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Current Advance and Future of mRNA Vaccine in Cancer Therapy

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Abstract:

After years of development, cancer vaccines have gradually become an important part of tumor immunotherapy, and have shown a more rapid development momentum under the background of the current era. The vaccine has the advantages of high efficiency, safety, rapid development potential, cost-effectiveness, etc. In recent years, with the continuous improvement of mRNA technology, relevant technologies in the field of mRNA molecules have also made breakthrough progress, and mRNA vaccines have achieved certain results in cancer treatment. Compared with traditional vaccines, mRNA vaccines can induce the body to produce humoral immunity and cellular immunity at the same time, and the research and development cycle is short, the cost is low, and it can quickly develop candidate vaccines to deal with virus mutation, which is conducive to cancer control. mRNA vaccines have become a current research hotspot and have wide application prospects in the prevention and treatment of tumors and infectious diseases. This article comprehensively discusses the structural characteristics, types, unique advantages and future prospects of mRNA vaccines, in order to help understand the vaccine function and clinical application of mRNA, provide a direction for the development of mRNA drugs, and expect that mRNA cancer vaccines will be used in clinic as soon as possible to benefit patients.

Keywords: mRNA; vaccine; cancer.

1. Introduction

There are many kinds of cancer, which has always been one of the most important diseases endangering human health. At present, there are about 20 million new cancer cases and about 10 million deaths due to that every year all over the world, the severity of which is second only to cardiovascular diseases. Surgery and radiotherapy and chemotherapy are still the foundation for the treatment of various cancers, especially surgery is still the radical treatment for most solid malignant tumors. Exploring effective cancer treatment methods has always been the main goal of researchers around the world. Fortunately, the revolutionary development of certain targeted therapy and immunotherapy has overturned conventional ideals. The mechanism of action of immunotherapy is to use the immune system of the human body to find and destroy those cancer cells, thereby strengthening the immune system so that it can do more things to find and kill those bad cells. The mRNA vaccines and drugs to treat cancer belong to immunotherapy. The mRNA vaccines do not contain viruses that cause disease. Instead, they contain "messenger molecules" that can give your body instructions for a particular formula. Due to the delay in the diagnosis and treatment of many cancer patients caused by the COVID-19 pandemic, the persistent epidemic in recent years has also accelerated the exploration and application of novel coronavirus vaccines and promoted the development of cancer vaccines. With the gradual in-depth understanding and research on cancer mRNA vaccines, such vaccines are gradually being applied to various cancers and obtaining better and better efficacy. This review introduces mRNA vaccines and discusses current advances and the future of mRNA vaccines [1].

2. Structure of mRNA Vaccine

The basic structure of mRNA vaccines is similar to that of eukaryotic mRNAs. They are all single-stranded molecules, and affect the strength and specificity of immune responses by increasing the nucleoside modification of mRNA molecules and structural elements. Structural elements such as cap structures (Cap), Poly A tails, and untranslated regions (UTR) can directly affect the stability and translation efficiency of mRNAs, especially Cap and Poly (A) tails located at the 5′ and 3′ ends of mRNAs are crucial for the stability of mRNAs in the cytoplasm. mRNAs also require open reading frames. Besides, RNA structure, translation efficiency, and protein folding mechanism are most likely altered by rare codon replacement of mRNA sequences or insertion of modified nucleotides.

The cap structure at the 5 ‘end is a significant part of mRNA and can initiate protein translation by binding to eukaryotic translation initiation factors. During the in vitro transcription of mRNA, capping can be performed using an anti-reversal cap mimic (ARCA) or CleanCap capping technology. In addition, post-transcriptional capping can also be performed using vaccinia virus capping enzyme. Capping modification can regulate the initiation of antigen protein translation by recruiting translation initiation factors. The purpose is to protect mRNA transcribed in vitro from degradation by exonuclease and avoid excessive activation of innate immunity.

The Poly A tail structure at the 3 ‘end can protect mRNA from degradation by poly A-binding protein (PABP) nuclease, so the addition of the Poly A tail structure at the 3’ end can also improve the stability and translational activity of mRNA. In addition, tailing can be carried out by adding Poly A sequences to gene fragments or by extending mRNA molecules after transcription in vitro using Poly A tail polymerase. Tail length is an important factor in the stable expression of mRNA, and a longer Poly A tail can improve the stability and translation efficiency of mRNA, but it is worth emphasizing that this effect is not linear. The optimal length of the tail depends on the type of target cell.

UTR can affect the translation rate and stability of mRNA. Default mRNA UTR sequences of high-level expressed genes (such as the mRNA UTR of widely used α/β-globin) or self-designed and screened high-efficiency nucleic acid sequences can be used as mRNA UTR sequences, which can improve the translation rate of mRNA and prolong the half-life of mRNA. In addition, the translation efficiency of mRNA can be improved by introducing modified nucleotides and using optimized codons [2].

3. Classification Based on Types of mRNA

mRNA vaccines represent a groundbreaking technology in the field of vaccine development, offering a versatile platform for preventing and treating infectious diseases, as well as certain types of cancer. These vaccines leverage the body’s natural processes to produce antigens and elicit an immune response. Here, we delve into the classification of mRNA vaccines based on the types of mRNA they use and the routes of administration.

3.1 Based on Types of mRNA

3.1.1 Non-replicating mRNA (nrRNA) Vaccine

At present, mRNA vaccines that are being widely studied can be divided into two types, including non-replicating mRNA vaccine and self-amplifying mRNA vaccine. Non-replicating mRNA vaccines are complicated fragments of mRNA encoding antigenic proteins transcribed in vitro, upstream and downstream containing 5 ‘cap structures and 3’ poly A tails, respectively, encoding only the target antigen. It only encodes the target antigen. The molecular weight is small and the structure is simple. Since no other proteins other than the antigen protein are encoded, the possibility of non-essential immune responses is reduced. However, the expression of non-replicating mRNAs is limited due to their transient characteristic. Higher dosage of mRNA may be required to achieve high-level expression of the antigen proteins. Efforts can be made to overcome this bottleneck in the development process by using sequence optimization and formulation adjustment.

3.1.2 Self-amplifying mRNA (SAM) Vaccine

The principle of action of the self-amplifying mRNA vaccine is to add a replicable sequence to the mRNA sequence, and after entering the cell, it can use the host cell for self-replication like a virus. Compared with traditional mRNA vaccines, this type of RNA vaccine self-amplifies in vivo, with a higher level of antigen expression, and even a smaller dose can cause a very strong immune response. Self-amplifying mRNA usually uses the sequence of single-stranded RNA viruses, such as alpha virus, flavivirus and small RNA virus. Evaluation of the self-amplifying mRNA vaccine protecting mouse models from H1N1/PR8 infection shows that the dose required for the self-amplifying mRNA vaccine to induce an immune response is only 1/64 of that of the non-replicating mRNA vaccine. However, the self-amplifying mRNA vaccine faces unique challenges in research and development. Since the molecular weight of self-amplified mRNA is much larger than that of traditional non-replicating mRNA, the risk of adverse reactions caused by high antigen levels is difficult to predict. Therefore, future vaccine research and development of this type requires special design or formulation adjustment of delivery vectors.

3.1.3 Trans-amplifying mRNA Vaccine

Trans-amplified mRNA vaccine is a certainly new type of mRNA vaccine. Trans-amplified mRNA is based on self-amplified mRNA. The sequence encoding replicase and the sequence expressing antigenic protein are inserted into two templates for expression. These vaccines consist of two components: a non-replicating mRNA that encodes the antigen and a separate self-amplifying mRNA that drives the expression of the antigen. The self-amplifying component provides the replication machinery, while the non-replicating mRNA encodes the antigen. The evaluation of trans-amplified mRNA vaccine for protecting mice

from influenza virus infection shows that trans-amplified mRNA vaccine can induce antibodies in mice and can produce protective effects. Compared with self-amplified mRNA, trans-amplified mRNA is safer and has a wider range of applications. On the basis of ensuring high yield and high quality, it is less difficult to produce shorter mRNA, so the research and development cost of trans-amplified mRNA vaccine is lower. However, compared with other mRNA vaccine types, clinical experience is limited.

3.2 Based on Route of Administration

mRNA vaccines must cross the cell membrane to reach the cytoplasm for antigenic protein expression. mRNA is negatively charged and has a large molecular weight, which is easily degraded by nuclease. Different delivery strategies are needed to solve this problem. The route of administration for mRNA vaccines can influence the efficacy, safety, and distribution of the vaccine within the body. Here are the various routes of administration.

3.2.1 Subcutaneous Injection

Subcutaneous injection delivers the vaccine to the skin layer directly below the dermis. This route is suitable for vaccines that do not require deep tissue penetration and can stimulate a strong immune response at the injection site. This method is easy to administer and stimulates local immune responses, but there is a possibility that it will not be effective against systemic diseases.

3.2.2 Intradermal Injection

Intradermal injection is injected directly into the dermis of the skin. This route is beneficial to vaccines designed to activate skin-resident immune cells, such as dendritic cells, which are important for initiating the immune response. Direct delivery to immune cells can enhance the immune response. However, the accuracy of the injection technique is very high and may cause more local inflammation.

3.2.3 Intramodular Injection

Intranodal injections directly target lymph nodes, which are key sites for immune cell activation. This route can potentially enhance the immune response by delivering antigens to where immune cells are activated. It can be delivered directly to immune cells, enhancing the immune response. But precise localization is required, and current clinical experience is limited.

3.2.4 Intramuscular Injection

Intramuscular injection is the most common route for mRNA vaccines, including COVID-19 vaccine. This route ensures rapid absorption and distribution of the vaccine throughout the body, resulting in effective antigen expression and immune activation. It has rapid systemic distribution and mature injection techniques. However, it may cause muscle soreness in patients.

3.2.5 Intravenous Injection

Intravenous injection sends the vaccine directly into the blood, a route less common in mRNA vaccines but potentially useful in specific therapeutic settings, such as cancer treatment. Capable of immediate systemic distribution, it is suitable for systemic diseases. However, medical supervision is required and the risk of adverse reactions is high.

3.2.6 Intratumoural Injection

Intratumoral injection delivers the vaccine directly into the tumor. This method is mainly used in cancer immunotherapy, with the goal of stimulating an immune response against tumor cells. It is suitable for local immune responses and can enhance anti-tumor immunity, but may not be suitable for all tumor types.

3.2.7 Intrathecal Injection

Intrathecal injection delivers the vaccine to the cerebrospinal fluid that surrounds the brain and spinal cord. This route is mainly used for diseases affecting the central nervous system and can be delivered directly to the central nervous system [3].

4. Advantages of mRNA Cancer Vaccines

4.1 Low Cost

Compared with many other current vaccination strategies (such as DNA vaccines, etc.), the manufacture of mRNA vaccines does not require cell culture, avoiding the risk of contamination. In addition, mRNA vaccines are directly transcribed in vitro, producing faster and cheaper, and playing an important role during the novel coronavirus pandemic. The mRNA vaccine technology platform can express multiple and arbitrary proteins at one time, which is suitable for the development of different types of mRNA vaccines and drugs, reducing costs and shortening the research and development cycle. Therefore, mRNA vaccines are expected to become a boon for cancer patients with often poor economic conditions [4].

4.2 Relatively High Safety

RNA nucleic acids can be naturally degraded in 2 to 3 days after entering the human body, and have more safety advantages than DNA-based vaccines, because the translation of mRNA occurs in the cytoplasm, it is easy to be degraded by the human body will not accumulate in vivo, and because it does not enter the nucleus, there is no risk of integration with the human genome, avoiding the risk

of insertion mutation; and, by using body cells to produce protein, cell-free culture, antigen extraction and purification techniques, the mRNA delivery system can reduce the inflammatory response caused by the mRNA vaccine, thereby further enhancing the safety of mRNA vaccines and avoiding immunogenicity and cytotoxicity caused by viral pollutants [5].

4.3 High Efficiency by Combination With Immunological Drugs

Early clinical trial results have indicated that mRNA vaccines have generated are liable immune response and are well-tolerated by healthy individuals with relatively high efficiency. In order to improve the efficacy, mRNA vaccines and drugs are often combined with other immunotherapies. So far, a variety of immunotherapies based on mRNA vaccines and drugs have entered clinical trials and achieved some results in the treatment of solid tumors. Immune checkpoint inhibitors (ICIs) are the most commonly used tumor immunotherapy drugs. ICIs are a class of monoclonal antibodies that can target specific receptors on the surface of immune cells or tumor cells in vivo, inactivating host cytotoxic T lymphocytes induced by tumor cells, thereby producing anti-tumor effects. However, due to immune escape, most cancer patients still have disease progression several years later. In this case, the combination of mRNA vaccines and ICIs can play a role in reversing drug resistance pathways, which is expected to become a powerful adjunct to ICIs, and is more conducive to the implementation of precise treatment and individualized treatment for patients [6].

5. Conclusion

With the advent and development of mRNA vaccines and the continuous harm of cancer to human health, the urgent need for new cancer mRNA vaccines will continue to increase. It can be expected that at a time when the world is vigorously developing COVID-19 vaccines, the lessons learned by researchers can be used to further promote the improvement and innovation of cancer immunotherapy based on mRNA vaccines. Under the background of the times, a large amount of money has been invested in the research of cancer mRNA vaccines worldwide. The structure, stability and delivery system of mRNA vaccines are constantly being optimized. In addition, the potential audience is huge, and this field is bound to have further development. This article summarizes the research status, structure, classification, advantages and disadvantages of mRNA vaccines. Based on the current status of tumor immunotherapy and the limitations of mRNA vaccines, future research should focus on developing the best preservation vector of mRNA vaccines, optimizing immune adjuvants, co-administration regimens, simplifying administration methods and improving transformation efficiency to enhance targeting, thereby improving their anti-tumor effects.

References

[1] Meng Wenjun, Peng Xingchen. Research status, challenges and prospects of cancer mRNA vaccines [J]. Journal of Practical Oncology, 2019,38(03)

[2]Chang Dongfeng, Sun Zhaopeng. Structure and clinical application of mRNA drugs [J]. Advances in Biotechnology, 2019,14(01)

[3] Hu J X, Zhang X L. Principle, research status and prospect of mRNA vaccines [J]. Journal of Wuhan University (Medical Science Edition),2023,44(09)

[4] Li Can, Liu Shuang, Zhang Xue. Research status of mRNA vaccine in cancer and infectious diseases [J]. Chinese Journal of Clinical Pharmacology, 2019,40(11)

[5] Miao L, Zhang Y, Huang L. mRNA vaccine for cancer immunotherapy [J]. Molecular Cancer, 2021, 25,20(1)

[6] Rengaraj P, Obrdlík A, Vukić D, Varadarajan NM, Keegan LP, Vaňáčová Š, O'Connell MA. Interplays of different types of epitranscriptomic mRNA modifications [J]. RNA Biol. 2021,15,18(sup1)