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The advantages and disadvantages of different types of vaccines: DNA vaccine, mRNA vaccine, and inactivated vaccine

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Abstract. The use of vaccines to combat disease by humans has been ongoing for centuries and has produced significant results. However, with the development of technology, different types of vaccines have emerged, and often people are confused as to which is the best. This paper have analyzes three main types of vaccines that have been developed and commercialized: DNA vaccines, mRNA vaccines, and inactivated vaccines, to gain insight into the issues associated with vaccines. This paper explained the mechanisms of action and the process of their production, and identified some of their potential advantages and disadvantages. Finally, this study draw the conclusion that each type of vaccine has unique properties that cannot be replaced by others and that it was not easy to determine the best among them.

Keywords: vaccine, mechanism of action, manufacture, plasmid, immunize.

1. Introduction

Since 1796, when English physician Edward Jenner proved the effectiveness of a vaccine by inoculating an eight-year-old child with material from a cowpox wound and found that it successfully made the child resistant, the development of vaccines has never ceased. Especially at the end of the last century, when the technology of genome editing was introduced, the genetic vaccines emerged with various advantages. In the context of the recent COVID -19 pandemic, there are currently already 178 different vaccines in clinical development [1], using a variety of technologies. And undoubtedly, they have played a key role in staving off the pandemic at its height, as well as preventing its further spread in the aftermath. However, there are occasions in which the effect of vaccine was not ideal, as many citizens who have been vaccinated still catch COVID-19, although a relatively small proportion. Also, it is appropriate to say that if we can develop the vaccine more in advance, the situation could be even less severe. Therefore, with these various types of vaccines, it is important to know their advantages and disadvantages in order to identify their prospects, and to point out some potential harm if they are not used or manufactured properly.

There has been some research being done in this field, mainly by conducting experiment to reveal the adverse effects of vaccines after injected. This paper mainly focus on the theoretical level to explain the advantages and disadvantages of different types of vaccines. Thus, it can be seen as an overview of the safety and the feasibility of production of different types of vaccines.

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2. Analysis of vaccines

2.1. Classification of vaccines

Although there are a variety of vaccines named after their active ingredient, this paper covers three main types of vaccines here: DNA vaccines, mRNA vaccines, and inactivated vaccines. The traditional live vaccine can serve as a comparison between these three types of vaccines.

2.2. The working mechanisms of vaccines

2.2.1. DNA vaccines' working mechanism. DNA vaccines contain a specific DNA sequence that codes for cellular production (protein biosynthesis) of an antigen [2, 3], in contrast to conventional vaccines that contain either specific antigens of a pathogen or attenuated viruses that elicit an immune response in the vaccinated organism. At the heart of the DNA vaccine is the use of plasmids, a small circular DNA molecule found in bacteria and some other microscopic organisms which typically have a small number of genes and can be passed from one cell to another as part of the processes by which microorganisms reproduce, to introduce a gene from a bacterium or virus to trigger an immune response [4, 5]. For example, the recently developed DNA vaccine ZyCoV-D, recently licensed in India as COVID-19, contains a plasmid carrying a gene encoding the SARS-CoV-2 spike protein [6].

However, the process for the plasmid to function successfully can be challenging. After entering a human cell either by endocytosis or by direct entry into the cytosol and then crossing the cortical actin layer, possibly by actin-based motility [7], it must cross the cytoplasm and reach the nucleus [4] to function successfully. However, according to research, the cytoplasms could have a significant effect on degrading the plasmid DNA (E.g. the cytoplasms of HeLa and COS cells degrade plasmid DNA with a half-life of 50-90 minutes [8]).To prevent this, each DNA is linked to different proteins within the cell. This protein DNA then balances interactions with intercellular pathways, reducing the effective size of the plasmid and thus protecting the DNA from rapid decay to reach the nucleus [9]. Enzymes in the nucleus then convert the viral or bacterial gene carrying the plasmid into messenger RNA (mRNA). The mRNA must return to the cytoplasm to be transformed into a bacterial or viral protein by enzymes. By doing this, the immune system can recognize the bacterial or viral protein as a foreign substance and launch an immunological reaction, which is often slow because the immune system has never come into contact with the bacterial or viral protein before.

Vaccination leads to the formation of memory immune cells. When infection occurs, these cells quickly recognize the bacterium or virus and prevent severe disease [4]. After functioning, the plasmid DNA is usually degraded within a few weeks, but these memory immune cells, with their long lifespan, provide continued immunity to the pathogen. Some extreme cases may also occur: Very elderly people who did not contract swine flu in 2009 can largely be attributed to their previous exposure to a similar strain that was widely used in the 1918 epidemic [10, 11].

DNA vaccines clearly offer some benefits over other vaccination types in terms of the way they work: They substitute "actual" pathogens with plasmids, as was already described. The introduction of weak or dead viruses into the human body has grown to be a significant component of traditional vaccinations, which may cause certain worries, which is why this may be a benefit. One is that, especially with live attenuated vaccines, which are regarded as excellent candidates for vaccine manufacture because they elicit a long-lasting, balanced immune response, the pathogen strain used for vaccination might mutate and become harmful again through a process known as reversion. Therefore the biggest problem with this type of vaccine seems to be safety, as attenuated viruses can eventually revert to a virulent phenotype [12]. In our view, this would have significant serious consequences if the attenuated pathogen has reversed in the vaccine which has been already widely used. The DNA vaccine, on the other hand, appears to be a safer alternative because it does not contain any pathogen.

Although the use of DNA sequence gives the DNA vaccine its safety, it also limits its use because it is effective only for those pathogens that have proteins as immunogens. For other pathogens that do

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not have protein immunogens, such as nucleic acids, polysaccharides, and glycolipids [13], the DNA vaccine would not be applicable, thus proving vulnerable in combating these pathogens, such as some sugar-coated bacteria that cause pneumonia [14].

2.2.2. mRNA vaccines' working mechanism. mRNA vaccines function quite similarly to DNA vaccines in that they also provide genetic material to human cells for synthesis into one or more bacterial or viral proteins [15]. The specific process taken place is divided in three parts: initiation, elongation, and termination. The small ribosomal subunit attaches to the beginning of the mRNA sequence during initiation. The mRNA sequence's so-called start codon then binds to a transfer RNA (tRNA) molecule carrying the amino acid methionine. Every mRNA molecule has an AUG-coded start codon that represents methionine. The subsequent binding of the big ribosomal subunit forms the entire initiation complex. When a nonsense codon (UAA, UAG, or UGA) is encountered, translation is terminated. These nonsense codons are recognized by protein release factors that resemble tRNAs when they align with the A site. Peptidyl transferase is then instructed by the releasing factors to add a water molecule to the carboxyl end of the P-site amino acid. This reaction causes the P-site amino acid to detach from its tRNA, resulting in the release of the newly formed protein [16]. In this process, the non-sense codon which functions to terminate the synthesis would be an important aspect to improve the efficacy of mRNA vaccine, which will be demonstrated in the following part of the article.

Although the nature remains constant, there are some key differences, however, between mRNA and DNA vaccines: Since it is ultimately mRNA that enzymes use to obtain information for antibody synthesis, plasmid DNA must first cross the cytoplasm to be converted to mRNA and is then returned to the cytoplasm to function; mRNA vaccines, on the other hand, deliver mRNA, which can be utilized immediately upon its entry into the cell, to the cytoplasm. And that's a remarkable advantage: It provides a much faster and stronger immune response than DNA vaccines, which have to go the extra step into the nucleus.

However, it is important to note that plasmid DNA may exist in many copies and contain anything from a few dozen and hundreds of genes [17]. Consequently, a single plasmid DNA can generate many of mRNA copies, so that they can create more bacterial or viral protein than a single molecule of an mRNA vaccine once it has entered the nucleus, which result in that several doses are needed for the vaccination of mRNA vaccine to further boost the immune response to the corresponded pathogen [18].

Compared to conventional vaccines, mRNA vaccines, similar to DNA vaccines, again appear to be safer because they do not contain pathogens and can effectively prevent human infection through vaccination by eliminating the possibility of reversion for weakened pathogens.

2.2.3. Inactivated vaccine's working mechanism. The inactivated vaccine is quite similar to the "traditional vaccine" as we have already discussed. However, the inactivated vaccine consists of dead pathogens rather than weakened ones. It turns out that even though these viruses are inactivated, they still carry the identifying features that alert the immune system to their existence and trigger an immune response: in vaccinated individuals, the antigen is taken up by an antigen-presenting cell (APC) and transported to a draining lymph node. An epitope of the antigen, along with an MHC molecule, is placed on the surface of the APC by the immune system. Since it can now contact and activate T cells, the immunological response can be triggered [19, 20]. In inactivated vaccine, because the genetic material of the pathogen has already been destroyed, there is no risk of reversion here. In addition, the inactivated vaccine is easy to transport because of the killed pathogen contained in the vaccine. Live vaccines need to be stored at certain low temperatures to maintain their function [21], and if the temperature is sufficient, there would be problems exporting the vaccine, and in developing countries with inadequate technology, it would be difficult to store the vaccine for a long period of time. Even if we were to store in regions where modern technology allows us to ensure the condition all the time, it would come at a significant additional cost. Therefore, the inactivated vaccine is a better candidate for widespread use than the live vaccines.

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However, a single dose of inactivated vaccines, like mRNA vaccines, may not be effective enough to provide sufficient resistance to the disease, requiring boosters. In this case, surprisingly, live vaccines have an advantage because the response they elicit is so strong that a single dose is sufficient to immunize a person. This is because they do not effectively stimulate an element of the immune response called mucosal immunity, which is an important line of defense that wards off many pathogens before they enter the general circulation [22]. However, although inactivated vaccines have some advantages over conventional vaccines, they are dwarfed by those of DNA and mRNA vaccines because they are even easier to transport and effective.

2.3. The manufacture of vaccines

2.3.1. DNA vaccine production. Although DNA vaccine production can be challenging (e.g., numerous impurities with structures similar to the target product are generated during the production process, making mass production of highly pure plasmid DNA particularly difficult [23]), a sufficiently mature technology for production has been developed. Usually, a microbial source is used for fermentation of plasmid DNA used in vaccines. The main downstream purification begins with cell collection, lysis, and clarification after fermentation. Cells are concentrated during cell harvest, and the fermentation broth is then removed by centrifugation, microfiltration, or tangential flow filtration. Plasmid DNA is then released from the collected cells by special methods. The first stage of separation of supercoiled plasmid DNA is called precipitation or flocculation. This process selectively precipitates and eliminates contaminants such as high molecular weight RNA and genomic DNA, proteins, and endotoxins. Later, depth filtration can be used to clarify the lysate [24].

Traditional vaccines, on the other hand, typically take 7-10 years to mature enough to be officially introduced [23]. For each target pathogen, optimal methods for propagation, attenuation, killing, and other steps must be developed while maintaining sufficient immunogenicity of the pathogens, which is not to say that these technologies are more difficult to develop, but rather that they seem to be very limited, only against the vaccine development industry. Plasmid DNA, on the other hand, has a wide range of applications, including the production of pharmaceutical proteins, antibodies, industrial enzymes, and molecular diagnostics [25]. Even in terms of vaccine production only, because once a process for producing DNA, mRNA, and viral vector vaccines is established, it can be readily used to produce vaccines against other viruses without the need for requalification [23]. Therefore, the development of DNA vaccine production technology will have a better cost-benefit ratio.

2.3.2. mRNA vaccine production

Vitro transcription, a rapid process that allows the synthesis of template RNA molecules, is used to produce mRNA [26]. In this process, the template is removed from the mRNA by digestion with DNAses, after which the mRNA can be purified. Vitro transcription technology is mature and has been applied to a variety of study field to produce large amount of mRNA efficiently, such as sgRNA synthesis for gene editing, RNA probe synthesis for hybridization, etc.

As demonstrated, the disadvantage of mRNA vaccine appears not to be in the process in which the mRNA is extracted, but the process in which the protein is synthesized according to it. Although the previous part suggests that the efficacy of mRNA vaccines is outweighed by DNA vaccines driven by plasmids due to their property, the direction for improvement seems clear: if we are able to further elongate the protein chains that are generated during mRNA translation, then this perhaps would greatly increase their capacity and thus improve the efficiency of mRNA vaccines [27]. In this case, these non-sense codons, which are responsible for terminating the synthesis reaction and preventing the degradation of mRNA in the cytoplasm, may be essential. The relationship between the length of the chains of the non-sense codon and the total length of the polypeptide chain has been studied. And they have been found to be highly interdependent [28]. All in all, more efforts need to be made to fully improve the mRNA vaccine with its great potential.

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2.3.3. Inactivated vaccine production. Like other vaccines, inactivated vaccine manufacture is a multi-step process. The creation of the antigen that initiates the immune response is the first stage. In the past, viruses were often cultivated in pathogens like bacteria or eggs so they could be effectively replicated as a whole. It is now feasible to immunize a person using an isolated version of the antigenic protein of a pathogen rather than the viral particles as a complete cell or virus, thanks to advancements in the technology used to make recombinant proteins. In order to get an organism to express a recombinant gene in high quantities, gene expression in the organism must often be altered. To produce enough of the required protein, methods including strain selection, codon optimization, fusion systems, co-expression, mutagenesis, and isotope labeling are frequently utilized. The protein is subsequently extracted from the lysate using procedures including chromatography, cleavage of fusion units, and protein refolding. The vaccine is finally created by including an adjuvant to boost the immune response, etc. [29]. As we can see, the complicated process of inactivated vaccine production involves several expensive treatments. This not only creates obstacles for the inactivated vaccine to be largely produced, but also, when it reflects on the injected person, means the cost would be greater compared to other types of vaccines, especially when we take the fact that boosters are needed into consideration.

Additionally, there have been instances where the pathogen's harmful effects were not entirely reversed by the treatment. Although it had been known since the 1930s that the method for inactivating viruses was not without risks, the Cutter incident with the poliovaccine in 1955 focused attention on the issues surrounding the process, and several outbreaks of diseases that occurred in America and Europe are finally found to be related to the inadequately killed pathogens in vaccines [30]. Therefore, paying more attention to the process of vaccine manufacture to verify that all the pathogens included in a vaccine have been properly destroyed is a much simpler, yet crucial, component to increase the safety of the application of inactivated vaccine.

3. Conclusion

In analyzing the mechanisms of operation and production of the three types of vaccines, it is apparent that each has comparable advantages over the others, but also inevitably some shortcomings. DNA vaccine is safer, but the technology used can be complicated, and its use is limited to pathogens with protein immunogens; mRNA vaccine, which also belongs to the genetic vaccine category, is currently less efficient than DNA vaccines because plasmids can make many copies, but has great potential and is constantly being improved; inactivated vaccine contains pathogens that are killed. Inactivated vaccines contain pathogens that are killed, but this can have disastrous consequences if they are not adequately killed, which has led to several disease outbreaks in the recent past, and the cost can be very high for both consumption and production.

This study has potential limitations as it focuses only on the theoretical level of analysis, but not some adverse effects such as fever, headache, fatigue and pain at the injection site. Therefore, it may be insufficient to conclude which preparation is better. In addition, we did not consider some externalities such as the development of technology in different countries around the world. In some less developed countries, the conventional live attenuated vaccine might be better than the DNA and mRNA vaccines, which require innovative technology.

Although this article has highlighted some of the advantages and disadvantages of the different types of vaccines, as stated, it is still difficult to say which vaccine is best suited for widespread use. Further research needs to be conducted to carefully weigh the impact of these characteristics on the human individual and society as a whole to find the most balanced solution.

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