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mRNA Vaccines: Structure, Mechanism and Applications

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Abstract: The present paper focuses on mRNA vaccines. Firstly, it is pointed out that the excellent results of the new mRNA vaccine have led to the active exploration of its application in therapeutic protein expression, and many clinical trials for different diseases have been carried out accordingly. The subsequent discussion delves into the intricacies of mRNA structure and function, meticulously analysing the pivotal roles of its components (5' end cap, UTR, open reading frame, 3' end polyadenylate tail structure) in protein synthesis and immune response. The study further delves into the multifaceted mechanisms through which mRNA vaccines exert their effects on viruses and cancers, offering a comprehensive exploration of this fascinating field. The text goes on to highlight the significant advantages of mRNA vaccines, including safety, ease of mass production, and ease of antigen sequence optimisation. Furthermore, the applications of mRNA vaccines in antiviral, anticancer, autoimmune, allergy, tissue regeneration, anti-aging and other fields are described. In conclusion, mRNA vaccines have a broad application prospect, although some applications are still in the exploratory stage. Nevertheless, they have provided innovative ideas for disease treatment.

Keywords: mRNA vaccine, mechanism, application.

1. Introduction

The excellent efficacy of the Covid-19 vaccines has reignited enthusiasm for the researches on mRNA vaccines of mRNA. Besides mRNA vaccines for the novel coronavirus, the initiation of clinical trials has been commenced., such as the utilization of mRNA-expressed vascular endothelial growth factor (VEGF) for heart failure treatment [1].

In the clinical application realm, mRNA vaccines for various infectious diseases, including influenza, foot-and-mouth disease, rabies, and POWV, have demonstrated feasibility in preclinical animal studies, with some advancing to clinical trials. In oncology, mRNA-based cancer vaccines expressing tumor-associated antigens (TAAs) have been investigated in use. For example, the combination of dendritic cells (DCs) and specific mRNA electroporation in melanoma patients has shown certain efficacy [2]. In tumor therapy, attempts to modify the tumor microenvironment (TME) through diverse means to enhance anti-cancer immunity using mRNA vaccines have been made, although the number of clinical trials for some delivery methods remains limited. A substantial body of research has demonstrated the efficacy of mRNA vaccines in the prevention of infectious diseases, including but not limited to the influenza virus, Ebola virus, and Zika virus. Furthermore, these vaccines have been shown to be effective in the development of immunotherapies for various forms

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of cancer. [3]. With the advancement of new lipid nanoparticles (LNPs) and non-LNP vectors, the amelioration of side effects, the enhancement of production capacity, and the progress in freeze-drying technology, etc., significant strides are anticipated. It is expected that existing issues such as cold chain transportation will be resolved, bringing new hope for patients who have difficulty accessing other therapeutic options and propelling mRNA therapy to a new level [4].

Nevertheless, several challenges must be overcome before mRNA can become a universal treatment for both rare and common diseases. The integration of the advancements is expected to unlock the potential of mRNA therapeutics beyond vaccines for treating multiple disease types. The extensive global administration of mRNA vaccines, with their safety and efficacy widely validated, indicates the promise of developing a new generation of mRNA therapeutics.

2. General Information

2.1. mRNA Structure and Function

mRNA serves as a template for protein synthesis, playing a crucial "middleman" role in genetic information transmission. The transcription of mRNA is catalyzed by RNA polymerase using a DNA template.

2.2. Mechanisms

2.2.1. Rationale

The fundamental principles lie in introducing mRNA sequences encoding specific antigenic proteins into human cells. Subsequently, the ribosomes and other organelles within the cells act as "production facilities" to translate and synthesize the corresponding antigenic proteins using the mRNA as a blueprint. This process can be compared to providing a manufacturing "blueprint" for cells to produce specific products [5].

2.2.2. Mechanism of Viral Vaccines

Viral antigenic proteins synthesized by cells are processed through intracellular mechanisms and then presented on the cell surface, where they are recognized and taken up by antigen-presenting cells. These antigen-presenting cells then migrate to immune organs like lymph nodes to present antigen information to T lymphocytes (including helper T cells) and B lymphocytes [6]. Helper T cells release cytokines to further activate B lymphocytes. Simultaneously, cytotoxic T lymphocytes (CTLs) are activated, possessing the ability to destroy infected cells, thereby establishing both humoral and cellular immunity as dual defense lines. Consequently, when the actual virus invades, it can be promptly detected and eliminated, achieving the goal of preventing viral infection [7].

2.2.3. Mechanism of Therapeutic Cancer Vaccines

The identification and synthesis of tumor-specific antigens involve several steps. Initially, the patient's tumor tissue undergoes gene sequencing and other analyses to identify novel antigens (tumor-specific antigens) generated by tumor cell mutations. Then, the corresponding mRNA sequences are designed. Afterward, the patient is administered a customized mRNA vaccine, which directs the synthesis of tumor-specific antigen proteins within the cells [8].

Activation of the response occurs when these tumor-specific antigen are presented to T-lymphocytes and other immune cells in the patient's immune system, leading to their recognition and specific attack on cancer cells bearing these antigens. This approach minimizes damage to normal cells and relies on the body's immune system to inhibit tumor growth and spread, achieving cancer

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immunotherapy. The personalized nature of this vaccine ensures a better fit for the patient's tumor characteristics, enhancing its accuracy.

2.3. mRNA Vaccine Structure and Function of Each Structure

An mRNA vaccine consists of a synthetic mRNA molecule that generates an antigen to stimulate a response. This mRNA molecule comprises five parts: a cap structure at the 5’ end, an untranslated region (UTR) at the 5’ end, an open reading frame encoding an antigen, an untranslated region at the 3’ end, and a poly (A) tail structure at the 3’ end.

2.3.1. 5’ End Capsid

The 5’ end cap of mRNA, similar to eukaryotic mRNA, contains a 7-methylguanosine linked to the 5’ end of the mRNA. In mammals, nucleotides at the 5' end are often methylated, preventing cytoplasmic organelles from recognizing it as viral RNA and thus avoiding an immune response. The 5’ cap also protects mRNA from degradation by nucleic acid exonuclease enzymes. Moreover, it cooperates with the 3’ end poly(A) tail structure, poly(A) binding protein, and eIF4E to form a loop and recruit ribosomes for protein translation initiation.

2.3.2. 5’- and 3’-End UTRs

The UTRs, including the 5’ and 3’ ends of the UTR adjacent to the antigen-encoding open reading frame, plays a vital role in regulating mRNA translation, half-life, and intracellular localization. However, since UTR function can vary depending on cell type, the UTR sequence can be adjusted and optimized according to the target cell. Optimized UTR sequences can reduce mRNA degradation by excluding microRNA binding regions at the 3’ end of the UTR with abundant A and U nucleotides. Additionally, the optimizations involve specific regions within the UTR that impede ribosomal scanning of mRNAs [9,10].

2.3.3. An Open Reading Frame Encoding an Antigen

The frame encoding the antigen is the most critical part of the mRNA as it holds the coding sequence for protein translation. Although it has less flexibility compared to non-coding regions, it can be optimized by replacing rarely used codons in the body with more prevalent ones. This optimization has been shown to enhance protein translation. For instance, CureVac, a German biotech company, found that few human mRNA codons have an A or U in the third nucleotide position. Their research led to the replacement of such nucleotides in the codon of the open reading frame with C or G, as seen in their vaccine candidate CVnCoV, where a slower translation rate of rare codons is beneficial for protein folding in some cases [11].

2.3.4. 3’ end Poly (A) Tail Structure

The length of the 3’-end poly (A) tail structure has been demonstrated to regulate mRNA translation and half-life. It interacts with poly (A) binding proteins to form a complex that initiates translation and protects the 5’-end cap structure from enzymatic degradation. Hence, it is essential for the tail-like structure to be adequately long (100-150bp) [12].

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3. Advantages

3.1. Improved Safety

mRNA vaccines do not pose the risk of "virulence reversion" seen in live attenuated vaccines or cause severe diseases in some individuals (as was the case with 80% of infants and young children vaccinated with live attenuated respiratory syncytial virus (RSV) vaccines who became infected with RSV, severely ill, hospitalized, and some even died). Unlike DNA vaccines or certain viral vector vaccines, mRNA vaccines do not integrate into the DNA of vaccinated individuals, eliminating the risk of insertional mutagenesis.

3.2. Improve the Efficiency of Large-scale Production

The development of mRNA vaccines offers significant advantages over traditional vaccine methods. Firstly, they do not rely on live viruses for in vivo action, eliminating the need for specialized laboratory equipment and biosafety laboratories. Secondly, in contrast to chicken embryo vaccines, mRNA vaccines are not limited by chicken embryo production and can be used to vaccinate individuals with allergies to chicken embryos. Thirdly, there is no risk of bacterial contamination as no live cells need to be cultured during production.

The chemical components of mRNA vaccines are well-defined and consistent, enabling rapid responses to emerging or seasonal epidemics. For example, in the event of a novel coronavirus strain emergence, a vaccine against the mutated strain can be quickly prepared by replacing the coding mRNA sequence with the original delivery system [13].

3.3. Rapid Antigen-specific Sequence Optimization

Another advantage of mRNA technology is the ease with which the coding antigen can be continuously optimized by modifying the nucleic acid sequence. This process is relatively straightforward compared to the bioengineering techniques used to produce different proteins or peptides. BioNTech has maximally exploited the potential of mRNA technology, initiating clinical trials on at least five novel coronaviruses mRNA vaccines [14].

4. Applications

4.1. Antiviral

Viral mRNA vaccines have seen significant progress, demonstrating robust specific T-cell and humoral immune responses. Presently, mRNA vaccines that can target both homologous and heterologous subtypes of the influenza virus have been developed and are capable of eliciting a broad innate protective immune response [15,16]. Furthermore, mRNA vaccines have been designed for in humane use, for example in the context of protecting mice against foot and mouth disease virus (FMDV) challenge. In the context of the recent outbreak of the SARS-CoV-2 virus, known as CoV-19, the deployment of mRNA vaccines has assumed significant importance. The mRNA vaccines have demonstrated efficacy in protecting against the virus, with protection rates exceeding 90 per cent. In contrast, several inactivated and adenoviral vector vaccines have exhibited protection efficiencies ranging from 50 to 85 per cent. These findings underscore the considerable potential of mRNA in the field of antiviral research and development [17,18].

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4.2. Anticancer

Vaccination with mRNA-expressing TAA is the most fundamental application of mRNA vaccines in oncology [19]. Numerous preclinical studies have been conducted on mRNA cancer vaccines and a number of vaccine candidates have entered clinical trials [20]. The potential of mRNA vaccines to be used in combination with other cancer treatments also has been demonstrated. For instance, when administered in conjunction with drugs like immune checkpoint inhibitors, it has been observed to reverse the suppression of the immune system by tumour cells. In addition, mRNA vaccines have been shown to enhance the immune system's ability to recognise tumour cells. The combination of these two treatments has been demonstrated to enhance the anti-cancer effect, thereby improving both the survival rate and the quality of life of patients. Combination therapy showed a higher incidence of tumour responses in patients with stage III or IV melanoma [21].

5. Other Applications

In addition to applications in infectious disease prevention and cancer therapy, mRNA vaccines have shown other potential uses. In autoimmune diseases, they are expected to modulate the immune system's misdirected attack on its own tissues by delivering mRNAs for specific autoantigens and inducing immune tolerance, as in multiple sclerosis research [22]. In allergic reactions, they can encode allergen-related components that induce the immune system to produce tolerogenic antibodies and regulatory T cells to alleviate allergic symptoms, as has been achieved in peanut allergy research [23]. In the field of tissue regeneration, mRNA encoding growth factors can promote angiogenesis and cell proliferation, accelerating the repair of myocardial infarction, skin trauma and other tissues [24]. In the field of anti-aging, mRNAs can target senescent cells or regulate senescence-related signalling pathways to slow the aging process and the development of related diseases. Although these applications are still at an exploratory stage, they open up a new direction for the future development of mRNA vaccines, which are expected to provide innovative solutions for the treatment of various diseases. However, challenges remain in the areas of stability, delivery efficiency, immunogenicity regulation and safety assessment, which require further research breakthroughs.

6. Conclusion

The potential of mRNA vaccines in modern medicine has been demonstrated by their impressive applications in the new crown epidemic, and their role in the prevention and control of infectious diseases has been highlighted. The exploration of mRNA vaccines in other disease areas has been inspired by these applications. The unique mechanism of action and advantages of mRNA vaccines have become evident in the treatment of cancer, autoimmune diseases, allergic reactions, tissue regeneration and anti-aging. It is anticipated that mRNA vaccines will provide a complementary and innovative direction for traditional therapeutic means, and that they will open a new chapter in precision medicine. With researchers' in-depth understanding of the structure and function of mRNA, as well as continuous innovation and improvement in production technology, sequence optimisation, delivery system and other aspects, it is reasonable to expect that mRNA vaccines will break through the existing limitations in the future, and be The widespread use of mRNA vaccines in the prevention and treatment of various diseases is anticipated to make significant contributions to global health, and to promote the development of medical science and benefit more patients. The development of mRNA vaccines is expected to be an important force in reshaping the human response to diseases, and to lead medical treatment to new heights.

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