Research Progress of Ebola Live Vector Vaccine

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Abstract: Ebola virus is a highly lethal virus belonging to the Filoviridae family. The virus is mainly transmitted through the patient's body fluids and may cause Ebola hemorrhagic fever, with a mortality rate of up to 25% to 90%. The early manifestations of Ebola hemorrhagic fever commonly involve fever and muscle pain, followed by severe symptoms such as vomiting, diarrhea, internal and external bleeding, which may eventually lead to organ failure and death. Live vector vaccines created an innovative class of immunization. It employs attenuated viruses or bacteria as delivery vehicles. These carriers transport specific pathogen antigens into host cells, thereby stimulating the body's immune system to generate a protective response. With the advancement of genetic engineering, this vaccine has been widely used in the prevention and treatment of various diseases. Among them, the Ebola vaccine (Ervebo) has been widely used in many African countries. This article reviews the current status and progress of Ebola live vector vaccines by combing and analyzing relevant domestic and foreign literature. Focuses on the therapeutic mechanism of the Ebola vaccine and the drug production process. By comparing drugs currently on the market or in the clinical stage, this article found that there are some difficulties in the current Ebola vaccine research field, mainly in terms of vaccine specificity and storage technology. In the end, this paper comprehensively reviews the existing research, points out the shortcomings of current research, and predicts future development trends, aiming to provide a reference for researchers for further exploration in the field of Ebola live vector vaccines and provide some ideas and suggestions for subsequent research.

1 INTRODUCTION

The Ebola outbreak will bring about negative impacts such as restricted transportation, economic damage, collapse of the medical system, and social disorder in the epidemic area. These impacts will last for a long time. In the past few years, the Ebola outbreak caused serious economic damage to African countries such as Liberia, Sierra Leone, and Guinea.

The Ebola virus mainly invades the human body by infecting epithelial cells of the skin and mucous membranes. The virus enters the dendritic cells or macrophages by binding to receptors on the surface of host cells, damaging these immune cells and thus weakening the body's immune capacity. Once inside the host cell, the virus uses the host cell's mechanism to replicate itself and produce a large number of virus particles. These newly produced viruses will further spread to various parts of the body through blood circulation. Early symptoms include fever, fatigue, muscle pain and sore throat. As the virus attacks endothelial cells, ruptures the blood vessel walls, causing bleeding and edema in the body, severe patients may suffer from multiple organ failure and die. This virus was first discovered in Sudan and the Democratic Republic of the Congo in Central Africa in 1976. Since then, the virus has broken out several times in central and western Africa (Selvaraj et al.,2018), and in 2014 it caused the largest Ebola outbreak in history, resulted in more than 28,000 confirmed cases and 11,000 deaths (Malvy et al.,2019), triggering global panic. In response to the threat posed by the epidemic, scientists began to study the treatment and prevention of Ebola hemorrhagic fever. In 2015, the World Health Organization declared that the outbreak had been largely contained. Although breakthroughs have been made in the development of Ebola vaccines and prevention and control of the epidemic, the Ebola virus remains a major challenge facing the public health field because the vaccine is still not widely used in remote mountainous areas.

At present, with the accumulation of clinical experience, supportive treatment (such as fluid supplementation, electrolyte balance, complication

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management, etc.) has become the main treatment for Ebola virus through Fluid replacement by intravenous injection to maintain electrolyte balance, this method can significantly improve the survival rate of Ebola patients in high-incidence areas. In addition, monoclonal antibodies such as REGN-EB3 and mAb114 have shown significant effects in controlling viral replication and reducing mortality, becoming one of the most effective ways to treat Ebola (Mulangu et al.,2019). On the other hand, although vaccines are not a treatment method, they play a key role in disease prevention and control and minimize the risk of infection to individuals exposed to the strain in the early stages of an epidemic. For example, the approval and widespread use of the Ervebo vaccine marks an important progress in prevention and control work and enhances the ability of countries to respond to the epidemic. However, there are still challenges in treating Ebola: many areas with limited resources lack sufficient medical facilities and expert guidance, which is not conducive to early intervention of the epidemic. From the perspective of disease prevention, the lack of universality of vaccines against virus strains and storage issues in tropical regions are also difficult problems that need to be overcome.

This article will focus on the mechanism and production process of rVSV-ZEBOV Ebola vaccines and provide some feasible solutions to the difficulties encountered in the development of this field.

With the development of genetic engineering technology, live vector vaccines in various countries play an increasingly important role in disease prevention. However, there are still some technical problems in Ebola vaccine in terms of specific immunity and storage. To solve these problems, this article aims to explore and propose solutions through literature research to promote the sustainable development of live vector vaccine technology in the field of Ebola prevention and control.

2 EBOLA VACCINE

The Ebola virus is wrapped into an endosome, it enters the host cell by binding to a receptor which triggers endocytosis of the cell membrane: The surface glycoprotein of virus undergoes proteolytic processing in the endosome so that it is able to interact with the cellular receptor cholesterol transporter Niemann-Pick C1 (NPC1) protein in order to fuse with the endosomal membrane, and to release the ribonucleoprotein into the cytoplasm (Baseler et al., 2017). After the negative-strand RNA genome of the virus enters the cytoplasm, it uses the host cell's machinery for transcription and replication. The RNA polymerase on the viral RNA will replicate the viral RNA in the cell, generate a large amount of positive-strand RNA as a template to produce new negative-strand RNA. The proteins encoded by the viral genes (such as glycoproteins, nucleocapsid proteins, etc.) are synthesized on the ribosomes of the host cell and transported to the cell membrane or corresponding parts of the cell. The newly synthesized viral RNA and proteins are assembled into new virus particles in the cytoplasm of the host cell and released outside the host cell to further infect other cells. By this process, EBOV spreads from the infection site via monocytes to regional lymph nodes, and to liver and spleen via blood (Geisbert et al., 2003). When the virus spreads in the body, it attacks the host's endothelial cells, especially the vascular endothelial cells, causing damage to the blood vessel walls and increased vascular permeability. Blood components will leak into the tissues, causing massive bleeding. As the virus spreads, it will cause multiple organ failures, including the liver and heart.

There are many challenges in treating the Ebola virus, with the biggest one being the lack of specific drugs. Treatment mainly relies on symptomatic support such as fluid replacement, blood pressure maintenance and oxygen supply. Although some antiviral drugs are under development, there is still no completely effective treatment plan. At the same time, Ebola outbreaks mostly occur in resource-scarce areas in Africa. Incomplete medical conditions and citizens' lack of awareness of disease prevention due to lack of education have further accelerated the spread of the virus.

3 EXISTING TREATMENTS

There are currently three main response methods to the Ebola epidemic: supportive therapy , Drug treatment and vaccination. Supportive therapy such as fluid replacement Massive internal bleeding caused by Ebola virus destroying blood vessel walls. Related research shows that this intervention can increase the chance of survival efficiently during the early phase of the disease (Goeijenbier et al., 2014). This will reduce the harm caused by the epidemic in the early stages. On the other aspect, drugs are also widely used in disease treatment by the support of governments. Scientists injected the triple monoclonal antibody ZMapp as the control group, in contrast to antiviral

agent remdesivir (MAb114). The experimental results indicate that the mortality rate in the Mab114 group was 35.1%, slightly lower than that of the ZMapp group, which had a mortality rate of 49.7% (Sabue et al., 2019). However, the aforementioned data further indicate that pharmacological interventions are ineffective in lowering the mortality rate associated with the Ebola virus. Therefore, improving the resistance of susceptible people in Ebola-affected areas to the virus and promoting universal immunity became one of the important tasks for scientists, and the Ebola live vector vaccine came into being. The mechanism of this vaccine is inserting the protective antigen gene of other pathogens into the non-essential region gene of the vector genome to form a new recombinant virus. This new virus is going to be implanted into human body and triggering an immune response. The immune system will produce specific antibodies and immune cells by recording the information of the viral genome. When a real virus invades the human body, the immune system is able to produce a large number of corresponding antibodies to respond to the virus in a short period of time. This vaccine has advantages such as simple production, applicability to a variety of pathogens and long immunity.

4 THE rVSV-ZEBOV EBOLA VACCINE

4.1 Treatment Principle

Scientists use the genetically modified vesicular stomatitis virus (VSV) as an Ebola vaccine vector. The reason why VSV is able to become the vector is that it can be classified as a single-stranded negative-sense RNA virus so that it lacks a complex cleavage mechanism or segmented genome, making it amenable to insert foreign genes. Besides, this virus primarily impacts livestock and the infection is meek and asymptomatic in humans. Human infections have been reported only in a small number of cases, primarily among animal handlers and laboratory researchers (Bishnoi et al. 2018). That means it is almost harmless to humans and can be engrafted in the human body.

To begin with, people will remove the glycoprotein gene of VSV. This process would render VSV unable to infect other cells and ensure that it cannot replicate within the human body for an extended period for safety reason. After that, insert the glycoprotein(GP) gene of the Ebola virus to enable its expression in the VSV vector. Finally, by using reverse transcription technology, a stable recombinant vesicular stomatitis virus–Zaire Ebola virus(rVSV-ZEBOV) strain expressing the Ebola glycoprotein gene is constructed.

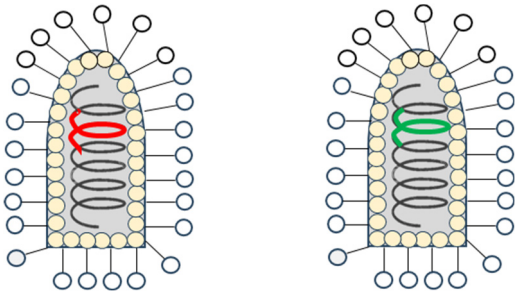

Figure 1: Example of Insert the Ebola Virus Glycoprotein Gene.

As Figure 1 shows, GP gene of VSV has been removed, in favor of GP gene of Ebola virus to form a rVSV-ZEBOV. When this recombinant virus enters the human body, the immune system will produce corresponding antibodies based on the ZEBOV genome, thereby having the ability to prevent the true virus.

4.2 Development and Production Process

After obtaining the recombinant virus, the researchers used serum albumin and buffers to prepare the vaccine, and by adjusting and maintaining the pH value of the vaccine, they ensured that the vaccine would not lose its activity due to changes in pH during storage and use, thereby maintaining the effectiveness of the vaccine and reducing the stimulation of the drug to the human body during injection. The rVSV-ZEBOV vaccine was produced using recombinant human serum albumin and a tris aminomethane buffer, with each vial containing a concentration of 100 million plaque-forming units (PFU) per milliliter. Pharmacists utilized normal saline as a diluent to prepare the vaccine doses, achieving concentrations of either 3 million PFU or 20 million PFU (Regules et al.,2017).

Once a candidate vaccine is developed, it must first be tested in rodents and non-human primates to ensure the safety and effectiveness of the vaccine. In 2007, researchers used three animal models: mice, guinea pigs, and rhesus monkeys to consider the post-exposure therapeutic effect of rVSV-ZEBOV

vaccine. They found that mice and guinea pigs immunized 24 hours after ZEBOV infection could obtain 100% and 50% protection respectively; while rhesus monkeys immunized within 20 to 30 minutes after infection could obtain 4/8 protection (Feldmann et al.,2007). This research result confirms the rVSV-ZEBOV vaccine's protective effect on mammals by producing an immune response in the test subject and provides a theoretical basis for subsequent human experiments.

After passing mammal experiments, the vaccine will be administered to human volunteers on a small scale for Phase I-III clinical trials. In 2014, two Phase I clinical trials of the vaccine were conducted in the United States. These two studies verified for the first time the safety and immunogenicity of the rVSV-ZEBOV vaccine in humans. An immune response can be produced about 6 days after a single intramuscular injection (Regules et al.,2017). After a double dose, the body produces a secondary immunity, and the antibody immune effect is enhanced, confirming the effectiveness of the vaccine in humans.

Subsequently, a phase II clinical trial conducted in Liberia showed data on the immune effect of 2.0×107 PFU rVSV-ZEBOV. One month after immunization, the geometric mean of GP antibodies in the rVSV-ZEBOV group was 1000 EU/ml, with a positive rate of 83.7%; 12 months after immunization, the geometric mean of GP antibodies in the rVSV-ZEBOV group was 818 EU/ml, with a positive rate of 79.5%(Kennedy et al.,2017). This suggests that the rVSV-ZEBOV vaccine maintains high antibody levels and has a strong immune effect for a long period of time after vaccination. During the Phase III study stage, the sample size needs to be further expanded to ensure the universal applicability of the vaccine. In experiments conducted by the Canadian Center for Vaccinology and other institutions in 2019,1197 healthy adults were randomized 2:2:2:2:1 to receive 1 of 3 consistency lots of rVSV-ZEBOV(2×10^7 plaque-forming units [pfu]), high-dose 1×10^8pfu, or placebo. At 28 days, more than 94% of vaccine recipients seroresponded, with responses persisting at 24 months in over 91%(Halperin et al.,2019). This result confirms that the vaccine has a wider audience and has immune efficacy for a longer period of time. Since then, the rVSV-ZEBOV vaccine has been officially put into large-scale production.

4.3 Drugs Currently on the Market or in Clinical Stages

The vaccines currently available on the market can be divided into three categories: DNA vaccines, mRNA vaccines and viral vector vaccines. DNA vaccines, such as the Ebola vaccine INO-4212 developed by Inovio Pharmaceuticals and GeneOne Life Science, are used to express plasmids that are immunogenic antigens. DNA vaccine production mainly relies on large-scale fermentation and purification of plasmid DNA, without the need for complex cell culture or virus inactivation, and the steps are relatively simple, with low production costs. However, due to the need to encode different Ebola virus subtypes, it has the disadvantages of complex immunization procedures and has a long production cycle.

Unlike DNA vaccines, which deliver DNA encoding antigenic proteins to the cell nucleus, mRNA vaccines deliver mRNA encoding antigenic proteins directly to the cytoplasm. After entering the cell, the lipid nanoparticles encapsulating the viral antigen protein mRNA fuse with the cell membrane, releasing the internal substances into the cytoplasm. The cell ribosomes will read the mRNA sequence, synthesize the viral antigen protein, activate the immune system to produce a specific immune response, and then form immune memory to provide long-term protection. Scientists vaccinate guinea pigs with Ebola mRNA vaccine to induce EBOV-specific IgG and neutralizing antibody responses. The experiment result indicated that 100% of guinea pigs survived after EBOV infection (Meyer et al.,2017). This confirms the effectiveness of the Ebola mRNA vaccine in mammals. However, mRNA has poor stability and needs to be stored at low temperatures. It also requires a complex lipid nanoparticle delivery system, which also greatly increases the cost of vaccine production.

Viral vector vaccines such as rVSV-ZEBOV use modified viruses as vectors to deliver the antigen genes of target pathogens into host cells, thereby stimulating an immune response. The vaccine was developed by the Public Health Agency of Canada and then licensed to Merck (product name V920) for later development of the vaccine. In May 2018, Merck and its partners provided a large number of vaccines to WHO during a new round of Ebola outbreaks in the Democratic Republic of the Congo and other places for ring vaccination (forming a circular population around each contact of a new Ebola case, with an immediate vaccination group and a delayed vaccination group) to prevent further spread

of the epidemic. According to statistics, a total of 300,000 residents in epidemic areas were vaccinated from 2018 to 2020(Wolf et al.,2020). Despite the modification, viral vectors may still trigger an immune response in the human body, bringing potential risks. Therefore, the safety of viral vector vaccines will still be an issue that needs to be paid attention to in the future.

4.4 Challenges and Prospects

Although the rVSV-ZEBOV vaccine is currently the most effective vaccine against Ebola virus, its safety still needs to be improved: In clinical trials conducted in Africa and Europe, 103 out of 110 subjects (94%) who received an immunization dose exceeding 3.0×10^6 PFU (plaque-forming units) still exhibited vaccine viremia three days after immunization. (Agnandji et al.,2016). This finding highlights the persistence of the vaccine virus in the bloodstream shortly after administration, causing some potential side effects and needs further optimization of the vaccine's safety profile. Researchers used systems vaccinology to deeply analyze vaccine clinical trial data and interpret the causes of adverse reactions to guide further optimization of vaccine design and reduce drug side effects. As a result, rVSVN1CT1GP3 (N1) was successfully developed.

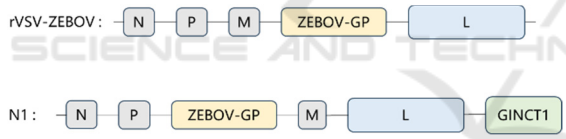

Figure 2: Comparision Between Gene Structure of the First Generation Vaccine and N1 Vaccine.

As Figure 2 shows, compared with the first-generation rVSV-ZEBOV vaccine, the N1 vaccine swaps the positions of the ZEBOV-GP gene and the M gene, and adds the gene sequence (GINCT1) with a reduced length of the cytoplasmic tail of the VSIV glycoprotein after the L gene.

The above optimization steps for the vaccine genome can effectively reduce the side effects of vaccines. People found through animal experiments that the probability of viremia in crab-eating macaques after a single immunization with the modified vaccine was 10 times lower than that of the first-generation rVSV-ZEBOV vaccine (Mire er al.,2015), which proved that this modification can effectively improve the safety of the vaccine. In the future, based on further understanding of rVSV-ZEBOV vaccine clinical data, the safety of the vaccine will be greatly improved.

Besides, rVSV-ZEBOV only targets the Zaire Ebola virus (EBOV-Z), but there are still different Ebola virus strains such as Sudan (SUDV) and Bundibugyo (BDBV). Scientists are actively developing multivalent vaccines designed to target multiple strains, including the Ebola Sudan vaccine (rVSV-EBOV-SUD), which is built on the rVSV platform and is currently undergoing clinical trials.

5 CONCLUSION

Ebola vaccines are of great significance in public health security. The development of Ebola vaccines can control the epidemic and reduce the mortality rate of patients in poor areas. At the same time, it can prevent possible Ebola outbreaks in the future and protect people in high-risk areas. Current vaccine research focuses on developing multivalent vaccines that can target multiple Ebola virus strains and reducing dependence on the cold chain to facilitate promotion in areas with limited resources.

This article deeply explores the relevant literature in the field of Ebola live vector vaccines and uses the method of literature research to deeply analyze this technology. However, in terms of vaccine safety and broad spectrum, the development speed of Ebola live vector vaccines has been restricted to a certain extent. In order to promote further development in this field and mitigate the adverse impact of the Ebola outbreak in West Africa, it is particularly urgent to solve the above problems and promote the comprehensive construction of Ebola live vector vaccine.

Ebola live vector vaccines will continue to play an important role in the future, providing stronger protection for global public health security through technological innovation and multi-field cooperation: With the advancement of genetic engineering and viral vector technology, future Ebola live vector vaccines will be safer and more efficient, and vaccines for different Ebola strains will also be produced. In addition, by improving the vaccine formula or using more stable vectors, it may be possible to reduce dependence on the cold chain in the future, reduce storage and transportation costs, make it more suitable for promotion in resource-limited areas, and meet the vaccine needs of the vast poor areas of Africa.

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