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Review

mRNA Vaccines

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ABSTRACT

Vaccines are solutions made with the aim of providing immunity against diseases by giving the body the attenuated disease virus, parts, or secretions of the disease agent. They are based on the principle that the immune system gives a strong response and eliminates this factor as a result of re-encounter by introducing the disease agent to the immune system and creating an immune memory. Vaccination has lowered the prevalence of many diseases around the world since its inception. One type of vaccine that has emerged in recent years is messenger ribonucleic acid (mRNA) vaccines. mRNA is a nucleic acid molecule that takes part in the production of proteins from deoxyribonucleic acid (DNA). Since it has an important role in protein synthesis, it can be used as a tool to produce the desired protein. With this principle, in mRNA vaccines, a part of the antigen that causes the disease is produced, and this antigen is introduced to the immune system. These vaccines have many advantages and convenience over conventional vaccines, as well as certain difficulties. mRNA vaccines can be used to prevent viral pandemics as well as bacterial pathogens. At the same time, mRNA vaccines have been produced for cancer treatment in recent years. In this review, how vaccines stimulate the immune system, from the types of mRNA vaccines, how they are produced and used; advantages, disadvantages, clinical use of these vaccines, and some current studies on mRNA vaccines were mentioned.

Keywords: Cancer vaccines, immunity, mRNA vaccines, vaccine.

Vaccines prevent millions of diseases and save lives every year.[1] Vaccination began in 1796 when Edward Jenner showed that vaccination with cowpox virus was protective against later smallpox infection. With this event, the term "vaccine" originated from the Latin root "vacca" meaning cow.[2] As a result of the widespread use of vaccines, smallpox has been extinguished completely and the incidence of polio, measles and other childhood diseases has remarkably reduced.[1]

The vaccine is defined as a biological preparation used to immunize against a disease or treat disease.[2] Vaccination can be made passive or active. Passive immunity occurs by transferring preformed antibodies to an unvaccinated individual. That individual then develops a temporary immunity against a specific organism or toxin, thanks to the existence of these antibodies. Active vaccination occurs when an unvaccinated individual is exposed to a pathogenic substance. This individual's immune system initiates the process of developing immunity against this substance. Active vaccination generates long-term immunity by contrast with passive vaccination.[3]

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VACCINE AND IMMUNE SYSTEM

The immune system is basically divided into innate and adaptive immunity. Both the innate immune system and the adaptive immune system constantly interact with each other to provide an effective immune response.[4]

The innate immune system works consistently and provides the first line of defense against pathogenic agents. There are pattern recognition receptors (PRRs) on cell surfaces that contribute to innate immune response. PRRs are not specific for any pathogen or antigen, however, they are able

to provide rapid response by recognizing antigens. PRRs recognize pathogen-associated molecular patterns (PAMPs) that can trigger cytokine release. Examples of PAMPs include lipopolysaccharide (endotoxin), peptidoglycan (cell walls), lipoproteins (bacterial capsules), and flagellin (bacterial flagella). These antigens are produced only by microbial cells, not human cells. Recognition by PRRs of PAMPs provides activation of the immune response, cytokine release, and phagocyte activation. In other words, it is the first step in the formation of the immune response.[3]

On the contrary to the immune system, the adaptive immune response is an antigen-specific response, and it occurs through the interaction of three significant cell types. These cells are antigen-presenting cells (APCs), lymphocytes produced by thymus (T cells), lymphocytes produced in bone marrow (B cells). Among APCs, dendritic cells (DCs) (known as Langerhans cells in the skin) are most significant, because they are responsible for capturing, processing, and presenting antigens at the cell surface for recognition of the T cell receptor. B cells, on the other hand, are capable of directly recognizing foreign antigens. Recognizing foreign antigens by immunoglobulin (Ig) receptors in B cells enables the production of plasma cells. Plasma cells, then, secrete subclasses of antibodies (IgA, IgE, IgG, and IgM). These antibodies kill infected cells to prevent or limit infection. A most significant feature of the adaptive immune system is the production of memory B and T cells and long-lived plasma cells that provide protective immunity against recurrent infectious antigens.[5] Immunological memory produces a rapid increase in response after re-exposure to an antigen. This feature plays an important role in the function of the immune system and is one of the principles of vaccination. When memory B cells re-encounter previously recognized antigens, they divide rapidly and differentiate to generate antibody-secreting plasma cells.[6]

Most vaccines induce active immunity by promoting antibody development in the recipient, which is a persistent response.[2] Attenuated vaccines include an original pathogen that has been laboratory attenuated. For this reason, these vaccines produce a strong antibody response and provide long-term immunity. In addition to this, owing to the fact that these vaccines contain live organisms, there is a possibility that the pathogenic agent will revert to its original virulent form. Also, as vaccines produce real disease, it is risky to give live vaccines to people with weakened immune systems.[3]

Recombinant vector vaccines are experimental vaccines that use an attenuated virus or microbe to introduce microbial DNA into body cells. These viral vaccines stimulate the immune system by mimicking a natural infection.[3]

The purpose of active immunization with the vaccine is to stimulate the host to produce a primary immune response, usually by inducing B cell proliferation, antibody response, and T cell sensitivity. If that person is later exposed to the pathogen for which the vaccine was directed, a secondary stronger reaction occurs, including increased B-cell proliferation and antibody production and this immune response protects the person from suffering from the disease.[2]

MESSENGER RIBONUCLEIC ACID (mRNA)

Messenger ribonucleic acid is the intermediate step between the translation of the protein-encoding DNA and the production of protein by ribosomes.[7] The cell uses a molecule called RNA to retrieve the information in DNA while encoding proteins, and this molecule is called messenger RNA or mRNA. All proteins made by a cell go through this process. DNA is copied into RNA and this mRNA is translated into protein.[8]

The mRNA consists of a 5 'CAP (header), a 5' UTR (untranslated region) (also called leader RNA), a stop signal coding sequence, a 3 'UTR, and a poly (A) tail. This molecule carries the DNA template of the protein to be encoded as a messenger to the ribosome. This template is translated in the ribosome and multiple copies of protein are created from each mRNA template.[9]

MESSENGER RIBONUCLEIC ACID VACCINES

Messenger ribonucleic acid, as an intermediate carrier of genetic information, is used as a template for protein expression. Therefore, like DNA, mRNA is an interesting tool for the production of desired proteins by adding exogenous nucleic acid molecules to cells.[10]

Creating an mRNA structure simply by knowing the genetic sequence of the desired antigen is a relatively rapid method for producing vaccines in case of an epidemic or disease.[7] Messenger

ribonucleic acid vaccines are created by producing synthetically encoded mRNA sequences for the disease-specific antigen.[11] Synthetic mRNA is generally designed in accordance with the scheme of eukaryotic mRNA for therapy. For a successful RNA vaccine, stability, purity, and translation of the mRNA are crucial. Cap and poly (A) tail positioned at the 5′ and 3′ end of the mRNA is required to stabilize the mRNA. In addition, mRNA needs 5′ and 3′ UTRs surrounding the ORF (open reading frame) to further increase both translation and stability. UTRs must be chosen carefully because they determine protein production and stability of the mRNA. Purification process of mRNA is made through FPLC (fast protein liquid chromatography) or HPLC (high-performance liquid chromatography).[12]

For an mRNA vaccine to be translated and generate an antigen-specific immune response, the mRNA must reach the cytosol of target cells.[13] Messenger ribonucleic acid, before being taken up by cells, is in danger of being degraded by ubiquitous ribonucleases. Thus, complexing agents are often used to protect RNA from degradation. Messenger ribonucleic acid is generally complexed with lipids or polymers.[9] The main delivery ways for mRNA vaccines are intramuscular, intradermal, or in vitro subcutaneous injection.[14]

The mRNA vaccine instructs our cells to make a bacterial or viral protein. Our immune system responds to these proteins and develops tools to react to future infections with pathogens. Thanks to the mRNA vaccine, after the pathogen is produced in the body, the pathogen is introduced by the immune system and the body is ready to fight it when it encounters the real pathogen.[11] When memory B cells re-encounter this previously recognized pathogen, they divide rapidly and differentiate to create antibody-secreting plasma cells, by this means immunization against the intended antigen is ensured.[6]

In conventional vaccines, a full virus or bacteria are used to teach the body to develop immunity to pathogens. These pathogens are neutralized or attenuated. In recombinant vaccine technology, yeast and bacteria cells are used to produce multiple copies of certain viral or bacterial proteins or a small portion of the protein. In mRNA vaccines, this step is skipped. Messenger ribonucleic acid vaccines; it carries information that enables our own cells to produce proteins or protein fragments of the pathogen itself. They are synthesized chemically without the need for cells or pathogens, which facilitates the manufacturing process. In addition, mRNA vaccines only carry the information required to make a small part of the pathogen. It is not possible for our cells to make the entire pathogen.[14]

Messenger ribonucleic acid vaccines are divided into non-replicating and amplifying mRNA vaccines.

Non-replicating mRNA vaccines are traditional mRNA vaccines. They contain antigen sequences that are chosen alongside the UTRs. In contrast with self-amplifying mRNA, advantages of using non-replicating mRNA vaccines are simplicity of the structure, small size of the RNA, and the absence of any additional encoded proteins that could elicit undesired immune responses.

Self-amplifying mRNA vaccines are based on the alpha virus genome, in which the genes encoding the structural protein are replaced by the preferred antigen. This mRNA is replicated at very high levels and produces the chosen antigen. Therefore, any genetic information that is encoded by self-amplifying mRNA vaccine will be amplified many times, and also, in contrast with non-replicating vaccines, results in high levels of antigen expression at relatively low doses. Self-amplifying mRNA vaccines are of remarkably greater length. The low yield as a result of the great size of these vaccines makes them more difficult to produce than non-replicating vaccines.[14]

ADVANTAGES AND DISADVANTAGES

When the mRNA vaccine is assumed to be clinically safe and effective, there are many advantages. One of the main advantages is production rate. Thanks to synthetic production, it is a process that does not require eggs and cells. Clinical groups can be generated by producing vaccines within weeks after the genetic sequence of immunogen is founded. Thanks to mRNA technology, vaccines against multiple targets can be rapidly produced and expression is possible for complex proteins that are difficult or impossible to produce.[14,15] Since RNA vaccines are not made with pathogen particles or inactivated pathogens, they are not contagious, there is no risk of the pathogen mutating. For instance, mRNA coronavirus disease (COVID-19) vaccines that have been developed in recent months can not cause COVID-19. They do not carry all the information for our cells to produce the entire severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) they only make certain proteins and thus do not cause infection.[13]

RNA does not integrate into the host's genome, and the RNA chain in the vaccine is disrupted after protein production occurs.[11] Enzymes called ribonucleases (RNases) degrade mRNA after instructions are delivered to our cells for protein formation.[13] Early clinical research results indicated that mRNA vaccines create a reliable immune response and are well tolerated by healthy individuals with few side effects.[11]

The delicate and fragile structure of mRNA leads to some difficulties. The biggest challenges are the storage and transportation of the vaccine. mRNA vaccines require to be stored frozen at very low temperatures and must be transported by cold chain.[11] For example; it has been said that mRNA COVID-19 vaccines must be kept at a very low temperature of -70°C.[13]

In addition, delivery of the vaccine to cells is challenging because the free RNA in the body is rapidly degraded. mRNA can cause an inflammatory response by disrupting rapidly after injected. Scientists have found that by coating the mRNA with tiny bubbles of oil (a lipid nanoparticle), they will last longer. While providing transmission, it can indicate an inflammatory response to mRNA. Messenger ribonucleic acid vaccine, to decrease this risk, is incorporated into much bigger molecules and/or packaged into particles or liposomes to help stabilize the RNA chain. Another disadvantage of mRNA vaccines is few unwanted effects. Messenger ribonucleic acid chains in vaccines cause an unwanted immune reaction because body cells designed foreign sequences to resemble those produced by mammalian cells.[11-14]

USE IN CLINIC

Recent Ebola and Zika outbreaks have shown how quickly infectious diseases can spread and the need for a quick-responsive vaccine platform technology has emerged. Messenger ribonucleic acid vaccine has entire features of a vaccine towards this requirement. Many studies have shown that mRNA vaccines are effective in combating various types of cancer and infectious pathogens that conventional vaccine platforms may fail to stimulate protective immune responses. Various preclinical studies have indicated that mRNA vaccines induce immune responses and protect against pandemic potential pathogens such as Zika virus, Ebola Virus, and influenza.[14]

As the Ebola Virus vaccine, based on the production of EBOV envelope glycoprotein, LNP-encapsulated mRNA has been shown to induce EBOV-specific immunoglobulin G (IgG) production, protecting against lethal infection and clinical signs of disease.[16]

Several studies have shown that mRNA vaccines have the ability to reveal protector immune responses against influenza. Petsch et al.[17] were the first to demonstrate to scientists that applying mRNA vaccines encoding influenza HA (a glycoprotein found on the surface of influenza viruses) was protective in mice from exposure to influenza H1N1, H3N2, and H5N1.[18]

In research on mRNA vaccine encoding rabies lyssavirus glycoprotein (RABV-G) formulated with protamine for the first time in humans, it was observed that this vaccine generates a protective immunity in mice against a deadly virus threat.[15]

Against Zika virus, a strong anti-ZIKV vaccine is designed to encode pre-membrane and envelope (prM-E) glycoprotein by mRNA. Vaccination was done through encapsulation with lipid nanoparticles (LNP) and a single low dose intradermal vaccination in mice has been shown to produce strong and persistent antibody responses.[19]

Messenger ribonucleic acid-1273 vaccine candidate that produced against COVID-19, which is today's pandemic, imitates the Spike proteins of the virus by encoding the S-2P antigen, which is a transmembrane anchor of SARS-CoV-2, consisting of glycoprotein, and enables the immune system to recognize the virus.[20] When immune system cells realize the SARS-CoV-2 Spike protein floating around, they see it as a threat. Protein alone can not damage us, and it can not bring our cells to the point of getting sick. However, it is sufficient to deceive immune cells to create antibody protection.[21]

Immunization against more than one antigen at the same time is an interesting concept with the potential to immunize against multiple pathogens, different antigens of the same pathogen, or complex polyproteins. Chahal et al.[22] demonstrated that six mRNA replicons can be formulated together, express each of the encoded antigens and induce protective immunity.[14]

MESSENGER RIBONUCLEIC ACID CANCER VACCINES

Cancer relapses after cancer treatments such as chemotherapy and radiation therapy,

and almost all patients become insensitive to these treatments after long-term application (or prolonged administration).[23] In conjunction with inefficacies of these treatments, in addition to applications in infectious diseases, both academic and industrial researchers pursue the use of mRNA vaccines to boost the immune system in cancer-fighting. Cancer vaccines are developed not to prevent the diseases, however, to treat cancers. In one approach, scientists took genetic profiles of the patient's cancerous cells and healthy cells, used various algorithms to compare them, and then created a personalized vaccine designed to help the immune system learn to fight cancer. Messenger ribonucleic acid vaccine studies made in Pennsylvania University, mRNA vaccines have been demonstrated to induce potent T cell responses that can efficiently kill tumor cells.[24]

Immunization with mRNA encoding tumor antigen is a novel vaccine strategy for cancer treatment. Providing induction of CD8+ cytotoxic T lymphocytes (CTL) particular to tumor antigen is the main purpose of cancer immunotherapy.[25] Specific immunotherapy is based on the ability of the patient's immune system to distinguish healthy cells from tumor cells based on the expression of tumor antigens.[26]

Activated CTLs flow in lymphoid organs and peripheral tissues to find cells that express antigen previously recognized and locate and directly lyse tumor cells. Immunization with the genetic material that will encode the tumor antigen or by modifying the DC that will express the tumor antigen forms the cancer vaccine strategy. Activated CTLs flow in lymphoid organs and peripheral tissues to find cells that express antigen previously recognized and locate and directly lyse tumor cells. In addition, adding mRNA encoding tumor antigen to DCs enables the induction of tumor antigen-specific by presenting these antigens on the cell surface of the DCs.[25]

In addition to finding and destroying cancer cells that have spread, these T cells can build immunological memory and therefore provide defense against recurrent cancer cells.[26] It is important that the antigen of interest is made available by antigen-presenting cells, especially DCs, for the efficacy of mRNA vaccines.[27] Because dendritic cells are the strongest antigen-presenting cells that can activate T cells. Electroporation (electropermeabilization) is the preferred method for transferring mRNA to DCs and has been used successfully.

Most patients with prostate cancer, kidney cancer,[28] and skin cancer[25] vaccinated with mRNA-transfected DCs have had a vaccine-induced T cell response.[28]

CV9103 and CV9104 are novel mRNA-based anticancer vaccines for prostate cancer treatment. Positive immune activation has been documented after phase I/II studies of CV9103. Also, the CV9104CV9104 vaccine is currently undergoing clinical testing in specific clinical settings, such as castration-resistant prostate cancer, and in men with high-risk prostate cancer.[23]

A liposome-packaged mRNA vaccine named MART1 enabled the specific and significant protection against B16F10 melanoma tumor progression in mice.

Conclusion

Messenger ribonucleic acid vaccines are seen as the beginning of a new era in medicine. Unlike conventional vaccines, it does not work to introduce a pathogen to the body from outside, it works on the principle of introducing a certain part of the pathogen to the immune system by producing it in the body. These vaccines have been shown to immunize viral and bacterial pathogens, and even more than one pathogen at the same time. In addition to these, it has been observed that they act for therapeutic purposes in different types of cancer.

The basic technology of mRNA vaccines has been developed for years, however, it has come up with the COVID-19 pandemic. In mRNA vaccine produced for COVID-19, it was aimed to produce Spike proteins, the transmembrane anchor of the virus, in the body, instead of the entire virus. This enables the vaccination without risk of infection, without the need to insert a virus into the body. As mRNA vaccines have many advantages, mRNA has difficulties such as storage and transportation because it is a very sensitive and unstable molecule. At the same time, reliability and side effects of these vaccines are not clearly known due to a novel vaccine strategy. In addition, the immunogenicity of these vaccines may depend on the injection route of the vaccine and mRNA formulation. However, the fact that its production is faster than other types of vaccines provides a great advantage in an unexpected pandemic situation. In clinical studies conducted so far, these vaccines have not seen any major side effects, it has been observed that they induce T cell responses and provide a protective effect in accordance with their purpose.

Due to the insufficiency of today's cancer treatment methods, mRNA vaccines are also promising for cancer treatment. With mRNA cancer vaccines, the treatment has been deemed possible by encoding the tumor antigens or by enabling these antigens to be presented to T cells by DCs. In mRNA vaccine studies on prostate cancer, kidney cancer, and skin cancer, it was observed that the vaccines gave positive results and provided protection against tumor progression. These vaccines are currently implemented in some high-risk cancer cases. However, clinical researches on cancer vaccines are still ongoing.

COVID-19 and other mRNA vaccines are still in experimentation, but vaccines that could soon demonstrate to work could help other mRNA projects attract more funding and attention. By giving more intensity to mRNA vaccine studies, it is seen as a therapeutic method that will hope to many cancer patients.

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