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Advances in the Study of mRNA Vaccines and Their Application in Tumor Therapy

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Abstract: The active ingredients of traditional vaccines are pathogen antigens, mainly proteins, extracted from cells, and their production relies on large-scale cell culture, which greatly limits the speed of vaccine production and makes it difficult for humans to face large-scale epidemics such as COVID-19. In contrast, mRNA vaccine production technology is a vaccine production technology independent of cell culture. In the 1980s mRNA in vitro transcription methods were invented, in which the mRNA could encode the most effective proteins, which greatly increased the production rate. However, the body's immune system can recognize foreign mRNA, which can trigger an inflammatory response and greatly reduce the amount of mRNA in the body and the efficiency of translation. The nucleotide in mRNA is modified by adding a Cap at 5' end [1], adding Poly(A) tail at 3' end, optimization of UTR, optimization of ORF codon, nucleoside, etc., can play a role in protecting the mRNA from being broken down by enzymes, and greatly reduce immune response triggered by mRNA. At present, there are three mRNA tumor vaccines entering the clinical application stage, namely: naked mRNA cancer vaccine, formulation mRNA cancer vaccine and dendritic cell vaccine. In the future, mRNA vaccines are expected to become effective drugs for tumor therapy. This paper reviews the working principle, mechanism and research progress of mRNA vaccines, the base modification of mRNA vaccines, and the application of mRNA vaccines in tumor therapy, with a view to providing theoretical references for the subsequent research on mRNA vaccines.

Keywords: mRNA vaccine; Nucleoside modification; Tumor therapy

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1. Working principles and mechanisms of mRNA vaccines

There are two approaches to vaccine preparation. One is to directly provide or enable the vaccine recipient to produce the target pathogen antigen; the other is to use infection signals that activate the host's immune system. The methods adopted include using intact viruses or bacteria, retaining only the antigenic parts that activate the immune system, and using genetic materials. mRNA vaccines are prepared using genetic materials, utilizing the central dogma where RNA is used to synthesize proteins.

The working principle of mRNA vaccines is that mRNA is encapsulated in lipid nanoparticles (LNPs) [2]. After the vaccine is injected, it enters cells through fusion endocytosis and releases mRNA, which then combines with ribosomes in the cytoplasm to translate into corresponding proteins. On one hand, these proteins are embedded in the cell membrane to activate B cells and induce them to produce antibodies. On the other hand, the proteins are broken down into small peptide segments by proteases. Some key small peptide segments bind to MHC and are presented on the cell surface to activate T cells (CD8+), thereby inducing cellular immunity [3].

mRNA vaccines without base modification have safety issues related to inflammatory reactions and the problem of protecting RNA from degradation. The use of liposome technology can prevent RNA degradation. With the development of drug delivery systems, people have developed various materials for in vivo drug delivery [4,5], such as lipid nanoparticles (LNPs) 101, polymer nanoparticles [6,7], and lipid-polymer hybrid nanoparticles 19211. Their purpose is to protect mRNA from rapid degradation by the ubiquitous RNases and help it cross multiple biological barriers.

The use of base modification can alleviate the safety issues caused by inflammatory reactions. Common base modifications are the conversion of uridine to pseudouridine and N1-methylpseudouridine. Pseudouridine is connected to ribose at the position of the 5th carbon, and N1-methylpseudouridine is formed by adding the corresponding methyl group to pseudouridine. In the actual synthesis process, inserting modified nucleotides into the raw materials can reduce inflammatory reactions.

2. Research progress on mRNA vaccines

Due to the good tolerability of mRNA vaccines, their ease of degradation, and the fact that they do not integrate into the host genome [8,9], scientists have never stopped researching mRNA vaccines. The development of mRNA vaccine technology has a history of more than 30 years. In 1961, scientists from the California Institute of Technology successfully extracted mRNA for the first time. In 1990, Wolff's team from the University of Wisconsin [10] injected RNA and DNA expression vectors containing genes for luciferase, β-galactosidase, and chloramphenicol acetyltransferase into the skeletal muscles of mice, and detected the expressed proteins and the resulting immune response in the muscle cells. In 1992, scientists injected mRNA encoding hormones from normal rat hypothalamic cells into the hypothalamus of rats with diabetes insipidus, and observed a temporary reversal of diabetes insipidus within hours after injection [11]. In 1995, researchers injected the carcinoembryonic antigen gene into mouse muscles as a cancer vaccine [12]. In 2002, Heiser's team [13] found that dendritic cells (DCs) transfected with mRNA encoding prostate-specific antigen could effectively stimulate T cell-mediated anti-tumor immune responses in vitro, and clinical trials were conducted. In 2005, Hungarian biochemist Karikó discovered that the incorporation of modified nucleosides (m5C, m6A, m5U, s2U, or pseudouridine) into mRNA inhibited the potential of RNA to activate DCs, that is, reduced the immunogenicity of mRNA in vivo [14]. In 2009, Weide et al. [15]. successfully injected protamine-mRNA vaccines into melanoma patients and proved that it was safe and feasible. In 2017, Sahin et al. [16]. demonstrated the clinical feasibility, safety, and anti-tumor activity of targeting individual cancer mutations through RNA neoantigen vaccines. In 2019, the COVID-19 pandemic broke out, and a variety of mRNA vaccines were granted emergency authorization and put into use as COVID-19 vaccines, such as the COVID-19 variant mRNA vaccine jointly developed by Fudan University/Shanghai Lanque/Walvax Biotechnology, and the COVID-19 mRNA vaccine (SYS6006) under CSPC Pharmaceutical Group, as officially announced [17].

3. Base modification of mRNA vaccines

mRNA plays a crucial role in the process of gene expression. mRNA is derived from DNA through post-transcriptional splicing or modification, carrying the genetic information from DNA and transferring it to ribosomes in the cytoplasm for protein synthesis, thus serving as a bridge between DNA and proteins.

mRNA typically consists of hundreds to thousands of nucleotides, and its structural elements include a 5' cap, a 3' poly A tail (polyadenylate tail), 5' UTR and 3' UTR (untranslated regions), as well as an ORF (open reading frame that encodes proteins).

3.1. Addition of cap at the 5' end

The simplest cap structure is 7-methylguanosine (M7G), which is linked to the triphosphate of the first transcribed nucleotide (M7GpppN) through a 5'-to-5' triphosphate bridge (5'ppp5'), with methylation modification at the 2'-O position (denoted as m7G(5')ppp(5')Xm, where X is the first transcribed nucleotide) [18,19]. The 5' cap can not only protect mRNA from cleavage by exonucleases but also regulate pre-RNA splicing and nuclear export. It can eliminate free phosphate groups in the mRNA sequence, and after such elimination, the stability of mRNA is enhanced, and the translation of mRNA is accelerated [20]. Adding a cap at the 5' end can reduce immunogenicity and improve stability.

Up to now, there are two capping methods: one is to add a synthetic Cap analog during in vitro transcription; the other is to perform capping with recombinant vaccinia virus-derived capping enzyme after the end of in vitro transcription. The former is the co-transcriptional capping method, which involves adding anti-reverse cap analogs (ARCA) during transcription; the latter is the enzymatic capping method [20,21]. ARCA represents an innovative breakthrough in the field of mRNA capping. mRNA transcripts with forward products can be recognized during translation, while those with reverse products cannot be correctly recognized. ARCA avoids the problems encountered in standard caps [22,23].

3.2. Addition of Poly(A) tail at the 3' end

The 3' end of mRNA has a polyadenylic acid (poly A) tail structure, known as the Poly(A) tail. The generation of a poly A tail on newly synthesized RNA involves the cooperation of many proteins and sequence elements. Almost all eukaryotic animal mRNAs contain a polyadenylation signal (PAS). The PAS and the downstream GU- or U-rich sequences guide the formation of the poly A tail by recruiting protein complexes involved in the initial 3' end processing [24,25]. Other sequence elements can regulate the efficiency or precise location of polyadenylation. Polyadenylation occurs within 10–30 nt downstream of the PAS, and then poly(A) polymerase (PAP) adds the poly(A) tail. Once 11–14 adenosines are added, nuclear poly(A)-binding proteins can bind to the poly(A) tail in the reaction [26], after which PAP can rapidly synthesize the full-length polyA tail [27,28].

The Poly(A) tail plays a role in translation, as it can prevent the synthesized mRNA from being degraded, is of great significance to the stability of mRNA, and promotes its binding to Poly(A) tail-binding proteins, which is beneficial to protein expression [21]. In many cases, the poly(A) tail protects mRNA. For an enzyme to degrade mRNA starting from the 3' end, it must first degrade the poly(A) tail.

There are currently two recognized tailing methods: one is the transcription of mRNA from a DNA template containing a Poly(A) tail, and the other is enzymatic polyadenylation. The length of the Poly(A) tail has a significant impact on the translation efficiency of mRNA [20]. Only when the length of the Poly(A) tail is greater than 30 nt can the stability of mRNA translation be ensured [21]. However, the length of the Poly(A) tail is not as

long as possible. The optimal length of the Poly(A) tail varies among different mRNAs [21].

3.3. Optimization of UTR

UTRs are the non-coding parts of mRNA sequences in the upstream and downstream domains of the mRNA coding region. They are related to mRNA stability, specific recognition of mRNA by ribosomes, the translation process, regulation of mRNA secondary structure, as well as regulation of gene translation, half-life, and subcellular localization [19]. UTRs play an important regulatory role in the translation process [20].

The 5' UTR can directly affect the translation of the ORF. To prevent incorrect initiation and substitution of the ORF during mRNA translation, 5' UTR gene sequences different from the ORF can be used [19]. How the 5' UTR regulates translation includes: regulating the translocation of ribosomes on mRNA, and binding to eukaryotic initiation factor 33 (eIF3) to mediate translation initiation [20]. As for the 3' UTR, it is a region where unstable factors in mRNA are concentrated. Therefore, when synthesizing the 3' UTR, we can improve mRNA stability and extend its half-life by avoiding the use of unstable sequences or introducing relatively stable elements [19]. Since the 3' UTR can regulate translation by binding to microRNAs (miRNAs) [20], it has been identified as an important regulator of subcellular mRNA localization [29, 30].

3.4. Optimization of ORF codons

The ORF (Open Reading Frame) is the coding sequence for translating proteins. Within this region, using appropriate codons can enhance the translation efficiency of mRNA. Replacing rare codons with similar common codons can increase translation yield [19]. We can utilize RNActive technology to increase the content of guanine and cytosine in the open reading frame of mRNA, thereby improving translation efficiency and delaying mRNA decay.

It is not necessary to replace rare codons with similar common codons for all ORF codons in every mRNA. This is because some proteins require slow translation to fold correctly, effectively, and stably, in which case rare codons should be used. Therefore, different codon optimization strategies should be applied to different mRNAs to improve translation efficiency and quality [19].

3.5. Nucleoside modification

Uracil (U) is linked through its N-1 to the C-1' of the pentose sugar, while modified pseudouridine is linked via its C-5 to the C-1' of the pentose sugar. This base modification causes changes in the codons on mRNA. Due to the wobble property of genetic codons, where the first and second bases typically determine the type of amino acid, and the third base allows a certain degree of wobble, simply put, if uracil (U) is at the third position and can be modified to pseudouridine, the tRNA responsible for transport can still recognize this codon. However, RNA enzymes cannot recognize it, enabling escape from the body's innate immunity and resolving the issue of excessive mRNA immunogenicity. Later, people discovered various nucleoside modification methods, such as 5-methylcytidine and N1-methylpseudouridine.

4. Application of mRNA vaccines in tumor therapy

4.1. The mechanism of mRNA vaccines in treating tumors

Like other vaccines, the basic principle of using mRNA vaccines is to stimulate and enhance the anti-tumor immune response in the body [31]. The antigens related to tumors encoded in the body are delivered by dendritic

cells and some mRNA injections [32]. When APCs (Antigen-Presenting Cells) receive antigen signals, mRNA is transported to the cytoplasm, and MHC molecules transduce and process the signals in a cascade manner. APCs present tumor-associated antigens on MHC class I and class II molecules, thereby activating CD8+ and CD4+ T cells. Meanwhile, they can induce the activation of B cells to produce humoral immune responses [31,33].

4.2. Clinical research progress of mRNA vaccines in tumor therapy

In 1996, the first mRNA-based cancer vaccine study tested dendritic cells pulsed with RNA in vitro [34]. To date, no mRNA vaccine has been approved for clinical treatment [21]. However, three major types of tumor vaccines—naked mRNA cancer vaccines, formulated mRNA cancer vaccines, and dendritic cell vaccines—have achieved significant breakthroughs and entered the clinical trial stage.

Naked mRNA vaccines apply the concept of personalized vaccines. Researchers design and manufacture personalized vaccines for each cancer patient by comprehensively identifying individual mutations, calculating, and predicting new epitopes. This marks the first study based on melanoma. Researchers identified mutations expressed in 13 patients with stage III and IV melanoma. Naked mRNA vaccines are generally administered via intradermal or nodular injection [35,36]. Controlled by ultrasound, the vaccine is injected into the inguinal lymph nodes. In mouse models, the lymph nodes effectively absorb these mRNA antigens, which are then recognized by dendritic cells. All patients developed a T-cell immune response to the vaccine, with two patients showing vaccine-related clinical responses [37,38]; the remaining specific results have not yet been published.

Formulated mRNA vaccines are optimized versions of naked mRNA vaccines. They refer to mRNA combined with specific carriers or packaging materials to improve stability, delivery efficiency, and immunogenicity [39]. These carriers or packaging materials can include liposomes, polymers, proteins, etc. This facilitates the recognition of vaccine mRNA antigens by APCs [38-40]. Clinically, clinical trials for non-small cell carcinoma patients are currently underway. The vaccine CV9201, which encodes five lung cancer tumor-associated antigens, has been designed. It showed good tolerability in 7 patients with stage IIIb and 39 patients with stage IV disease [41]. In the phase 1b clinical trial of CV9202 vaccine, antigen-specific immunity to CV9202 was detected in 21 out of 25 evaluable patients [42].

Dendritic cell vaccines are currently the most promising type of mRNA vaccines. Studies have shown that these cells can regulate immune types and induce strong and long-lasting CD8+ and CD4+ T-cell immune responses. In dendritic cell vaccines, a patient's dendritic cells are usually collected, processed, combined with specific antigens (such as antigens from cancer cells), and then reinjected into the patient. A key advantage of dendritic cell vaccines is personalized treatment. By using the patient's own dendritic cells, the vaccine can be customized according to the patient's specific immune system and disease characteristics, improving the targeting of treatment [43,44]. However, the process of obtaining and preparing suitable dendritic cells is time-consuming and labor-intensive, resulting in a relatively slow development process. The anti-CTLA-4 antibody ipilimumab was combined with TriMix dendritic cells encoding tumor-associated antigens mRNA in patients with advanced melanoma. Among 39 patients who received the vaccine injection, 15 achieved partial or complete immune responses [45]. Scientists injected dendritic cell vaccines carrying tumor-associated antigen-encoding mRNA into patients with acute myeloid leukemia. The experimental results showed that the 5-year overall survival rate of vaccinated patients was favorable, with approximately 43% of patients experiencing delayed disease recurrence [46].

In the field of oncology, mRNA tumor vaccines are in the early stages of clinical research. Some preliminary clinical trials have demonstrated the potential of mRNA tumor vaccines to induce immune responses in patients,

but more research is still needed. Therefore, in the design and application of mRNA tumor vaccines, many challenges need to be overcome to ensure their targeting, safety, effectiveness, and other aspects.

5. Conclusion

mRNA vaccine technology represents a breakthrough in vaccine production by eliminating dependence on cell culture, enabling rapid response to pandemics like COVID-19. Through innovations such as 5′ capping, Poly(A) tailing, and nucleoside modifications, mRNA stability and translational efficiency have been significantly enhanced while minimizing immune-triggered degradation. Currently, three mRNA cancer vaccines (naked mRNA, formulated mRNA, and dendritic cell vaccines) are in clinical trials, demonstrating promising potential for tumor therapy. This review summarizes the mechanisms, optimization strategies, and therapeutic applications of mRNA vaccines, providing a foundation for future research and development in this transformative field.

Disclosure statement

The authors declare no conflict of interest.

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