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BIOLOGY OF MRNA VACCINE, ADVANTAGES AND DRAWBACKS

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ABSTRACT

Nowadays, there are several new emerging and ongoing diseases which still lack an effective vaccine. The current situation of the COVID-19 pandemic is a great example indicating that a vaccine is urgently required in order to control the disease spreading and transmission. mRNA vaccine is a new technology that allows a rapid manufacturing and cost-effective process suitable to manage the pandemic. Various delivery systems are studied and developed for efficient mRNA protection and penetration into the cytoplasm of the host cell. Delivery of mRNA by Lipid nanoparticles (LNPs) provides good results as clearly shown in mRNA vaccines against SARS-CoV2.In this article, we aim to review the 2 main types of mRNA vaccine, mode of action, major manufacturing process, delivery systems, advantages, and drawbacks of the mRNA vaccine to increase understanding about mRNA vaccine.

Introduction

Recently, there are several ongoing and emerging diseases which cause public health threats and economic loss. These diseases include various types of cancers and infectious diseases such as influenza, dengue, malaria and COVID-19. Vaccine is required to effectively control these illnesses.

There are several types of vaccine including the live-attenuated vaccine, subunit vaccine, viral vector vaccine, subunit vaccine and nucleic acid vaccine (1,2). Each type of vaccine has a different effectiveness against one pathogen and also different limitations (3). Designing vaccines against some pathogens is very difficult due to the low vaccine efficacy. Therefore, many diseases are still lacking an effective vaccine such as dengue (4). As a consequence, new vaccine technology is required for the efficient controllation of the diseases.

Nucleic acid vaccines including DNA and mRNA vaccines are developed and now are used to prevent many diseases such as yellow fever, measles, mumps, and rubella (5,6). A principle of nucleic acid vaccine is to encode the information for the interested antigens. After the antigen is produced from the nucleic acid, it stimulates the host immune response and prepares for the natural infection (7). Unlike the live-attenuated vaccine, nucleic-based vaccines require a delivery system to increase their constancy and induce more effective cell-internalization (8,9). The nucleic acid-based vaccines can be rapidly produced and the manufacturing processes can be flexible (10,11). Moreover, any interested antigens that have base sequence information can be utilized for vaccine production (12). Therefore, different vaccines can utilize the same production platform and manufacturing facilities with small adaptations (10). This outstanding advantage in reducing cost and time made DNA/RNA vaccine strategy suitable for fighting against new emerging pathogens and pandemic situations.

Comparing the DNA and mRNA vaccines, mRNA vaccines offer more therapeutic advantages and safety benefits than the DNA vaccine (13). In this review, we focus on the types of mRNA vaccine, production and delivery system, mode of action, clinical applications, and also the advantages and drawbacks of the mRNA vaccine.

Structure of mRNA vaccine

The structure of the mRNA vaccine is mainly composed of 4 parts. The first part is the base sequence coded for the interested antigen while the remaining part is the cap, UTRs and poly (A), which is added in order to mimic human mRNA and mediate the translation process These components are also essential to the stability of mRNA molecules, access to ribosomes and react with the translation machine (14).

mRNA vaccines can be divided into 2 major types based on the ability of self-amplification; non-replicating and self-amplifying mRNA vaccines. The conventional mRNA vaccines usually contain only the antigen coding region in addition to the specified areas. The advantages of this type is a simple form and the relatively small size of RNA molecules. However, the duration of expression of the conventional mRNA is limited in vivo. Optimization of RNA structural elements and formulation can increase antigen expression and durability (15).

The second type is a self-Amplifying mRNA vaccine which is based on the engineered RNA genome of positive-sense single-stranded RNA viruses. The most currently used self-amplifying mRNA vaccines are based on an alphavirus genome (16). This type of mRNA vaccine is produced by replacing viral structural genes with antigen genes of interest. Therefore, when the vaccine is delivered into the cytoplasm of target cells, it is able to perform self-amplification to increase the level of RNA expression. This platform provides a large amount of protein production from an extremely small dose of vaccine (17,18,19).

mRNA vaccine delivery

Delivery of naked mRNA may result in lower internalization into target cells. The naked mRNA is also highly sensitive to the degradation by RNase enzyme in the cytoplasm which can lead to translation inhibition and lower yield of antigen production (22). Therefore, the delivery system is required to increase the uptake rate of mRNA vaccine into target cells (14). Several approaches are invented to deliver the mRNA vaccine including the protamine, cationic lipids and polymers, lipid nanoparticles (LNPs), modified dendrimer nanoparticle, and polysaccharide particle. Nowaday, the common and widely used techniques that provide high efficiency are the protamine, Cationic lipids and polymers, and lipid nanoparticles (LNPs).

The protamine is a cationic peptide which was demonstrated to prevent mRNA degradation by RNases (23,24). Using protamine-complex mRNA promotes balancing of both humoral and T cell mediated immune responses and mediated antitumor response in vivo. However, it can lead to disrupted protein expression levels of the vaccine (25).

The cationic lipid and polymers are high-efficiency transfection reagents which are performing well in many primary cell and cancer cell lines (26,27,28). Nowaday, the development and designing of complex reagents are ongoing in order to increase the effectiveness and safety of this delivery system (29). Cationic lipids and polymers, including dendrimers, have become generally utilized apparatuses for mRNA vaccination in the previous few years while are used for small interfering RNA (siRNA) delivery over a decade (14).

Lipid nanoparticles (LNPs) platform is one of the most engaging and widely used delivery approaches for mRNA vaccines. LNPs regularly are composed of four segments. The first segment is ionizable cationic lipid, which promotes self-assembly into very small sized (~100nm) particles and permits the mRNA releasing from the endosome into the cytoplasm. The second part is lipid-linked polyethylene glycol (PEG), which aids in the half-life expansion. The third part is cholesterol that acts as a stabilizing agent. The final component is phospholipids lipid bilayer similar to our cell membrane (30). Several studies have shown that LPNs provide a potent tool for siRNA, conventional RNA and also self-amplifying RNA delivery in vivo (31,32,33).

Production

In order to produce the mRNA vaccine, prior genomic sequence of the targeted pathogen is required. Therefore, the first step is performing genome sequencing of the interested pathogen followed by data analysis. The candidate antigens used for vaccine production are selected based on the

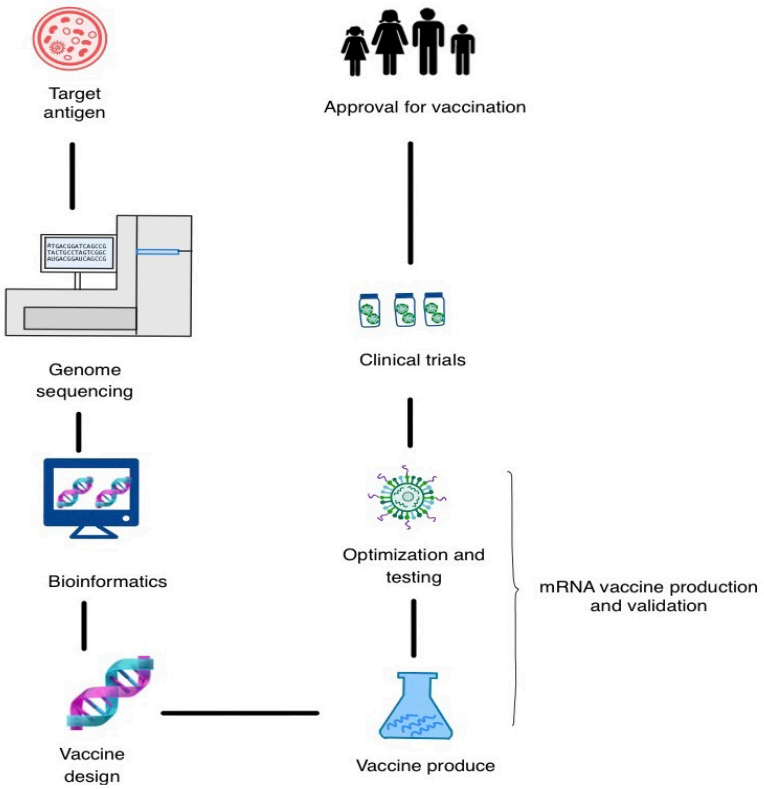

Figure 1. Processes of mRNA vaccine production

clinical data and immunological study. After antigen selection, the based sequence coded for the antigen is identified and used to design the vaccine. During the designing step, the appropriate vaccine structure, delivery system and vaccine adjuvant are selected in order to construct vaccines with highest efficacy. After the designing processes, mRNA are constructed, purified and formulated into a pilot vaccine. This vaccine will be tested for its efficacy and safety both in vitro and in vivo before being tested in clinical trials. After its effectiveness is clarified, approval for vaccination with long-term side-effects observation is the final step (Figure 1) (20,21).

Mode of action

The mRNA vaccine can be administered by conventional needle-base approaches such as intramuscular or intradermal injection. After reaching the target tissues, the RNA vaccine is uptaken into cytoplasm of human host cells where the mRNA vaccine is recognized by free ribosomes. After that, a translation process occurs in order to produce the coded protein antigen. The pathogen proteins are either secreted from the producing cells or presence on the cell surface of host cells. Our immune system notices the presence of foreing antigen in the protein form and mediates the elimination. After the clearance process, memory T cells and B cells which are specific to the antigen are accumulated mainly in the lymph nodes. Upon the natural infection, these memory cells respond quickly and strongly in order to eliminate the pathogens. This rapid and appropriate response contributes to lower clinical severity from the infection thus reducing hospitalization and mortality rate (10,34).

Advantage and disadvantage

Unlike protein-based vaccines, mRNA vaccines can be produced by encoding any antigen of interest. Moreover, It allows a high degree of flexibility and adaptability since production of the different vaccines can utilize and share the same available facilities and manufacturing processes. Besides, mRNA immunizations cannot induce an immune response against viral vectors as noticed for certain vector-based vaccines (35,36). This advantage allows multiple immunization times for mRNA vaccines. Compared to the DNA vaccine, vaccination with mRNA vaccine is simpler since they do not require additional vaccination tools such as gene guns or electroporation. Vaccination with mRNA vaccine can be performed via conventional needle-based injection similar to other types of vaccine. These outstanding advantages of mRNA vaccines are vital when under a pandemic threat which require a rapid platform for an effective vaccine production (37).

However, mRNA vaccines also show some disadvantages. Because of the presence of the extracellular ribonuclease that has the ability to digest the foriegn mRNA, injection of naked mRNA is extremely sensitive. Therefore, administration of mRNA requires a vaccine delivery system for vaccine protection and maintaining stability as mentioned earlier. In addition, high hydrophilic characteristics and negative charge of the mRNA can cause the difficulty of host cell membrane penetration, which can also be resolved by the vaccine delivery system. Finally, adverse effects of the new delivery systems and the induction of autoreactive antibodies have to be considered for the safety of mRNA vaccines (38).

Conclusion and future perspective

Under the current situation of COVID-19 pandemic, mRNA vaccines show an outstanding effectiveness when compared to other types of COVID-19 vaccine. Advantages of the mRNA vaccine are also demonstrated by several studies. The major advantages are rapid production, cost-effectiveness and any targeted antigen can be selected. However, there are some disadvantages that can be solved by using the appropriate delivery system as described above. For example, the high-efficiency carriers; new generation of LNP, which can protect mRNA from ribonuclease and allows prolonged expression of the antigens in the body. However, some studies found that mRNA vaccines can induce mild to moderate adverse symptoms upon the clinical trials (39,40). Therefore, further studies about long-term side effects are required for vaccine safetyness.

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