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Analysis of the invasion mechanism of novel coronavirus and the novel coronavirus vaccine

Tian Yu

Jiangsu TianYi High School, Wuxi, Jiangsu, China, 214000

1707628256@qq.com

Abstract. From the time the first case was identified to the time the novel coronavirus swept the world, developing a reliable, defensible vaccine has been a priority and the common aspiration of the people. Through literature analysis and review, this paper mainly explores the invasion mechanism of the novel coronavirus and the relevant principles of the novel coronavirus vaccine. Based on the above research, this paper finds that the research process and development of coronavirus disease 2019(COVID-19) vaccine is a course of continuous enrichment of varieties and continuous maturation of biochemical research components. Amid the innovation and progress, it is clear to all that vaccines can better cater to the needs of different populations. This paper collects a few typical vaccine examples to reflect a comprehensive. At the same time, the intrusion mechanism of virus is explained in detail. Basic questions about COVID-19 vaccines and how they work can be answered in this paper.

Keywords: Recombinant protein vaccine, Virus invasion mechanism, COVID-19.

1. Introduction

During the years when theIn the years between the emergence of the novel coronavirus and its co-existence with the population, millions of medical workers and researchers have used their own efforts to create a protective barrier between the virus and the body with vaccines, thus saving countless lives. The design and production of COVID-19 vaccines have also become a hot research topic in the medical community. The study mainly discussed the invasion mechanism of the novel coronavirus and the research and analysis of the novel coronavirus vaccine. As a review, this paper is studied by enumeration, horizontal and vertical comparison, point analysis and other methods. This study is more convenient for researchers in the field of novel coronavirus vaccine research to explore the types and efficacy of major vaccines on the market so far.

2. Invasion mechanism of COVID-19

2.1. Introduction of COVID-19

The novel coronavirus is essentially an enveloped Ribonucleic Acid (RNA) virus with a diameter between 60nm and 220nm. Among them, membrane surface sugar proteins that are relatively important

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in the expression of physiological functions are: Spike Protein(S Protein), Envelope Protein(E protein), MembraneProtein(M protein), and Haemaglutinin-esterase (HE protein). HE protein is only found in some coronaviruses. Among them, S protein, which is shaped like a rod granule, like a crown, and covers the entire surface of the virus, has also become the reason for the name of the novel coronavirus. What's more, S protein itself plays an indispensable role in the process of virus infection in the body, and its receptor binding region contains neutralizing antigen epitopes of different conformations, which is the key for the virus to bind to somatic cells. The novel coronavirus S protein has a trimer structure, and 3D classification of the frozen data shows that the Spike protein of the novel coronavirus has multiple conformation states, as shown in Figure1. Due to conformational heterogeneity, the SA and SB domains have poor resolution, and in general, the extracellular region of COVID-19 S is a 160A-long trimer with a triangular cross-section, similar to the closely related SARS-CoVS structure[1].

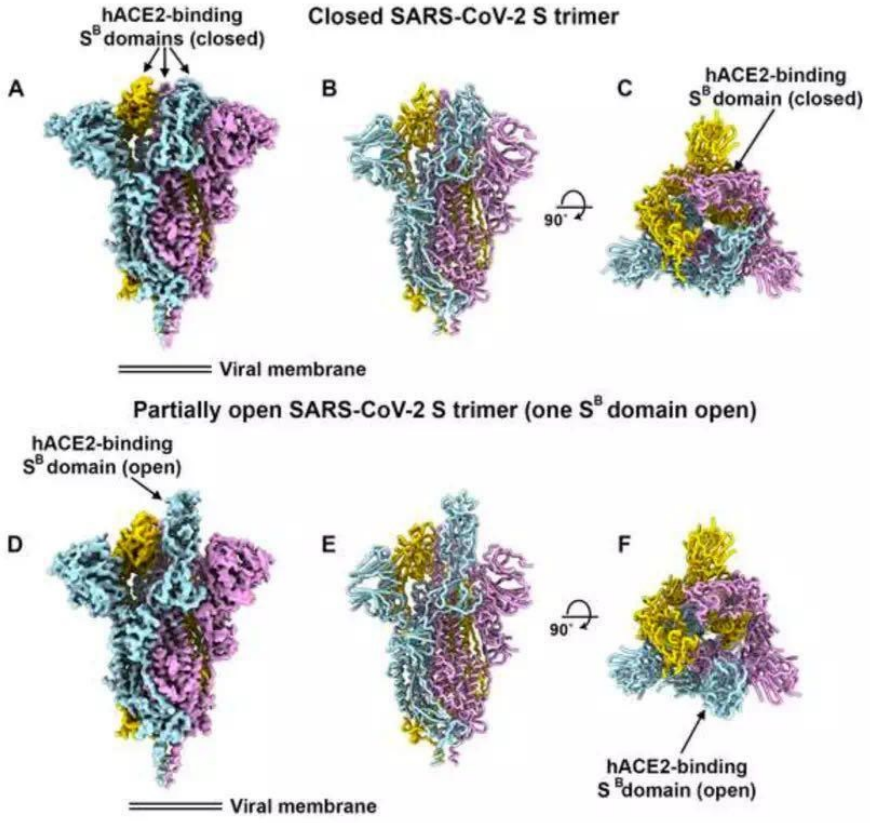

Figure 1. Spike protein of the novel coronavirus

2.2. Virus invasion mechanism

First of all, the virus most often enters the human body through the mouth, nose, lung and other organs, and the most critical step in the process of contact with somatic cells is the combination of angiotensin converting enzyme2(ACE2) protein and viral S protein in the human body. The main function of ACE2 protein is to regulate blood pressure and body fluid balance, and it is widely found in the heart, lungs, intestines and other organs. In addition, the gene encodes a protein that is a functional receptor for the S glycoprotein of SARS and HCoV-NL63 human coronavirus. It plays an important role in the pathogenesis of severe lung failure after viral infection. ACE2 and its homologues can bind to amino acid transporters and play an important role in the absorption of amino acids by the kidney and intestine. After binding to the cell membrane of ACE2 protein, the virus enters the cell through endocytosis. The lysosomal proteases inside the cell attempt to degrade the foreign body, but instead help the virus

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dissolve the outer protein, so that the genetic material RNA begins to replicate and express. Eventually, the host cell assesses the daughter RNA with the viral protein into a new virus and secretes it outside the cell to find the next host. In the continuous invasion and secretion, gradually occupy the major organs of the body, causing a variety of complications. Moreover, patients are more likely to suffer from poor lung breathing and heart failure, leading to death [2].

3. Research and analysis of covid-19 vaccine

At present, the types of vaccines developed are divided into several categories: inactivated vaccines, recombinant protein vaccines, viral vector vaccines, deoxyribonucleic acid (DNA) vaccines, RNA vaccines, etc. The advantages and disadvantages of various vaccines are also different. Inactivated vaccines grow the novel coronavirus in vitro and then inactivate it, but these viruses can still stimulate the body to produce antibodies, so that memory cells retain memories. The advantage of an inactivated vaccine is that the preparation method is simple and fast, and the safety is relatively high, which is the usual means to deal with acute disease transmission. China's commonly used hepatitis B vaccine, polio inactivated vaccine, JE inactivated vaccine, DPT vaccine and so on are inactivated vaccines. However, inactivated vaccines also have disadvantages, such as large doses, short immune period, single immune pathway, etc., and its most frightening disadvantage is that sometimes it will cause antibody dependent enhancement effect so that the virus infection is aggravated, which is a serious adverse reaction that will lead to the failure of vaccine development.

Recombinant protein vaccine, also known as genetically engineered recombinant subunit vaccine. It produces S protein, which is the most likely antigen of the novel coronavirus, through genetic engineering, and injects it into the human body to stimulate the production of antibodies. Instead of producing a complete virus, many of the key components of the novel coronavirus are produced separately and handed over to the body's immune system. China has mastered the technology of large-scale production of high quality and high purity vaccine protein, which is a technical route that can produce vaccines on a large scale and quickly. It is safe, efficient and scalable. There are successful precedents for this route, and the more successful genetically engineered subunit vaccine is the hepatitis B surface antigen vaccine. It has good safety, and the product composition is clear, but the ability to stimulate Immune T-cell response is weak and needs to be accompanied by adjuvants.

Adenovirus vector vaccine uses harmless modified adenovirus as a carrier, which is loaded with the S protein gene of the novel coronavirus to make adenovirus vector vaccine and stimulate the human body to produce antibodies. This is a relatively mature vaccine technology route. The advantages of the adenovirus vector vaccine are safety, high efficiency and fewer adverse reactions. This vaccine has a successful precedent: Previously, the "recombinant Ebola virus disease vaccine" jointly developed by Academician Chen Wei's team and Tianjin Kangxinuo Biotechnology Co., Ltd. also used adenovirus as a carrier. However, there may be antibodies in the human body that neutralize the adenovirus vector, which may attack the vector and reduce the effectiveness of the vaccine. In other words, the safety of the vaccine is high, but the effectiveness may be insufficient.

Messenger RNA (mRNA) vaccines and DNA vaccines are genes encoding S protein, mRNA or DNA directly injected into the human body, using human cells to synthesize S protein in the human body, and stimulate the body to produce antibodies. The development does not require the synthesis of proteins or viruses, the process is simple, and the safety is relatively high. Nucleic acid vaccine is a new vaccine research and development technology that is being actively explored all over the world [3].

In this paper, recombinant protein vaccines and inhalable vaccines will be used as typical examples to give a specific description.

3.1. Recombinant protein vaccine

3.1.1. Process principle of recombinant protein vaccine

The basic technological principle of recombinant protein vaccine is to identify the specific protein of the pathogen with immunogenicity, integrate the pathogen-specific protein gene into the appropriate

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expression system (such as yeast, Escherichia coli and other microorganisms) through genetic engineering methods, express the pathogen-specific protein through mass culture in vitro, and then purify it to prepare the vaccine. That is, by preparing pathogen-specific proteins in vitro, the human body is stimulated to produce antibodies.

3.1.2. Recombinant protein vaccine for SARS-CoV

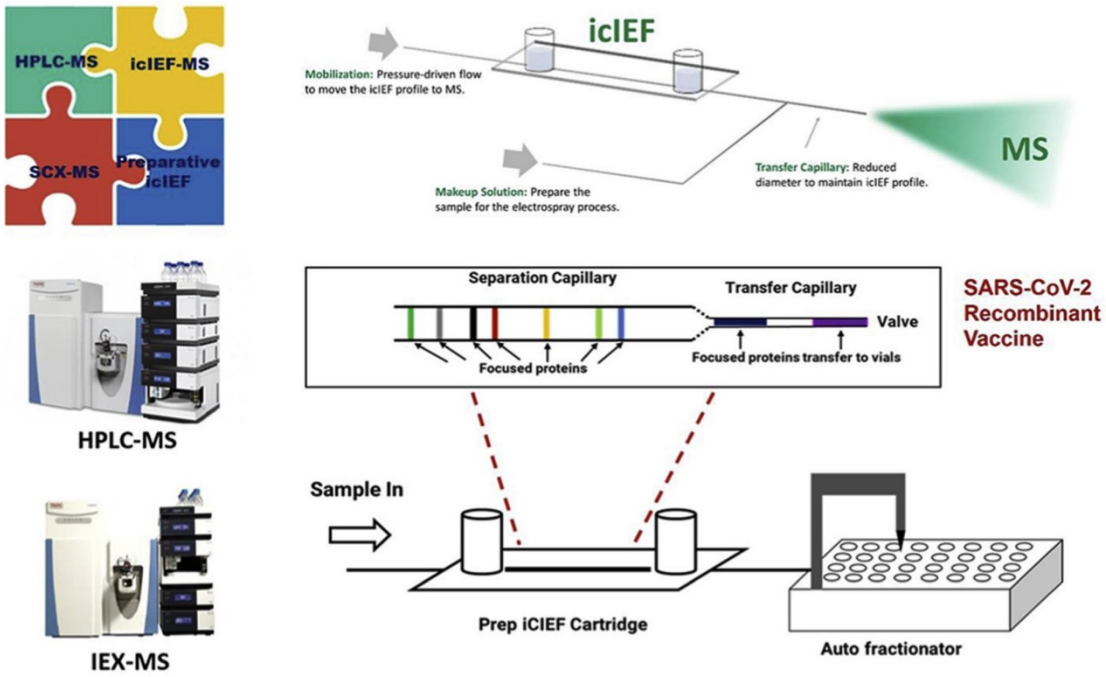

Figure 2. Part of the vaccine production process[4]

Figure 2 demonstrates how this vaccine is made. The S and N proteins of SARS-CoV are often used to prepare recombinant protein vaccines. It was found that the recombinant S protein vaccine induced a higher titer of neutralizing antibodies than the live attenuated SARSCoV vaccine, the poxvirus vector vaccine, and the DNA vaccine expressing the S protein. In addition, the N protein vaccine induced a high level of T and B cell immune response in mice, but there is a lack of vaccine effectiveness data under natural infection. The analysis of the neutralizing epitope of S protein and the selection of the best epitope of the virus is an important step in the development of a protein vaccine.

The S protein of SARS-CoV can be divided into two proteins: S1 at the n-terminal and S2 at the C-terminal. Among them, the S1 protein forms the spherical structure of the S protein and participates in the binding and adsorption of the virus and the target cell receptor ACE2. The S2 protein contains a fusion peptide and two 7-valent obtrin repeats, which are responsible for fusion between the virus and the target cell membrane. Both S1 and S2 proteins can induce the production of protective antibodies [5].

3.2. Aerosol inhalation vaccine

3.2.1. Pinciple of Aerosol inhalation vaccine

The principle of inhalation vaccine is to atomize the vaccine into tiny particles through the atomizer, and complete the vaccination through oral inhalation, without needling, to reduce the fear and concern of the vaccinated people. When inhaling, a special atomizing drug delivery device is used to atomize the vaccine into the atomizing cup. Each dose of the atomizing cup given to the seed recipient is 0.1ml. The seed recipient first takes a deep breath, holds the nozzle of the atomizing cup, and slowly inhales deeply

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until there is no fog in the cup, holding the breath for at least 5 seconds. If coughing or exhaling occurs in the process of inhalation or suffocation, it is considered that the vaccination has failed, and it is necessary to re-administer the inhalation vaccination, and only one repeat is allowed. Compared to the intramuscular version, the "inhalation" version only changes the route of administration, the formulation is the same, and the dose required to complete the vaccination is only 20% of the intramuscular version.

3.2.2. Pros and cons

Because of its physical form of vaccination, vaccination rates may be increased, and only one vaccination is needed to show its convenience. There are already some types of inhaled vaccines that can be made into freeze-dried powder situations, which greatly reduces the cost and difficulty of transportation, unlike ordinary vaccines that need cold chain transportation. In the case of the new coronavirus vaccine, the vaccine developed by Academician Chen Wei can theoretically be made into freeze-dried powder.

Because the novel coronavirus will invade the respiratory tract, the designer will first immunize the respiratory tract, so that when the virus attacks, it can be detected at the first time and make a rapid response to clear the infection. Local Immunoglobulin A (IgA) plays an important role in the antibodies induced by inhaled vaccines. Basically, antibodies induced by intramuscular vaccines are immunoglobulin G (IgG), which can circulate in most areas of the body and play a neutralizing role when encountering viruses. However, the novel coronavirus starts from the respiratory tract and comes into contact with mucosal tissues first. Mucosal tissue generally relies on IgA to protect itself, and unlike IgG, which travels throughout the body, IgA remains in mucosal tissue in a relatively small area. Thus, inhaled vaccines induce the production of many IgA, which reside in mucosal tissue and provide the most timely protection.

On the other hand, local immunity also includes cellular immunity, and the use of inhaled vaccines can also induce mucosal local formation of some resident immune cells, such as resident Central Memory T cells (Trm). These cells only stay in a small area to play a role, will not actively travel to other organs, and are only responsible for the part of their own residence to play a defense role, which is different from the body circulation and is beneficial to local key defense. When a virus invades and an emergency occurs, the wandering immune cells are far less responsive and protective than the resident cells.

Because it uses an adenovirus vector vaccine, it induces a higher level of T-cell immune response because antibodies are mostly neutralizing and are effective at clearing away the free virus. But cells that have been infected by the virus still need T cells to clear them. The ability of intramuscular inactivated vaccine to induce cellular immune response is relatively weak. The advantage of a vaccine using an adenovirus vector is that it has a step infection process, which will better activate CD8+T cells [6].

It should be noted that some inhaled vaccines are not recommended for the elderly at present, because they are related to the different immune microenvironment of the elderly lung. In some respiratory infections, the elderly lung will form more Trm. However, these TRMS do not play a positive role but can cause pathological damage to the lungs. Inhaled vaccines also have the ability to induce Trm formation, so in order to avoid the side effects of vaccination and induce an inappropriate immune response, it is not recommended for the elderly.

And there are some concerns after the public experience because the adenovirus vector is also a viral component, that will induce the body to produce an immune response. If the carrier used in this vaccination is also used by other vaccines in the future, and the human body is already immune to this carrier, the vaccine will be eliminated as soon as it comes in, and it will not be able to play a role, resulting in the failure of this carrier

4. Conclusion

This paper discusses the invasion mechanism of the novel coronavirus and the research analysis of its vaccines. Among them, the recombinant protein vaccine combines the mainstream biotechnology favored by the academic community, while the inhalable vaccine is a convenient and effective

innovation in the external form. All of them clearly reflect the dedication and innovative spirit of our medical workers. In the face of the increasing number of diseases, the majority of researchers and even all sectors of society need to work harder. There are many other vaccine situations that are not covered in this article and that still need to be improved. Future research can also focus on the targeted development of vaccines for different age groups or specific pathologies. Only in this way can we reach all levels of the population to meet the needs of more people and promote efficient portable vaccine prevention and control. There is also the possibility of focusing vaccine research on conditions with high mortality rates, such as cancer, which also has the opportunity to achieve major medical breakthroughs.

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