the vaccine [5]. Another mRNA vaccine with better performance is CV9202 developed by CureVac, which can encode 6 TAAs. In early clinical development, CV9202 can be used in combination with chemotherapy and radiotherapy for the treatment of patients with stage 3 non-small cell lung cancer [5]. In observations, the vaccine was found to be well tolerated, with only a very small fraction of reactions associated with flu-like symptoms. Eighty-four percent of patients who received CV9202 were observed to have an increase in specific immune responses, demonstrating its effectiveness [5].

In fact, mRNA vaccines can also be used to encode neoantigens and make personalized vaccines [12]. Many cancers cannot be treated conventionally due to their characteristics, mainly limited TAAs that limit their use, patients with broadly variable TAAs that lead to resistance to immune effectors, and peripheral tolerance responses to vaccines against TAAs, which can be addressed well by personalized vaccines [12].

Currently, Moderna and Mersk have collaborated on the development of mRNA-5671, a Kras personalized vaccine. By combining with the PD-specific antibody KEYTRUDA, IT can effectively treat some patients with pancreatic cancer [13]. By administering the vaccine intramuscularly every three weeks, after nine cycles, it was found that the anti-tumor immune response had developed and the vaccine was well tolerated [5]. Another personalized vaccine, mRNA-4157, which is encapsulated in LNPs, can effectively treat cancers such as melanoma and bladder cancer when used in combination with or alone with pembrolizumab [5]. In one experiment, the combination of pembrolizumab and mRNA-4157 elicited a very robust immune response, demonstrating its effectiveness to some extent [5].

5. Conclusion

Cancer has always been a difficult problem in human medicine, and many conventional treatments will lose their original effect when treating cancer. But the widespread use of mRNA has changed that. As a type of immunotherapy, mRNA vaccines have their own unique mechanism: they activate the originally suppressed T cells by encoding tumor antigens, so that the cancer cell killing process can begin. Compared with other vaccine platforms, mRNA vaccines have several significant advantages: they can be synthesized in vitro in a short period of time, mRNA fragments are not fused with the host genome, and safety can be guaranteed with a certain efficiency. At the same time, mRNA production is very simple and low-cost, which has the potential to help large-scale production in the future. In addition, the structure of the mRNA is also worth noting. The main structure of mRNA consists of 5'cap, UTR, ORF and Poly(A). Interestingly, it has been found that these parts can be modified to a certain extent to improve the performance of mRNA vaccines, which makes the development of this vaccine endless. The delivery of mRNA vaccines has always been a relatively difficult field to make breakthroughs. Once the mRNA enters the bloodstream, it may be degraded by nucleases and lose its original effect. At present, LNP is the main delivery method, which can effectively avoid mRNA being affected, but the effect is not ideal in some specific situations. At the same time, research on other delivery methods has stalled, and it is hoped that more effective delivery methods will be available in the future. After the effectiveness of mRNA vaccines has been widely recognized, they have gradually been used in practical cases. Current studies have shown that mRNA vaccines have a very promising future in the field of personalized vaccines. When a variety of personalized vaccines are developed, cancers that are difficult to conquer, such as pancreatic cancer, can also be effectively suppressed, and the development of medicine will also be greatly helped.

References

[1] Zhang Y, Zhang Z. The history and advances in cancer

immunotherapy: understanding the characteristics of tumor-infiltrating immune cells and their therapeutic implications. Cell Mol Immunol. 2020 Aug;17(8):807-821.

[2] Huang T, Peng L, Han Y, Wang D, He X, Wang J, Ou C. Lipid nanoparticle-based mRNA vaccines in cancers: Current advances and future prospects. Front Immunol. 2022 Aug 26;13:922301.

[3] Lorentzen CL, Haanen JB, Met Ö, Svane IM. Clinical advances and ongoing trials on mRNA vaccines for cancer treatment. Lancet Oncol. 2022 Oct;23(10):e450-e458.

[4] Li Y, Wang M, Peng X, Yang Y, Chen Q, Liu J, She Q, Tan J, Lou C, Liao Z, Li X. mRNA vaccine in cancer therapy: Current advance and future outlook. Clin Transl Med. 2023 Aug;13(8):e1384.

[5] Miao L, Zhang Y, Huang L. mRNA vaccine for cancer immunotherapy. Mol Cancer. 2021 Feb 25;20(1):41.

[6] Zhang G, Tang T, Chen Y, Huang X, Liang T. mRNA vaccines in disease prevention and treatment. Signal Transduct Target Ther. 2023 Sep 20;8(1):365.

[7] Liu J, Fu M, Wang M, Wan D, Wei Y, Wei X. Cancer vaccines as promising immuno-therapeutics: platforms and current progress. J Hematol Oncol. 2022 Mar 18;15(1):28.

[8] Xu S, Yang K, Li R, Zhang L. mRNA Vaccine Era-Mechanisms, Drug Platform and Clinical Prospection. Int J Mol Sci. 2020 Sep 9;21(18):6582.

[9] Kiaie SH, Majidi Zolbanin N, Ahmadi A, Bagherifar R, Valizadeh H, Kashanchi F, Jafari R. Recent advances in mRNA-LNP therapeutics: immunological and pharmacological aspects. J Nanobiotechnology. 2022 Jun 14;20(1):276.

[10] Cheng X, Lee RJ. The role of helper lipids in lipid nanoparticles (LNPs) designed for oligonucleotide delivery. Adv Drug Deliv Rev. 2016 Apr 1;99(Pt A):129-137.

[11] De Keersmaecker B, Claerhout S, Carrasco J, Bar I, Corthals J, Wilgenhof S, Neyns B, Thielemans K. TriMix and tumor antigen mRNA electroporated dendritic cell vaccination plus ipilimumab: link between T-cell activation and clinical responses in advanced melanoma. J Immunother Cancer. 2020 Feb;8(1):e000329.

[12] Guo Y, Lei K, Tang L. Neoantigen Vaccine Delivery for Personalized Anticancer Immunotherapy. Front Immunol. 2018 Jul 2;9:1499.

[13] Cafri G, Gartner JJ, Zaks T, Hopson K, Levin N, Paria BC, Parkhurst MR, Yossef R, Lowery FJ, Jafferji MS, Prickett TD, Goff SL, McGowan CT, Seitter S, Shindorf ML, Parikh A, Chatani PD, Robbins PF, Rosenberg SA. mRNA vaccine-induced neoantigen-specific T cell immunity in patients with gastrointestinal cancer. J Clin Invest. 2020 Nov 2;130(11):5976-5988.