Review Article



# mRNA vaccine treatment for cancer: a narrative review

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**Background and Objective:** The paper wants to present the development of mRNA vaccine, which includes its structural characteristics, molecular design, chemical modification, delivery methods and clinical application. Based on the statistics of World Health Organization, one-sixth of the total annual deaths worldwide resulted from cancer, which seriously threatens human health. At present, the mRNA vaccine for cancer becomes a hot pot in cancer treatment. Moreover, mRNA vaccines are expected to be a new treatment for cancer, due to their immunity, safety and flexibility. This review will provide a strong theoretical basis for the treatment of cancer with mRNA vaccines in the future.

**Methods:** References for the comments are from PubMed, CBM and CNKI, with keywords like mRNA vaccine and delivery vector. Most of these were published from January 1, 2011 to April 1, 2022, whose types include clinical trials, meta-analysis, randomized controlled trials, etc. And there are no language restrictions for these included articles.

**Key Content and Findings:** The review presents the development of mRNA vaccine, which includes its structural characteristics, molecular design, chemical modification, delivery methods and clinical application.

**Conclusions:** The mRNA vaccine has unique advantages and great potential in cancer treatment. As the research on mRNA vaccine continues, it will provide a new treatment for cancer certainly.

**Keywords:** mRNA vaccine; cancer; immune response to the mRNA vaccine; melanoma; dendritic cells (DCs)

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## Introduction

In 1990, mRNA was injected into mice and found to be expressed in mice, producing related proteins in dose-dependent manner. Meantime, the direct injection of mRNA was found to produce an immune response by expressing specific proteins (1). Since then, mRNA has become the focus of molecular medical research, especially in the field of vaccines.

There are often genetic mutations in cancer cells which will produce new antigens (neoantigen). Since such new antigens are typically present only in cancer cells, not in normal cells, making them ideal antigens for developing cancer vaccines (2). The RNA vaccine is a single-chain structure with the feature of more simple and rapid synthesis compared to the DNA vaccine. More importantly, mRNA, unlike a relatively stable DNA, will then be degraded after transcription and have no other toxic or side effects to the body. The usual strategy is to find new antigens specifically expressed in cancer cells from cancer patients due to gene mutations through gene sequencing, and then use these new antigens to build corresponding cancer vaccines, send them back to the body to activate immune cells, and kill cancer cells with the help of the above antigens (3).

Furthermore, this review focuses on the application of RNA vaccines in clinical treatment, such as the treatment of melanoma by dendritic cells (DCs). The review details

**Table 1** The search strategy for articles in the database

| Items | Specification |
|---|---|
| Date of Search (specified to date, month and year) | 2021.3.20 |
| Databases and other sources searched | PubMed, CBM and CNKI |
| Search terms used (including MeSH and free text search terms and filters) | Search terms: "mRNA vaccine", "mRNA Vaccine Constructs", "delivery of mRNA vaccine", "immune response to the mRNA vaccine", "cancer", "melanoma", and "DC cells" |
| | Search strategy of PubMed database: first, we used PubMed's advanced search for keywords, such as melanoma, and then set the search range to "Title/Abstract". Second, we set the year within 10 years. We then selected the literature with complete experimental steps and complete experimental results as a reference for this review. As an example, the references in this review are found in this search pathway |
| Timeframe | Between January 1, 2011 to December 31, 2021 |
| Inclusion and exclusion criteria (study type, language restrictions etc.) | Inclusion criteria |
| | (I) No language restrictions |
| | (II) Article types: clinical trials, meta-analysis, randomized controlled trials, and articles |
| | Exclusion criteria |
| | (I) The mRNA vaccines used for diseases other than cancer |
| Selection process (who conducted the selection, whether it was conducted independently, how consensus was obtained, etc.) | All literature in this review was selected by Tianzhen Tang |

DC, dendritic cell.

the development history, mechanism of action and clinical treatment application of mRNA vaccine, which provides a strong theoretical basis for future clinical trials of mRNA vaccine for cancer treatment. We present the following articles in accordance with the Narrative Review reporting checklist (available at https://biotarget.amegroups.com/article/view/10.21037/biotarget-21-8/rc).

## Methods

The references of this review are all obtained from PubMed, CBM and CNKI. The key words were "mRNA vaccine", "mRNA Vaccine Constructs", "delivery of mRNA vaccine", "immune response to the mRNA vaccine", "melanoma", and "DC cells". Most of literatures were published from January 1, 2011 to April 1, 2022. The literature types include clinical trials, meta-analysis, randomized controlled trials, and articles as well. The specific strategy was listed in *Table 1*.

## Discussion

### *Development of mRNA vaccine*

In 1990, mRNA served as a demonstration of a potential *in-vivo* gene transfer technique when a direct injection of "naked" messenger ribonucleic acid was shown to lead to *in vivo* expression of the encoded protein (1). However, various problems hinder the ability to use *in vitro* transcribed mRNA as a simple method to produce a protein immunogen *in vivo* immediately after a simple injection, which include instability *in vivo* mRNA due to the presence of almost ubiquitous ribonucleases (4).

The assimilation of pseudo pyridine in mRNA is an important milestone in the development of the mRNA vaccine. Kariko and Weissman found that the use of modified nucleosides resulted in reducing immunity stimulating effect by reducing stimulation of Toll-like receptor (TLR) in the use of *in vitro* transcribed mRNA was a major advance in mRNA vaccine technology (5). It

is reported that modified nucleosides, including s2U and Ψ, cancelled the activation of the 5'-triphosphate-mediated alternative RNA reactive immunereceptor-formate induced protein I (RIG-I) (6). If any *in vitro* transcript containing nucleoside modification could remain translational and avoid immune activation *in vivo*, then this RNA can be developed as a therapeutic tool for vaccination. Kariko and Weissman further demonstrated that the use of pseudo pyridine instead of uredines, the resulting mRNA was also more stable and have more translation ability (7).

Further development made by Thess and colleagues was that the production of mRNA similarly does not stimulate innate reactions and simply avoids reducing protein production through sequence engineering without the need for nucleoside modification (8). The development of the formulation, such as the development of lipid-derived nanoparticles (LNPs) and lipid nanoparticle, could benefit the mRNA stabilization and its entry into the cell and facilitate its release from endocytosis (9). LNPs consist of a variety of lipids, usually including phospholipids, cholesterol, ionic lipids, and polyethylene glycol-coupled greases, which form the water center where a charged mRNA molecule is located. By this way, mRNA was protected, and was facilitated access to cells, even was exited from lysosome in order to deliver mRNA (10).

### *Types of mRNA vaccine*

In general, the mRNA vaccine encodes the target antigen, which contains 5' and 3' untranslated regions (UTRs). Currently, there are two available types of mRNA vaccine constructs: a non-replication mRNA (NRM) vaccine construct and a self-amplified mRNA (SAM) vaccine construct (11). The structure of both types of mRNA vaccines synthesized by *in vitro* transcription contains the 5' end Cap structure (5'Cap), 3' end poly(A) tail, non-translation region (5' and 3'), and encoding antigen proteins (12).

### *NRM vaccine constructs*

The non-replication RNA vaccine is a complete mRNA which includes UTRs of 3' and 5', and poly(A) tail contributing to mRNA stability and transcription (13). In addition, multiple base modifications in mRNA could improve mRNA stability. The delivery of the mRNA was mainly through nanoliposomes to trigger an immune response (14).

### *SAM vaccine constructs*

SAM ribonucleic acid vaccines encode both the required antigen and key viral replicon proteins from different viruses rather than from the target virus (15). The production of virus replicons encoded by messenger ribonucleic acid causes transduction cells to produce many copies of the antigen mRNA, and much more protein antigens. Therefore, the SAM vaccine may be more effective and not depend on enhanced doses (4).

### *Characteristics of the mRNA vaccine*

First, mRNA has more immunogenicity compared with conventional vaccines. It can express specific target proteins to induce specific immune response. As an immunogen of nucleic acids, mRNA could induce the natural immune response of the human body, and combining with its "self-adjuvant" characteristic makes the vaccine more immunogenicity (16).

In addition, mRNA provides a powerful security advantage. Firstly, as a minimal genetic construct, it contains only the elements directly required to express the coding protein. Secondly, mRNA does not interact with the genome, although recombination between single-stranded RNA molecules may occur in rare cases (17). Therefore, potentially harmful genomic integration is excluded. Finally, the lack of genome integration, coupled with the fact that mRNA is non-replicable and metabolizes in a few days, makes mRNA merely a transient information carrier (18).

Furthermore, the mRNA vaccine has production advantages. The cost of the mRNA vaccine is five to one tenth of the conventional vaccine. In addition, production and purification have nothing to do with the antigen itself, due to the similar chemical structure. And the production of the same mRNA vaccine can be easily transformed into different antigen vaccines that meet the European Medicines Agency (EMA) or The Food and Drug Administration (FDA) standards. Therefore, it is easy to be developed and produced in a short time when dealing with sudden infectious diseases (19). What's more, transportation and storage of mRNA may be easier than protein-based vaccines because RNA is properly protected from ribonuclease (RNases) and is less likely to degrade than proteins (9).

Despite its attractive properties and advances in the field, transmission of messenger ribonucleic acids *in vivo* is

still challenging (20). The first challenge is the instability of mRNA, which is caused by the enzymatic degradation of RNase. RNA enzymes are prevalent throughout the human body which can degrade exogenous RNA. The mRNA consists of hundreds to thousands of nucleotides and must reach the full length of the cytoplasm for active translation. Therefore, the protection of ribonuclease is essential for most *in vivo* delivery strategies (21). Secondly, the efficient transfer of mRNA within the cell is another challenge due to the negative charge of mRNA and the large molecular size. Negative charge prevents most mRNA from transferring on the negatively charged cell membrane. Large size to make effective encapsulation and delivery is more challenging than other payloads. In each of these obstacles, different delivery strategies have been studied to address these obstacles (22).

The mRNA vaccine encodes for three major types of proteins: antigens, neutralization antibodies, and proteins with immune stimulating activity (23). Antigenic or neutralizing antibody formulation and delivery techniques for mRNA vaccines can induce a specific immune response, while proteins bearing immune-stimulatory activity such as CD70Lint S, and granulocyte-macrophage colony-stimulating factor (GM-CSF) enhance innate and/or adaptive immunity (24).

The biggest obstacle to the development of mRNA vaccine technology is its activation of innate immunity, which is a double-edged sword for the mRNA vaccine (25). On the one hand, mRNA induces the body's immune protection through immune activation. On the other hand, excessive activation of congenital immunity can stop the translation of mRNA and degrade mRNA. Congenital immunity is the first line of defense of the human immune system that can identify pathogen-associated molecular patterns (PAMPs), then performing an immune response through a series of complex sets of intracellular cascade responses (26). As an external nucleic acid substance, the mRNA vaccine is recognized by a series of pattern recognition receptors located on the cell surface, endoplasmic reticulum and cytoplasm, and stimulates the body's innate immune response (27). It was found that the congenital immune response induced by the mRNA vaccine promoted the maturation of human DCs. Mature DC further present mRNA to the body's immune system, induce the body to produce special T cells and B cells immunity, and produce the expected immunoprotective effect on the human body. From this perspective, the mRNA-induced congenital immune response is favorable (28).

### *Molecular design and chemical modification of the mRNA vaccine*

Molecular design and chemical modification of mRNA vaccine are the basis for the synthesis of mRNA vaccine. MRNA synthesis is generally composed of plasmid DNA or other DNA fragments containing the target protein open reading box as a template and synthesized through *in vitro* transcription technology (29). Since mRNA contains a cap structure at 5' end and poly(A) structure at 3' end, these elements generally need to be added after transcription of mRNA *in vitro*. MRNA synthesis can be performed using T3, T7 or SP6 RNA polymerase and linear DNA (linearized plasmid DNA or synthetic DNA prepared through PCR) (30). Then, the mRNA was optimized in the following aspects.

#### 5'Cap optimization

Adding caps with cap analogues is the most common method of transcribing mRNA *in vitro*. However, it was found that conventional cap analogs can reverse bind mRNA sequences. To avoid the negative effects, the anti-reverse cap analogs (ARCA) was used, which have been modified at C2 or C3 locations with higher translation efficiency. Another cap analogue was developed in 2018, called "Clean Cap". It utilizes the trigger closure trimers to produce a naturally existing 5'Cap structure, which improves the closure efficiency to nearly 90–99% (31).

#### Poly(A) tail optimization

Poly(A) sequences can slow the degradation process of RNA exonuclease, increase stability, prolong the *in vivo* half-life, and improve the translation efficiency of mRNA. Furthermore, the poly(A) binding protein (PABP) can be connected to the 5'Cap through translation initiation factors (such as elF4G and elF4E), in turn affecting the closed-loop structure of mRNA and jointly regulating the stability and translation efficiency of mRNA. Poly(A) sequences of different lengths can affect the translation efficiency of mRNA to varying degrees, due to the poly(A) sequences required for the high translation efficiency of mRNA in various types of cells. Therefore, the length of poly(A) tail should be adjusted to optimize mRNA translation efficiency (32).

#### UTR optimization

UTR is a non-coding part of the upstream and downstream domain of the mRNA coding area, related to the mRNA replication and translation process (30).

In order to avoid the false start during mRNA translation, the specific sequences could be added to 5' UTR to enhance the stability and translation accuracy of mRNA. For example, Kozak sequence meant to insert the sequence GCC-(A/G)-CCAUGG in the promoter region to begin the translation process more accurately (33).

Stability regulation elements are often related with 3' UTR, for example, widely used 3' UTR sequences derived from α-globin and β-globin which contain translation and stability regulation elements.

**Open reading frame (ORF) optimization**

Choosing the appropriate codon in the ORF region can optimize the overall translation efficiency of mRNA, and the optimized ORF sequences usually contain synonymous frequent codon with higher tRNA abundance to replace the rare codon in ORF, thus using the same codon translation of the host, high expression genes, and/or guaranteeing the integrity of tRNA during expression (34).

The complete functional mRNA has some basic structural elements and the molecular design and chemical modification of mRNA vaccine focuses on enhancing its stability and reducing its immunogenicity.

### *Delivery of the mRNA vaccine*

Efficient mRNA delivery is an important factor in the success of mRNA vaccine treatment. A good delivery system helps the mRNA vaccine achieve full therapeutic potential. The bare RNA is easily degraded by nuclease and difficult to pass through the plasma membrane and escape from the endocytosis (35). Therefore, appropriate transport is needed to help mRNA molecules reach the cytoplasm and remain intact to ensure adequate antigen expression (36).

Delivery of mRNA vaccines usually requires the assistance of the mRNA vaccine delivery carrier. mRNA vaccine delivery carriers mainly include viral carriers and non-viral carriers. The virus carriers, such as lentivirus, adeno-related virus, Sendai virus and other carriers, can carry out nucleic acid delivery (10). But they may be limited by the immune response caused by the carriers, affecting their application. Non-viral vectors mainly include liposomes, polymers, inorganic nanoparticles, and polypeptides (37).

**Liposome**

Currently, the lipid, lipid-like compounds and lipid derivatives have been widely used in the preparation of lipid and LNPs for the delivery of mRNA vaccines *in vivo* (10).

**Polymer**

Polymer materials, including polyamines, bendy macromolecule and copolymers, are functional materials capable of delivering the mRNA vaccine. Similar to lipid-based functional vectors, polymers can also protect RNA from ribonuclease-mediated degradation and promote intracellular delivery (37).

**Cationic nanoemulsion (CNE)**

CNE uses hydrophobic and hydrophilic surfactants to stabilize the oil core in the aqueous phase and produce particles for RNA vaccine delivery (38). MF59 is a kind of FDA-approved water-wrapped oil nanoemulsion adjuvant for an inactivated influenza vaccine in the elderly. Adding a cationic lipid to a squalene-based formulation, for example, DOTAP, can produce positively charged CNE particles that can absorb a negatively charged nucleic acid into the shell. This surface interaction still protects the mRNA from ribonuclease degradation (39).

**Polypeptide**

Peptides should be positively charged when the main carrier of RNA transmission. Since cationic polypeptides contain many lysine and arginine residues that provide positively charged ammonia, cationic polypeptides can be mated with nucleic acid through electrostatic action (40). The proportion of positively charged amino groups on the peptide to negatively charged phosphate groups on the RNA affects the formation of the nanocomplex. It was reported that less particle sizes, larger zeta potential, and higher envelope rates increase the ratio of charged ammonia and phosphate groups from 1:1 to 10:1 (41).

Autamine is a cationic polypeptide used in early studies in many studies to transport mRNA vaccines.

Delivery of mRNA vaccine can also be achieved through DCs. DCs can also be used to provide mRNA for cancer biological therapies, triggering an antigen-specific immune response, due of the targeting of DCs (28). In addition, it is also feasible to inject the mRNA vaccine directly into the human body. The naked mRNA vaccine works together with forest format buffer or forest format lactate, and muscle injection can minimize the exposure of mRNA with ribonuclease in the blood and prevent the degradation of mRNA vaccine. Besides, electric perforation is a kind of transcendence of the mRNA molecule through high pressure pulse directly into the human cell (42).

In addition to delivering the mRNA vaccine using a single method, a joint delivery method can be used. The mRNA

vaccine can deliver several mRNA molecules simultaneously, triggering synergies in vaccination. Combined delivery of the mRNA vaccine can assemble a protein complex, producing a multivalent mRNA vaccine, or producing a better immune response to a specific target (43).

### *Immune response of the mRNA vaccine*

**The mRNA vaccine and an adaptive immune response**

The immune response can be activated in two ways via the mRNA vaccine. Firstly, the mRNA enters the cytoplasm through endocytosis, then several mRNAs bind to host cell ribosomes to translate efficiently (37). After antigen protein synthesis, antigens are degraded into small antigen peptides in the cytoplasm through proteasomes. These small antigenic peptides are then presented to cytotoxic T lymphocytes (CTLs) through the primary major histocompatibility complex (MHC). Or, antigenic proteins can be released by the host cell. These antigens can then be ingested and degraded by DCs, presented to auxiliary T cells and B cells via MHC. Finally, Class MHC-I interacts with $CD8^+$ T cells and Class MHC-II interacts with $CD4^+$ T cells to activate $CD8^+$ T cells. B cells can also identify antigen proteins released by DCs. Finally, the B cells release the antibodies (44).

**The mRNA vaccine and a natural immune response**

mRNA can stimulate the immune response through the TLR pathway and further stimulate cells to produce large amounts of pro-inflammatory cytokines, type I interferon, and other interferons. These interferons or pro-inflammatory cytokine molecules can reduce $CD8^+$ T cells and ultimately terminate the immune response (28). However, this cascade may negatively impact on certain mRNA vaccines. Therefore, the self-adjuvant characteristics of the mRNA vaccine have both advantages and disadvantages.

### *Treatment of melanoma by mRNA vaccines and DNA vaccines*

Different mRNA-based cancer vaccines were designed for tumor-related antigens. These antigens are more common in cancer cells. Most cancer vaccines are therapeutic, not preventive (45).

Melanoma, a malignancy of melanocyte origin, is a very fatal disease, accounting for 75% of skin cancer deaths although it represents only 4% of skin cancer cases (46). DCs are responsible for the induction of immune responses and the maintenance of tolerance, and they are also considered to link between innate and acquired immunity (47). Antigen loading of DCs, one method is to introduce mRNA encoding the desired antigens. To target the entire antigen repertoire of the tumor, even the total tumor mRNA of gross dissected biopsy samples can be used (48), which includes co-incubation of mRNA with DC, lipid-mediated transfection of mRNA, and electroporation of mRNA by electropulse of mRNA molecules through the cell membrane. Melanoma patients treated with the DC vaccine. Objective response rate [complete response (CR) and partial response (PR)] was 9%, including 20 complete relief (3%) and 37 (partial relief of 6%). Clinical response rate [CR, PR, and stable disease (SD)] was 30% and 133 patients (21%) patients were stable (49).

In the context of many other tumors, the use of DC vaccines has reliable immunogenicity and, therefore, it is now best to combine other therapies, such as anti-CTL-A4 and anti-PD1 therapy (50).

After antigen-loaded DCs vaccination, the most common events were the local response at the DCs injection site, influenza-like symptoms (fever, chills, headache, and muscle pain), and fatigue. Meanwhile, these immune-related symptoms are considered as vaccine responsiveness and are seen as markers of therapeutic immune stimulation effects (48).

The safety profile of DC vaccines is very good—particularly for DC, including transgenic DC, when compared to any other regimen for advanced malignancy (51). But to use self-amplified total tumor RNA and autologous DC to obtain fully personalized products, both ongoing and future clinical trials are exploring more new methods (52).

DNA vaccines are antigens encoding melanoma embedded in DNA plasmids. They will be able to stimulate the host immune response, inducing cellular and humoral immunity, and DNA vaccines can enhance immune memory (53). However, DNA vaccines have shown poor immunogenicity in human trials. Second, DNA vaccines cannot treat cancer because of different resistance mechanisms during tumor development, such as loss or alteration of epitopes recognized by immune cells (54).

To date, only one therapeutic cancer vaccine has been approved for human use (DC cancer vaccine, Sipuleucel T), while most other cancer vaccines, including DNA vaccines, remain in clinical phase I or II (55).

## Summary

In 1990, mRNA was first injected directly into mice,

generating an immune response through the expression of specific proteins, opening human studies on mRNA vaccines. Subsequently, the assimilation of pseudo pyridine in the mRNA vaccine, and the reduced protein production by sequence engineering, make a deeper study of mRNA vaccines. mRNA vaccines have incomparable advantages to other vaccines in terms of their own characteristics, inducing an immune response, and favorable conditions for large-scale production. mRNA vaccines synthesized by molecular design and chemical modifications can improve their stability and reduce immunogenicity, greatly increasing availability of mRNA vaccines. In addition, the delivery of mRNA vaccines is an important factor in exerting the full therapeutic potential of mRNA vaccines, and good delivery systems can help mRNA molecules reach the cytoplasm and remain intact to ensure adequate antigen expression. Current research on mRNA vaccines has focused on improving mRNA stability, reducing its immunogenicity and developing new delivery technologies, and ongoing research on mRNA vaccines to prevent a variety of cancers. It is expected that the new efficient and stable mRNA delivery technology would become a key technology for the clinical application of mRNA vaccines, and the research of mRNA vaccine in tumor therapy have developed rapidly.

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## Footnote

*Reporting Checklist:* The authors have completed the Narrative Review reporting checklist. Available at https://biotarget.amegroups.com/article/view/10.21037/biotarget-21-8/rc

*Conflicts of Interest:* Both authors have completed the ICMJE uniform disclosure form (available at https://biotarget.amegroups.com/article/view/10.21037/biotarget-21-8/coif). The authors have no conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.



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