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Clinical application and future development trend of mRNA nanomedicine

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Abstract. mRNA therapy is an emerging clinical therapeutic approach. According to studies, mRNA technology has entered into a stage of rapid development, and there are several significant achievements about some illness cancer such as cancer treatment, with various of mRNA nano-medicine have shown some promising results in clinical research. In recent years, with the deepening of research, mRNA nano-medicine shows the excellent potential in the prevention and treatment of diseases. 2020, with the first mRNA vaccines, which have been used for the treatment of the novel coronavirus, mRNA technology become the main focus of medical attention in the last decade. Based on the literature about mRNA in past five years and reference to the data and results of several clinical trials, this article adopts an approach of summary overview reviewing clinical applications of mRNA nano-medicine and predicting the tendency of future development. In the future, mRNA nanotechnology will become the mainstream method of diseases treatment, and bring hope to more patients. In this paper, we conduct a comprehensive description of mRNA nano-medicine from the following aspects: history and action mechanism, clinical application, current research status and future development trend.

Keywords: mRNA therapy, mRNA nano-medicine, diseases treatment, clinical application.

1. Introduction

mRNA is a sort of single-stranded ribonucleic acid (RNA), which is transcribed from a single strand of DNA as a template, carries genetic information, and translates this information into corresponding proteins in ribosomes [1]. During the early research of mRNA, more attention was paid to its structure, function, metabolic activity, etc., it was not until 1990 that it was reported that mRNA could express encoded proteins in mouse muscle cells. With the development and deepening of research, mRNA has been indicated that it can show a variety of clinical treatment effects. Additionally, based on several characteristics of mRNA, such as translation in the cytoplasm of the cell, a small chance that mRNA can be integrated into the hose genome and measurable protein expression ability [1], lay the foundation of its future application in vaccines, cancer treatment, gene editing and other clinical aspects. According to the literature, emerging mRNA therapy can effectively treat COVID-19, which is caused by SARS-CoV-2 virus [2] and the mRNA vaccine is produced through the extraction of serum of infected people, this kind of vaccines plays an extremely important role in assisting people in fighting against the novel coronavirus during the period of COVID-19 outbreak. What's more, there are many papers illustrating that mRNA therapeutics or mRNA vaccines for the cancer treatment have become the main focus and trend of current clinical research. Admittedly, the disadvantages of mRNA are also factors that need to be taken into consideration during drug production, such as the low stability of mRNAs, tendency of immunostimulation and the lack of an effective delivery system, these factors make the initial clinical application encountering many different sorts of difficulties;in order to promote the wide application in the field of medical science, researchers use the chemical modification of mRNA, enhancing the translation effect and stability, using the drug delivery system and other approaches to eliminate positive impacts as much as possible. In this paper, based on the mRNA vaccines which are successfully used for the treatment of novel coronavirus pneumonia and the shortcomings of mRNA nano-drug in the treatment of other diseases, and combining with the current methods and technologies of drug production, the production of mRNA nano-medicine will be improved, we expect that mRNA nano-medicine is going to become a vital part of medical field in the future. Therefore, this paper revolves around three aspects of mRNA nano-medicine: history and action mechanism, clinical application, current research status and future development trend.

2. History and Mechanism of Action of mRNA Nano-medicine

2.1. History

The development of mRNA nano-medicine can be divided into four main phases. The first stage is the region and basic characteristics research stage. mRNA research began in the middle of the 20th century. 1961, researchers successfully extracted mRNA for the first time in a laboratory of California Institute of Technology (Caltech) [1], subsequently, researchers conducted studies about protein expression ability, self-stability and other basic forms of mRNA, laying the foundation for the vaccines and drugs based on mRNA therapy. The second stage is the technology development stage. In this stage, mRNA began to be used in clinical trials. 1990, Wolff et al. from the University of Wisconsin first discovered and reported an experiment and its result, i.e., the mRNA was injected into the skeletal muscle of mice by intramuscular injection, the corresponding coded protein could be attained, and mice produced an immune response; this trial not only brought inspiration to the researchers, but also greatly prompted the development of mRNA therapy. The third stage is the rapid development stage. 2020, according to the clinical data from two U.S. pharmaceutical companies, the effective rate of mRNA vaccines is over more than 90%, which indicates that mRNA vaccine therapy provides new ideas for the application of mRNA to the prevention and treatment of diseases [1]. With the formal approval and application of mRNA vaccine used for novel coronavirus pneumonia, mRNA therapy gradually begins to develop rapidly, in this stage, there is a research hotpot about other disease treatment of mRNA vaccine and mRNA therapy, providing new feasible solutions for traditional drug research and traditional disease treatment. The fourth stage is the recognition and honoring stage. 2023, the Nobel Prize in Physiology and Medicine was awarded to two scientists for their contributions to mRNA modification [3], his modification provides new insights for the relationship between mRNAs and immunotherapy and enable mRNA vaccines against COVID-19 to be used more efficiently and safely in clinical treatments [2]. Nowadays, much of the literature focuses on how mRNA therapy can be widely used in diseases treatment, there are research gaps of mRNA technology which remain to be addressed.

2.2. Mechanisms of Action

2.2.1. Structure of mRNA

Among different sorts of mRNA, mRNA is the first RNA which is used for protein production, and carries genetic information from ribosomes, and thus is named messenger RNA. The structure of mature eukaryotic mRNA mainly includes 5’ cap, 5’ untranslated region (5’ UTP), 3’ UTR, 3’ poly(A) tail, protein-encoding open reading frame(ORF) [4]. The cap structure is located at the 5’ end of the mRNA [4], and is the required for translation initiation and increases the stability of mRNA. The length and structure of 5’ untranslated region affects the translation efficiency of the mRNA, and tight secondary structure might prevent the combination of ribosome. When designing and compounding mRNAs, the introduction of the upper Open Reading Frame sequence and the start codon AUG in the 5’ UTR is supposed to be avoided. The Open Reading Frame is the region of coding antigenic proteins, which can optimize codon and improve the stability and translation efficiency of mRNAs [4]. The definite function and structural features of 3’ UTR are not described in detail, but the specific function and structural characteristics are related to the stability and the regulation of translation of mRNAs. The Poly(A) tail is located on the 3’ end of the mRNA and is associated with stability and transportation of mRNAs [4]. In addition, mRNA accounts for about 5% of the total RNA of whole cells, and these messenger RNA are usually found in eukaryotic cells.

2.2.2. Mechanism Action of mRNA Vaccine

Based on the structural integrity and self-regulation of mRNAs as described above, mRNA usually shows some properties, which are highly similar to those mRNA viruses, thus mRNA can be specifically recognized by antigen presenting cells, and activate pattern recognition receptors, such as Toll-like receptor 7(TLR7), TLR and so on. The combination of double-stranded RNA(dsRNA) and retinoic acid-inducible gene receptors elicits a strong type of I FN response and improve the ability of dissolving CD8+ T cells to cells, thereby achieving the goal of infecting or removing tumor cells. The mRNA binding to specific antigens needs to take place in the host cells, however, size of mRNA is not enough small So that mRNA cannot be freely diffused across the membrane into the cell. At the same time, delivery effects of mRNA is affected by its own and negative charge carried by the cell membrane, the delivery difficulty increases, therefore there are many mRNA delivery approach and delivery vectors which assist mRNA in completing the specific combination with cells.

3. The Clinical Application of mRNA Nano-medicine

3.1. Infectious Diseases

Novel coronavirus infection is an acute infectious disease, 2019, the first outbreak of novel coronavirus pneumonia occurred, clinical symptoms of most patients are high fever, cough, malaise, headache, myalgia, sore throat and sore throat etc., some patients suffered from symptoms of nasal congestion, runny nose, loss or temporary loss of smell and taste and diarrhea, etc., and a small number of patients were in critical conditions. January 10, 2020, under the joint efforts of several Chinese scientists, they published RNA sequence of the novel coronavirus for the first time. On January 24, the CDC successfully isolated first strain of the novel coronavirus. On March 16, the novel coronavirus vaccine was approved to start clinical trials. On April 12, Chinese novel coronavirus entered the stae of II clinical trials, on the same day, inactivated COVID-19 vaccine produced by the Wuhan Biological Products Research Institute of China Biologic of Sinopharm Group, obtained the license of clinical trials from National Medical Products Administration, and related clinical trials also were conducted, that vaccine had become the first inactivated COVID-19 vaccine which completed the clinical trials. August 23, 2021, the U.S. FDA formally approved mRNA vaccine BNT162b2, which was the first vaccine that obtained the approval and had complete Phase III data. The discovery and application of COVID-19 vaccine makes an greatly significant contribution to the global people’s fight against novel coronavirus pneumonia, dramatically increasing individual’s resistance to the virus and greatly reducing the chances of infecting novel coronavirus pneumonia. 2023, the Nobel Prize in Physiology and Medicine was awarded to U.S. scientists Katalin Karikó and Drew Weissman for their contributions to mRNA modification [3]. After a long period of research, they discovered that the mRNA modified by the nucleobase could effectively prevent immune-recognition receptors from responding to the mRNA, which greatly induced the side effects of the mRNA and decreased the harm to the human bodies, in addition, this kind of mRNA had higher translation efficiency. This discovery not only greatly enhances clinical effects of mRNA vaccine against COVID-19, but also completes the research and development of mRNA vaccine, and lays a great foundation for mRNA vaccine technology.

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3.2. Cardiovascular Disease

Cardiovascular disease is a type of disease which affects the normal functions of heart and blood vessels, the incidence of such disease in the population is extremely high, and has become one of the main reasons of death of the global residents. Current Diagnosis and treatment method can slow the deterioration of the patients with cardiovascular disease to a certain degree, while there are still disadvantages, which require further research and development, therefore the new cardiovascular disease treatment approach has become the main attention of medical research. With the continuous deepening and development of molecular biology, researchers pay more attention to the function of RNA splicing technology in genetic regulation. In March 2024, *EBioMedicine* published an article, which revealed the important role of RNA splicing technology in treating cardiovascular disease and pointed out that the causes of cardiomyopathy, ischemic cardiomyopathy, heart failure, arrhythmia and other diseases [5]. By multiply analyzing literature and data, research team pointed out that RNA splicing patter of heart and vascular smooth muscle cell had the elaborate regulation, splicing factors and their targets inextricably linked to the severity of cardiovascular disease [5]. In this paper, several key splicing factors were emphasized, including NOVA, RBFOX protein, CELF protein, QKI, TDP-43 and other factors, these factors were of tremendous importance in growth and function of heart [5]. Researchers found that the heart function of the animal model dramatically reduced and the myotome structure of cardiomyocyte was disturbed to some extent through knocking out RBFOX20 gene in the animal model [5]. Research team proposed several possible strategies of cardiovascular disease treatment by revealing the relationship between mRNA and cardiovascular disease, and provided new thinking and way of research for future clinical application, which are highly expected to take more effective, more precise and more available treatment ways for patients.

3.3. Tumor

Recently, with the continuous development of mRNA technology, therapeutic cancer vaccine has also become an emerging immunotherapeutic approach, including mRNA vaccine, cell vaccine, DNA vaccine, dendritic cell vaccine, nanovaccine, peptide vaccine, etc. Up to now, this type of immunotherapeutic approach has received the excellent therapeutic effect in treatment of malignant melanoma, lung cancer, glioma and other sorts of cancers, which is called the hope of cancer treatment [6]. mRNA-4157(V940) is a novel individualized cancer vaccine which is based on messenger RNA, and consists of mRNA molecule synthesized by 34 kinds of neoantigens [7]. This vaccine is designed based on different DNA sequences of different cancer patients, after patients receive the vaccine, specific responses are generated in the body, and the combination of this vaccine and PD-1 inhibitor KEYTRUDA can improve the immune ability of patients [7], thus enhancing the capacity to fight against cancer. In the past few days, U.S. Moderna company and Merck Sharp & Dohme jointly issued an announced that the cancer vaccine mRNA-4157(V940) combined with PD-1 inhibitor KEYTRUDA was injected into patients with Stage III/IV melanoma with high risk of recurrence after complete cancer resection [8], this vaccine continued to show advantages, and the risk of recurrence or death reduced by 40%, the risk of disease metastasis reduced by 62%.

4. mRNA Nano-medicine Research Status and Future Development Trend

4.1. Research Status

At present, mRNA nano-medicine can be divided into three major categories according to the sort of drug and medicine use, which are preventive vaccine, therapeutic vaccine and therapeutic drug [8]. According to the data statistics, a total of 56 kinds of mRNA drugs are in the clinical research, and the emphasis of medicine research mainly is the aspect of mRNA vaccine, In addition to the COVID-related vaccine, most parts of vaccines are still in the phase of clinical research, and are not really used in clinical therapy. Researchers optimized the design of mRNA vaccines, improving their immunity of anti-tumor, and lengthened the life of experiment organisms. They also made a breakthrough in the delivery system of mRNA drug [9], i.e., the use of lipid nanoparticles(LNP) as the delivery system of drugs [9], which

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could deliver the drug to the target cells with highly efficiency. The research of mRNA nano-medicine also focuses on how to improve the specific targeting and bioavailablity of the drugs, and how to enhance the safety and stability in the patient's body. Meanwhile, mRNA nano-medicine has achieved milestones in the field of anti-cancer. Several research teams had produced various of mRNA vaccine against cancer, these vaccines could prompt the lymphatic transportation and cytoplasmic delivery of mRNA and cyclic guanosine monophosphate-adenosine monophosphate(cGAMP), and could effectively activate the interferon gene stimulating factor(STING) to enhance immune effect of mRNA in target cells, in order to achieve the enhancement of anti-cancer. For instance, in the development of mRNA therapeutic vaccines, Wiszin Biologics'WGc-043 injection [10], is the world's first virus-related tumor mRNA therapeutic vaccines which gets the approval of IND, and provides a novel therapeutic approach for patients with EBV-associated tumors advanced solid tumors and viral-positive hematogolical tumors [10]. In conclusion, most of the mRNA nano-medicine are in the rapid development phase, and will bring more therapeutic options and hope for human health.

4.2. Challenges to the Clinical Applications

The use of mRNA nano-medicine for clinical treatment requires adequate translation of the genetic material in corresponding cells, and in some occasional case, the process of translation will cause unexpected immune response [1], such as mRNA vaccines containing artificially modified nucleotides. In the cells of eukaryotic organisms, mRNA is a class of single-stranded ribonucleic acid that carries the genetic information and translate the genetic information into specific protein within the ribosomes. In the normal circumstances, the translation of the genetic information conducts according to the sequence of nucleotides on the mRNA, but the translation process might occasionally be erroneous, for example, one or more codons will be skipped during the translation process, which means the reading error occurring in the translation, thus polypeptide chains are synthesized, that phenomenon is known as ribosome frame shifting. Several results of experiments show that mRNAs containing pseudouridine have the higher chance of ribosome shifting because the mRNAs with artificially modified nucleotides do not fit perfectly with the natural ribosome, thus the conformation of the natural ribosome is altered and the chance of ribosome shifting is increased. Although there is no direct evidence suggesting that adverse effects of mRNA vaccine in humans are related to ribosome shifting, the occurrence of this phenomenon could limit the future use of mRNA vaccines in higher doses, more frequently, and in the treatment of other diseases. Therefore, researchers state that it is important to continuously conduct the study of mRNA mistranslation and immunogenicity of its mistranslated products, because the products of ribosome shifting may bright more severe and unpredictable immune responses and have the negative impact on therapeutic effects of mRNA medicine. As a consequence, there are several challenges which are required to be tackled with, thus achieve the multifaceted clinical application of mRNAs.

4.3. Future trends of mRNA nano-medicine

The mRNA vaccine for the treatment of novel coronavirus pneumonia has made an outstanding contribution to the world, mRNA vaccine brings new hope for other diseases treating, therefore, mRNA is one of the hotpots of biomedical research in the past decade. On the grounds of the report of BBC research, global mRNA therapy has reached $6 billion by 2022, and the demand of non-COVID-related vaccine will be expected to grow dramatically, demonstrating the urgent need for novel therapeutic ways in the clinical market. Driven by the high demand of mRNA therapy, COVID-related mRNA vaccine shows a more complete system. From the delivery of virus sequence, the first batch of vaccine research, mRNA vaccine used for clinical prevention of novel coronavirus to the improvement of mRNA vaccine, this technology has been nearly completed, mRNA drugs for the treating other diseases are still in the phases of the discovery of mechanism action and clinical research of drugs, thus relevant mRNA therapies are being continuously improved. Taking the mRNA vaccine as the basic point, researchers will continue to deep their research, accelerate the development of mRNA therapies and produce the drugs with higher effectiveness and safety. In the future, the development trend of mRNA nano-medicine includes the expansion of application fields, more personalized treatment, the improvement of

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drug delivery, and the improvement of drug safety and stability etc. The multiple efforts of research and enhancement for mRNA technology will highly accelerate the application of mRNA therapies in the treatment of renal diseases, cancers and other diseases and replace the traditional treatment of diseases, meanwhile, the threat of diseases to global human health will be minimized.

5. Conclusion

In this study, we find that the COVID-related mRNA vaccine has already shown great clinical therapeutic effects, strongly and positively influencing people around the world to fight against the novel coronavirus pneumonia. With the continuous efforts and deepening of research, this vaccine has been further improved, its stability and safety have been enhanced to a certain degree. The mRNA vaccine against COVID-19 has inspired more researchers to participate in how to better enable emerging mRNA therapy to replace traditional diseases treatment and bring more hope to patients. Because of specific feathers of mRNA nano-medicine, mRNA nano-medicine has become the emphasis of medical research. Increasingly fields of medicine are conducting the clinical research of mRNA drugs, the experimental results are very promising. The main contribution of this paper is taking the development and current status of the novel coronavirus mRNA vaccine as the basic point, analyzing its development history, mechanism action and structural characteristics, stating applications in the different fields of medicine and looking forward to the future trend, which better assist researchers in learning about mRNA nano-medicine and promote the development of mRNA nanomedicine. Currently, the mRNA nano-medicine used for clinical therapy is only the COVID-related mRNA vaccine, and therapeutic drugs for other diseases are still in the phase of clinical research. Future research is highly expected to focus on how to accelerate the research and development of other therapeutic drugs, and how to significantly improve the stability, efficiency and safety of mRNA therapeutic drugs in patients' body and the development of mRNA individualized medicine. In the future, we expect that mRNA therapy will provide guarantee about the global health, this therapy will be the mainstream therapy approach.

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