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Comparative Insights on Traditional and Genetic Vaccines: Past Progress and Future Outlook

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Abstract: This review explores the evolution, mechanisms, and future potential of vaccines, with a comparative focus on traditional vaccines and emerging genetic vaccines. Traditional vaccines—such as inactivated, attenuated, and subunit types—have played a pivotal role in public health but face limitations in production complexity, efficacy, and storage. In contrast, genetic vaccines, particularly mRNA-based, offer higher efficiency, rapid development, and customizable antigen targeting enabled by gene-editing technologies like PCR and CRISPR. Despite challenges such as stability, delivery systems, and short-lived immunity in certain cases, genetic vaccines show promising adaptability in combating viral mutations and may redefine therapeutic strategies. The paper argues that with ongoing advances in biotechnology, genetic vaccines could gradually replace conventional types, shaping a new era in preventive medicine and global immunization.

Keywords: mRNA vaccines, genetic vaccines, traditional vaccines, immunization technology, public health

1. Introduction

Vaccines, as one of the most widely used and efficient strategies of epidemic prevention, have saved countless lives from illnesses. According to Our World in Data and the World Health Organization's record, almost every country's hospital around the world provides vaccination treatment. Take the COVID-19 vaccination as an example; most nations can obtain a coverage rate of greater than 40%. So far, countless people have been vaccinated, and approximately 150 million children have survived the disease due to the vaccine. Vaccines' unique principles explain why they have played such an important part in the history of human disease resistance [1]. The mechanism of vaccines is based on the adaptive immunity of humans, which is developed by postnatal learning [1-2]. The human immune system needs to capture and recognize pathogens at least once to form long-term immunological memory. Vaccines utilize this bio-mechanism, doctors inject processed antigens into the organism to form immunity [3-4].

Vaccines have a far-reach effect on social security and health [5]. After vaccination, healthy individuals can create a prevention circle that stops infectious diseases from spreading in unvaccinated populations, this concept is known as herd immunity [6]. Many newborns could prevent some infections through herd immunity due to the high vaccination rate in modern society [5-6]. However, the prevalence rate of some illnesses also rises in adults, such as chickenpox. The incidence rate of varicella among adults in China has grown recently, except for the decreased immunity, which may be attributed to the herd immunity protection in early childhood [7].

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The primary challenge of vaccines is maintaining proper storage conditions and handling patients effectively. Considering the effect of the rabies vaccine and the preliminary results achieved by the HIV vaccine, therapeutic vaccines may be able to rescue potential carriers [8-9]. For some intractable diseases that are difficult to treat with drugs, vaccine prevention may offer better protection, such as the HPV vaccine [10]. If the phage therapy concept proposed in the last century can be used as the core principle to develop vaccines, it may be possible to treat patients who are already ill [11-13]. This is the unique potential of vaccines. This review aims to provide a comparative analysis of traditional and genetic vaccines, outlining their mechanisms, advantages, limitations, and potential for future innovation. By evaluating these technological pathways, we seek to highlight the shifting landscape of vaccine development and the growing role of genetic approaches in shaping the next generation of global immunization strategies [14-16].

2. Traditional vaccines

Since this article focuses on different types of vaccines, the following discussion will classify them as traditional and genetic (new type) vaccines. Also, genetic vaccines will be discussed and compared based on the pathogens' families due to the specificity between bacteria and bacteriophages.

2.1. Mechanism

Depending on the cultivation and treatment of native pathogens, traditional vaccines can be categorized into attenuated, inactivated, and toxoid vaccines. They rely on naturally existing or media-cultivated strains and variants, such as smallpox and cowpox, IPV, and OPV (polio) [1].Attenuated and inactivated vaccines are the earliest types of vaccines. To create vaccines, they mainly farm and harvest pathogens and then use chemicals, temperature control, exposure to sunlight, and other methods to reduce or inactivate them to produce vaccines [17-18]. The entire procedure is not based on genetic technology.

Toxoid vaccines are vaccines specifically designed for bacteria. Certain bacteria can produce toxins that trigger immunological reactions and cause disease. Thus, toxins can be extracted and used as vaccines for these bacteria [1]. This type of vaccine does not require gene editing; also, it cannot prevent viral diseases.

Subunit vaccines are unusual, as they include some genetic technology with standard immunizations. These vaccinations are produced by tearing apart the pathogen and extracting the antigen portions that can stimulate the immune system individually. Some subunit vaccines, such as recombinant and conjugate vaccines, require gene editing techniques to create [19]. The modified DNA must be introduced into bacterial/animal cells to create polypeptides/glycoproteins [19-20]. Plasmid trimming can also be utilized to combine weak and strong antigens to improve immune responses [19-20].

2.2. DNA vaccines

In general cases like smallpox and chickenpox, whether vaccinated or recovering from illness, patients rarely experience a second onset in their lifetime [21-22]. The eradicated diseases indirectly demonstrate the effectiveness of herd immunity and the benefits of vaccination [6]. As a result, relatively few types of DNA virus vaccines are available now, and this number may continue to decrease over time. The substantial research costs involved in developing DNA-based genetic vaccines have led to a limited number of studies. Another point is that DNA cannot be translated directly; mRNA is still required to produce proteins. Thus, some studies may be substituted by RNA-related research.

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However, this does not mean that research on nucleic acid vaccines would not affect the prevention of DNA viruses. In fact, gene-edited vaccines, especially mRNA vaccines, can combine the benefits of both attenuated and inactivated vaccines, obtaining a strong immune response while minimizing infection risks [23]. Comparable DNA vaccines may also provide similar advantages. Considering the current maturity of CRISPR technology, editing DNA is easier than before [16].

2.3. Advantages and limitations of traditional vaccines

Traditional immunizations have various advantages and disadvantages. For example, all the vaccines listed above require a live cell culture medium. Inactivated and subunit vaccinations offer the lowest risk, the fewest side effects, and no need for restricted storage conditions.

However, being a "dead" vaccine, the efficacy is often lower than that of a "live" vaccination. For instance, HPV and hepatitis B both belong to subunit vaccines. antibody levels generated after a single dose are often not as high as those achieved with multiple doses. Long-term data from numerous HPV vaccination users show that, even after 7 months, HPV antibodies progressively diminish, and antibody levels created after a single treatment are frequently lower than those obtained with multiple doses [24]. Hepatitis B vaccine has a similar situation [25]. Therefore, hospitals typically recommend receiving 2-3 doses within the same year to ensure better defense effectiveness. If gene-editing technology could apply to these vaccines, it may reduce the frequency of vaccination.

Attenuated vaccinations, on the other hand, are effective but invariably carry the danger of infection. For example, the most widely used polio vaccine, "sugar sphere," has prevented the deaths of innumerable children. However, there are risks associated with vaccination, with an infection rate ranging approximately from 1/2.5 to 1/5 million [26].

3. mRNA Vaccines

It's important to recognize viruses' small size and high mutation rate when discussing them. Unlike antibiotics, relatively few antiviral drugs are available [27], making vaccines essential for preventing viral diseases.

3.1. Mechanism of RNA vaccines

Before the COVID-19 pandemic, the mRNA vaccine was relatively unknown to the public. The global response to the outbreak brought this technology to widespread attention [28]. Due to the advancements of mRNA vaccines compared to traditional vaccines, nucleoside base modification researchers were awarded the Nobel Prize in Physiology or Medicine in 2023 [29].

RNA is also the basic biological genetic material but lacks the stability of DNA. RNA has distinct functions and configurations which allow it to perform tasks that DNA cannot. For instance, messenger RNA (mRNA) is a crucial information carrier that mainly dictates how proteins synthesize [3]. Different methods of trimming pre-mRNA can result in the production of entirely different proteins. Due to its rapid metabolic cycle and easy processing and transcription, mRNA becomes the primary basis for genetic vaccines [28]. Native mRNA and the mRNA vaccination work on the same concept [1-2]. Once within the cell, the modified mRNA will translate straight into antigens. This characteristic makes mRNA vaccines have different advantages and disadvantages compared to traditional vaccines.

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3.2. Limitations and advantages of RNA vaccines

Due to mRNA's inherent instability, lipid nanoparticles (LNPs) are typically used as carriers to protect the molecule and facilitate its delivery into cells [30]. Base modification addresses the issue of naked mRNA being eliminated by inflammatory reactions, leading to increased protein production [29]. However, existing mRNA vaccines and therapy still require lipid transport systems. Secondly, some diseases face challenges with vaccine protection duration due to the high mutation rate of the virus. For instance, the COVID-19 virus evolves rapidly, while the influenza vaccine is updated annually [31-32]. However, vaccinations for DNA viruses may only require 1-3 doses in a lifetime. Therefore, extending the usage time of such vaccinations requires long-term research.

Despite these challenges, the benefits of mRNA vaccines outweigh their drawbacks. The most significant advantage is the editability of mRNA: current gene editing techniques allow researchers to add or remove regions from gene segments to translate or modify specific proteins [21]. Gene editing tools allow researchers to design mRNA sequences that express precise antigen targets, making them ideal for personalized immunization strategies. According to the principle of subunit vaccines mentioned previously, some gene-editing subunit vaccines may be replaced by mRNA vaccines, especially when antigens are proteins [19]. Accurately eliciting specific immune responses may allow the immune system to discover pathogens that were previously able to avoid immune system detection. The present research concept for therapeutic vaccines may have developed from this, and the current rabies vaccine has demonstrated the effectiveness of this strategy. [33] Vaccines are therefore at least certain to help possible carriers. The advancement of HIV vaccines in recent years has been fueled by the discovery of gene editing technologies and clinical evidence on therapeutic vaccinations [34]. These innovations suggest a future in which vaccines protect not only potential carriers but also treat infected individuals.

Another advantage is cytoplasmic translation: mRNA remains in the cytoplasm and does not enter the nucleus, eliminating the risk of genome integration and reducing vaccination-related infections [28]. Compared to traditional vaccines, mRNA vaccines are equivalent to holding the high efficiency of attenuated vaccines while having the same low infection risk as subunit and inactivated vaccines.

Second, cell matrices are required to cultivate the virus for later processing because RNA can be transcribed and amplified in vitro [15], which can save steps and increase production [28-29]. This can speed up the study of vaccines, such as the high iteration of the COVID-19 vaccine. Otherwise, gene editing makes vaccines more likely to defend multiple variants/viruses through one dose, if enough diverse antigen codons can be modified on one mRNA strand.

4. Bacteria vaccines and phage therapy

Bacterial vaccines appeared quite early; people concentrated on researching them during the 19th and early 20th centuries [35] However, not all vaccines work effectively, and the development of antibiotics has had a huge impact to corresponding research. Furthermore, a lot of bacterially caused epidemics are caused by environmental hygiene risks or compromised immunity. Making bacteria vaccines hardly reduces certain infectivity. Examples include cholera, typhoid fever, glandular pestis, and so on. Although these pathogens have vaccines, their carriers live far beyond human society, which makes it hard to prevent infection. Maintaining a clean environment and offering antibiotics in this situation is far more effective than vaccines.

The concept that bacteriophages kill bacteria is analogous to how viruses infect cells, and bacteriophages are highly targeted. Generally, one type of bacteriophage only infects a specific type of bacteria [35-36]. This trait prevents phage therapy from producing many side effects like antibiotics. However, the corresponding issues include the lack of broad-spectrum effects, the

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lysogenic phenomenon, the requirement for a specific culture for every therapy, and the possibility of being eliminated by immune responses after entering the organisms [35-36].

Nowadays, the development of genetic vaccines and therapy has expanded people's perspectives. If native bacteriophages are insufficient to perform the therapeutic task, gene-edited bacteriophages or vaccines based on the bacteriophage principle might be feasible.

According to this theory, if bacteriophage attacks can be considered a unique type of targeting, it may be able to identify the ligand code that binds to bacteria receptors and conjugate it with known antigen codes to create a conjugate/mRNA vaccination. Thus, if this antigen could bind to bacteria, it may stimulate an individual's immune response and physically affect the behavior of drug-resistant bacteria for adjuvant therapy. This makes little impact for phage resistance and lysogenic phenomena. Furthermore, using empty phage protein shells as carriers for mRNA, altered genes, and even antibiotics might enable humanity to do more.

5. Conclusion

Unlike antibiotics, gene-edited vaccines' potential is far from being fully developed. Although there are side effects, it originally proved its effectiveness to individuals throughout the outbreak. Due to current technological limitations, the potential of such vaccines has not yet been fully demonstrated. If it is possible to ensure its stability while reducing costs, then with the passage of time and technological innovation, gene vaccines may gradually take over the vaccine market and replace traditional categories such as attenuated, inactivated, and conjugate vaccines. This type of vaccine may achieve multiple defenses with one dose, not containing multiple antigens in one dose, but using one antigen to defend against multiple diseases. This is difficult to achieve with drugs, but vaccines may not be impossible.

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