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Evaluating the possibility of applying to COVID-19 based on peptide vaccine mechanism

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Abstract. At the end of 2019, a coronavirus outbreak affecting specific types of pneumonia broke out in Wuhan, China. COVID-19 was initially a rapid infectious disease caused by SARS CoV-2 virus. The main transmission route of COVID-19 is large droplet transmission. When it infects a person, can cause pulmonary fibrosis, and the main symptoms of patients include coughing and respiratory discomfort. This virus causes multiple infections and deaths in a short period of time and rapidly expands globally. Therefore, vaccination is crucial as the most cost-effective method for preventing and controlling the spread of COVID-19. In this context, peptide vaccines have been discovered and continue to receive attention as a new type of vaccine. This article introduces the advantages and drawbacks of peptide vaccine in detail from the source and mechanism of peptide vaccine, subdivides its different mechanisms of action, and further explores how peptide vaccine induces Th1 cell response, germinal center response and humoral immune regulation induced by peptide vaccine, and moral memory cell response in COVID-19. Taking COVID-19 as the background and starting from the existing research, explore the existing problems of existing peptide vaccines and their future development in detail.

Keywords: COVID-19, Peptide Vaccine, Immune Response.

1. Introduction

COVID-19 is a disease caused by SARS-CoV-2, which is highly contagious can be transmitted in various ways. The main transmission route of COVID-19 is through large droplets. The pathogen of COVID-19 does not exist independently but is wrapped in exhaled droplets with different particle sizes [1]. The spread of these droplets has characteristics such as larger droplet size, greater inertia, and less influence by airflow, making the virus highly infectious and capable of infecting a large number of people [2]. According to a statement issued by the World Health Organization on May 5, 2023, since the start of the COVID-19 pandemic, almost 300 million people globally have been infected, with around 20 million people have died as a result. The worldwide mortality rate is approximately 0.7% to 5.8%, while the average mortality rate in Mainland China is about 0.66% [3]. Although its mortality rate is not high, due to its easy and rapid spread, many people become ill, resulting in a large number of deaths. Therefore, the development of a COVID-19 vaccine, as a crucial and cost-effective method for preventing and controlling the spread of viral diseases, is particularly important.

There are two traditional vaccination methods available. One is inactivated vaccines, which artificially cultivate standard strains of pathogenic microorganisms. It is made by killing it after

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reproducing to a certain amount without damaging its antigenicity and preserving it in a suitable adjuvant. For example hepatitis B vaccine, influenza vaccine, rabies virus and pertussis vaccine. The advantage of using inactivated vaccines is that they have low toxicity and do not pose safety issues such as human infection and spread. However, its drawbacks are also very obvious. The immune effect of inactivated vaccines is poor, and it takes about 2-3 weeks to develop immunity after injection. In addition, its immune validity period is short, usually only between four to six months. The other vaccine is the mRNA vaccine, mRNA vaccine is a technology that transports mRNA into the body by selecting a suitable delivery system after in vitro transcription synthesis. Then, relying on the cell's own translation system, mRNA is translated into target proteins to achieve clinical therapeutic purposes. There are several advantages of mRNA vaccine. As mRNA is noninfectious and non-integrated, there is no potential risk of infection or insertion mutations. Besides, due to its high in vitro transcription reaction yield, mRNA vaccines have the potential for rapid large-scale production. However, because of the strong antigen response triggered by meRNA vaccines, it is highly likely to lead to a severe immune system response, resulting in side effects such as inflammation and allergies [4].

As a new type of vaccine under development, peptide vaccines have some benefits compared to existing vaccines. They were first suggested by Lerner in the early 1980s. To make these vaccines, scientists find out the building blocks of natural antigens and locate specific pieces that trigger our immune system. Then, they create these pieces, test if they can make our body produce protective substances, and choose the best ones to create the vaccine [5]. The good thing about peptide vaccines is that they focus on reducing or avoiding allergic reactions caused by vaccination by inducing highly targeted immune responses using short peptide antigen fragments. The fragments they used are pure and effective. So that it can be made in large amounts at a lower cost and can be kept cold. Also, since they are just parts of a virus, they don't cause infections. Lastly, peptide vaccine due to its entire synthesis, there is no risk of incomplete inactivation or a return of toxicity [6, 7].

The existing clinical research results show that the polypeptide vaccine has a good application prospect in the immunotherapy against COVID-19. At present, peptide vaccines are still in the clinical research stage, and there is still a certain distance from their true clinical application. Further exploration is needed for the selection of treatment targets, evaluation of efficacy, and the value of combination therapy. This assay analyzes the production principle, synthesis method and mechanism of peptide vaccine, introduces its research and development background, development goals, future development and market needs in the field of COVID-19 vaccine, and provides relevant research reports and data. At the same time, it aims to provide feasibility opinions and feasibility assessments for the development and future application of COVID19 peptide vaccines.

2. Mechanism of action of COVID-19 vaccine

2.1. Brief classification of COVID-19 vaccine

In exploring the mechanism of polypeptide vaccine, first of all, simply analogy all types of COVID-19 vaccines, and distinguish them from the perspective of mechanism. Up to now, COVID-19 vaccines, which have been delightfully and fruitfully developed and applied in different scopes and degrees, can be divided into three categories according to different types of antigens in vaccines. Moreover, due to the fundamental differences in antigen types, the immune response mechanism of the organism's immune system to vaccine injection is also completely different.

The first model, vaccine development, is bottom on proteins produced extracorporal. Inactivated vaccine (inactivated type 2 COVID-19), VLP vaccine (virus particles without nucleic acid or nucleic acid) and subunit vaccine (S protein expressed in vitro or binding domain of COVID-19 receptor (RBD)) all belong to the first model vaccine, and the polypeptide vaccine this paper will analyze also belongs to this type of vaccine.

The second model of vaccine development stems from the antigen genes expressed in the body. The immune response of viral vector vaccines (engineering viruses made by replicating and controlling

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defects in replication using mRNA carrying S protein or RBD), DNA vaccines (DNA sequences of S protein or RBD), and mRNA vaccines (RNA sequences of S protein or RBD) belong to the same model.

The third mode is the mode of action of attenuated live vaccines. This vaccine mainly acts on inducing antibodies to protect the receptor, which is to protect the body injected with the vaccine from virus invasion.

Next, this paper will elaborate on the first mode, which is the most noteworthy peptide vaccine that utilizes the body's immune response mechanism.

2.2. The mechanism of action of peptide vaccines

This type of vaccine, also known as acquired immunity, is an active immune response that can be triggered by peptide vaccines after being administered to the body. In the process of active immunity in the body, the immune system senses peptides and is activated, leading to a series of immune responses. This physiological change is briefly summarized as the following four significant changes:

Firstly, CD4+T cells, which are dependent on antigenic peptide (AP) - MHC (major histocompatibility complex) class II molecular complexes, divergence into helper T cells (Th cells).

Secondly, CD8+T cells, dependent on AP-MHC class I molecular complexes and divergence into cytotoxic T lymphocytes (CTLs).

Thirdly, B cells, which respond to the differentiation of CD4+T cells in the first change, are awakened to draw support from the Th cells they form and thus produce antibodies.

Fourth, after the antigen fully stimulates the whole immune system of the body, the B cells and T cells differentiated from the first three changes not only respond immediately and act on the antigen but also form corresponding memory cells, which respond faster and better in the subsequent antigen stimulation (i.e. repeated vaccination or COVID-19 infection), so as to secure the organism from the invasion of the same pathogen, This immune effect usually lasts for several years. That is to say, as of the fourth change, the body has really gained immunity to COVID-19 under the effect of the vaccine, which is the significance of the vaccine to the virus-infected body.

2.3. The Three Steps of the Body's Response to Peptide Vaccines

Based on this initial impression and general framework, the mechanism of action of peptide vaccines is further explored, and attempts are made to analyze the advantages, potential hazards, and avoidable problems of peptide vaccines from each small change. It is divided into three aspects.

The first aspect is vaccine-induced Th1 cell response. After the body recognizes the AP-MHC II sophisticated and T cell receptor (TCR), CD4+T cells are scattered fringe lymphatic organs are activated and differentiate into Th1 cells dependent on the AP-MHC II complex. Th1 cells will secrete various cytokines that directly play a role in subsequent responses, the case in point is interleukin-2 (IL-2), and concurrently upregulate the expression level of related receptors (IL-2R).

Afterward, the interaction between IL-2 and IL-2R, promotes the proliferation of T cells and the activation of CD8+T cells. In previous studies, clear CD4+ and CD8+T cell responses were surveyed in the Ad26 COV-2-S receptor, indicating that at least a small portion of this immune response has been confirmed. Furthermore, activated CD8+T cells differentiate into CTL for further cellular immune induction.

added to that, Th1 cells is capable of also secreting interferon γ (IFN- γ) And tumor necrosis factor α (TNF- α) interferon γ This paper will continue to induce the differentiation of CD4+T cells and enhance the overall magnitude of the immune response.

In the later stage of the immune response process, when the effector cells (i.e. Th cells and CTL) truly eliminate the antigen, the existing signals that maintain T cell survival and continue to proliferate disappear and are no longer produced, resulting in a decrease in cellular response and the immune system returning to a stable state. Nevertheless, the antigen-specific memory T cells mentioned above will not be excessively affected by this signal change will remain in the body for a long time, and will continue to play a role in the future body self-protection. Antigen-specific memory T cells for COVID-19 usually

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form for the first time in the T cell-mediated immune process, and will still make corresponding immune responses in this type of immune process.

Second aspect: Vaccine-induced germinal center response and humoral immune regulation

Besides the T cell reaction focused on in the first aspect, the vaccine based on the first mode will also induce the formation of follicle helper T cells (Tfh cells), which will trigger the response against the antigen-specific germinal center B cells (GC B cells) of COVID-19, and this type of response is extremely effective.

After triggering the interaction between T cells and B cells, a number of activated Th cells will specifically transfer to lymphatic follicles and continue to differentiate into Tfh cells within the follicles. Other activated B cells also proliferate and are divided by lymphatic follicles, forming germinal centers.

With the assistance of Tfh cells, the mutable region of the antibody gene in GC B cells undergoes high-frequency point mutations, as well as antibody class transitions. Based on this, memory B cells and plasma cells are ultimately formed, making it possible to produce high-affinity antibodies.

In addition, strong severe acute respiratory syndrome coronavirus type 2 S protein binding GC B cell response was detected in lymph node fine needle aspirates of BNT162b2 (based on full-length S protein) vaccine recipients [8]. This reaction can be found after the first vaccine injection, and even significantly upgraded after the second vaccine injection.

The core significance of GC B cells and GC B cell responses lies in the fact that the sustained existence of these cells is an important prerequisite for guiding long-lived plasma cells. However, GC B cells that have not been altered into plasma cells will not be inactivated but will form memory B cells. When running up against the same antigen (that is, when the body is really threatened by COVID-19), the differentiated memory B cells will be activated at an extremely fast speed with the help of memory Th cells, thus producing more antigen-specific antibodies than the initial immunization brought by the vaccine.

In summary, it can be concluded that the possibility of vaccine-induced immunity has been established. This possibility is based on the sustained response of GC B cells induced by vaccines and depends on the ability of these cells to secrete highly effective and long-lasting neutralizing antibodies, thereby triggering strong humoral immunity.

Next, this paper will explore the triggered immune components of the body. this study has learned that the memory cell response induced by the COVID-19 vaccine can guide Th1 and unrelenting germinal centers to react, cranking up strong cellular and humoral immunity. During this period, antigen-specific memory T cells and B cells, which have the most significant potential for long-term protection, will generally form.

This long-term protective ability differs significantly from the initial activation of T cells. The activation of memory T cells nevermores growths on antigen-presenting cells (which determines the speed of immune response), and can also induce stronger immune responses (which determines the effectiveness of immune response).

The majority of memory B cells, on the other hand, enter the bloodstream and continue to participate in circulation. When encountering the same antigen, they can also be quickly activated to produce potent antibodies. Moreover, due to its circularity, the scope of this immune effect will be even wider.

It has been confirmed that mRNA-1273 and BNT162b2 have the ability to induce higher levels of antibody production and memory B cell responses. Moreover, memory B cells have also been successfully found in COVID-19 rehabilitation patients. A single dose of vaccine has been able to guide the memory B cell response of these patients to reach its peak, which proves that previous infection and vaccination have the ability to induce memory cell response.

3. The characteristics and future development direction of peptide vaccines

After understanding its mechanism of action, a macroscopic impression has been formed. Up to now, the inactivated vaccine is still the most widely used type of COVID-19 vaccine in the world and has achieved good results in both the effect and adverse reactions after the vaccine injection. In theory, the peptide vaccine and inactivated vaccine that this article focuses on have the same mechanism of action,

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which means that the core efficacy and safety of peptide vaccines can be inferred. In addition to the more optimistic aspects, in actual production and application, Currently, approved replication-compliant and inactivated vaccines are limited by exceptional reactivity and poor safety profiles [9]. The characteristics of peptide vaccines fundamentally determine that they will not be limited by these two drawbacks. Compared to any other type of antigen, the benefits of peptides are reflected in many aspects, such as their good stability and the absence of materials that may cause damage. The complexity of the antigen itself is low, and the cost is low, making it more convenient for large-scale production [10]. Peptide vaccines also have clear characteristics, which are manifested in two aspects:

Firstly, the cellular expression system systematically expresses viral proteins or peptides.

Secondly, peptide vaccines can induce Th1 cell responses that are difficult to induce by other types of vaccines.

Next, this paper will explore in detail the subdivision and mechanism of peptide vaccines. Peptide vaccines are peptides that are systematically expressed using various cell expression systems and can be used in a wide range of cell types, the case in point is bacteria, yeast, insects, and mammalian cells (such as the currently effective and widely used human embryonic kidney cells). This also lays the foundation for the production of peptide vaccines.

The main problem with peptide vaccines is that their antigens may undergo denaturation and their immunogenicity may not be strong. The solutions that have been explored include the formation of dimer form stable conformation (similar to the dimer of RBD of S protein of type 2 COVID-19 of ZF2001 vaccine) and site mutation (similar to the full-length S protein adopted by NVX-CoV2373, the conformation before fusion contains Flynn site mutation and this modified S protein is generated by Sf9 insect cell expression system). Moreover, due to the unstable variability of the conformation before fusion or modification, which is the opposite of its metastability that can be utilized in vaccine development, the desired transformation can be achieved and facilitated.

Finally, this paper briefly reviewed the advantages and disadvantages of peptide vaccine against COVID-19 in research and practical application due to its own characteristics:

The advantages of peptide vaccines include many aspects. Firstly, it can induce Th1 cell responses that are difficult for other types of vaccines to induce. Moreover, it can also induce neutralizing antibodies, and its titer is even higher than that of inactivated vaccines and Ad5 virus vector vaccines. Finally, peptide vaccines have gained some successful experience in the past, which can basically ensure their effectiveness and safety; Peptide vaccine can not only be applied to COVID-19 and other influenza but also has been proven to be more widely applicable and has achieved good results. In the future, peptide-based vaccines are expected to successfully induce anti-tumor immune responses in patients with malignant glioma, generate clinical responses, and prolong survival without significant side effects [11]. It can be said that the research and development strategy and future development direction of peptide vaccines are already quite clear.

But no vaccine is perfect, and peptide vaccines also have their drawbacks. Firstly, the molecular weight of the underlying S protein is comparatively large. In relation to RBD, the expression efficiency of S protein is comparatively low, which may lead to more cumbersome preliminary work in vaccine development and a decrease in success rate. Try to avoid this problem and choose other peptide proteins with smaller molecular weights to replace S proteins. These proteins are more likely to be expressed, but they may not have clear, efficient, and abundant immune epitopes on S proteins, which makes them prone to antigen drift. The vaccine research community and even the entire immune academic community have not given up on the possibility of solving this problem, because peptide antigens themselves do not have the ability to induce substantive immune responses, but adjuvants can be integrated into this vaccine through an efficient delivery system, which is also a new field of development for peptide vaccines. However, adjuvants themselves have various limitations, and unfortunately, many adjuvants still have issues such as being too weak, toxic, or unable to bind to peptide antigens in practical applications [12]. In summary, we can clearly perceive that in the future, we must still adhere to the design of clinically effective peptide vaccines by addressing and optimizing various

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issues, including but not limited to the selection of antigen targets, as well as the attempt and selection of optimal adjuvants and the coordination of vaccine delivery arrangements [13].

4. Conclusion

With the continuous deepening of research, peptide vaccine technology has become increasingly mature. In this article, from the sources and mechanisms of peptides themselves, models and patterns, three induced changes, and the immune response caused by their advantages, peptide vaccines are superior to subunit vaccines, inactivated vaccines, etc. However, peptide vaccines are still in the second phase of clinical trials, and the time for large-scale simulation experiments is still short. Long-term adverse reaction monitoring is needed to verify their safety and effectiveness. So far, there are still bottlenecks in the investment of peptide vaccines in immunotherapy, which limits their application in treatment. The effectiveness and treatment methods of peptide vaccines in the treatment of various diseases still need to be further expanded. In summary, the research on peptide vaccines is of great significance in disease prevention, treatment, and other aspects.

Authors Contribution

All the authors contributed equally and their names were listed in alphabetical order.

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