Article @ Virology

Progress in research on herpes simplex virus type 2 vaccine

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ABSTRACT

Herpes simplex virus type 2 (HSV-2) belongs to the herpesvirus alpha herpesvirus family, which mainly causes genital infection. HSV-2 infection can also increase the risk of HIV infection. The use of condoms and antiviral treatment can reduce the infection rate of HSV-2, but can not fundamentally prevent the spread of the virus. Vaccination is an effective method, but no safe and reliable HSV-2 vaccine has been successfully marketed. This article will review the research status and progress of all kinds of HSV-2 vaccines.

Article history: Submitted: 19/07/2018; Revised: 22/08/2018; Accepted: 24/08/2018

DOI: 10.21092/jav.v7i3.102

Key Words: Herpes simplex virus type 2; infection; Vaccine;

Abbreviations: HSV-2, Herpes Simplex Virus type 2; GUD, Genital Ulcer Disease; HSP70, heat shock protein 70; rVCG, recombinant Vibrio Cholerae Ghosts vector; HLA, Human Leukocyte Antigen Serotype; MVA, Modified Vaccinia Virus Ankara;

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Summary

Herpes simplex virus belongs to the herpesvirus family, which is a linear double stranded DNA virus. There are two serotypes of HSV: HSV-1 and HSV-2. The genomic sequence of HSV-1 and HSV-2 is about 50% homologous. Except for type-specific glycoprotein gG, the structural similarity of HSV-1 and HSV-2 is high. The two subtypes of HSV are quite different in transmission routes and epidemiological characteristics. HSV-1 is transmitted through saliva, mainly causing lip herpes; HSV-2 is sexually transmitted, mainly causing genital ulcer disease（GUD）. According to statistics, about four hundred million of the world's 15~49 year old people are infected with HSV-2, of which about 19 million people are infected each year. The treatment of GUD is expensive. The United States spends $540 million a year on GUD [1]. Studies have shown that the risk of HIV-1 infection in HSV-2 seropositive patients is 3 times higher than that in HSV-2 seronegative subjects [2].

Measures to prevent HSV-2 from spreading sexually include condom use and antiviral treatment[3].The use of these measures can reduce HSV-2 infection by about 50%, but can not fundamentally stop the spread of the virus [4-5].The most effective and economical way to protect against HSV-2, whether from the point of view of individual protection or public health, is to inoculate HSV-2 vaccine.

Mechanism of HSV-2 infection

HSV-2 is characterized by redness, swelling, herpes and ulceration at the site of infection. Most initial infections of HSV-2 are asymptomatic virus exfoli--ation. After the first infection, HSV-2 enters the sensory nerve endings, ascends along the axons to the sacral ganglion and establishes a latent infection. HSV-2, which is latently infected, can be activated and replicated by a variety of factors, descending along the axon to the sensory nerve endings and recurring in the epithelial tissue near the sensory nerve endings. Studies have shown that the latent form of genital herpes exists in its genome, i.e. DNA. When it relapses, DNA copies in the ganglion begin to increase substantially, and then pack into viruses in the host cells and descend along ganglion axons to vaginal sites, leading to some symptomatic recurrent infections or asymptomatic infections detoxification state. Asymptomatic virus shedding from primary infection and recurrent infection further leads to the spread of disease[6]. Alpha herpes virus, including HSV-2, has co-evolved with primates for millions of years to develop strategies to escape host immune responses .Latent transcription of virus can prevent cell apoptosis and ensure the survival of nerve cells[7]. The results show that the virus and the host immune system have a continuous confrontation, even if the host has

established a mature immune response, HSV-2 can still use its own immune escape mechanism to achieve repeated activation and latency[8].

Research and development of HSV-2 Vaccine

Vaccine research on HSV is unknown whether mucosal immunity can be initiated by muscle vaccination. However, HPV vaccination has proved that muscle vaccination can induce highly effective mucosal immunity against genital mucosal viruses[9]. HSV vaccines can be divided into therapeutic vaccines and preventive vaccines. The goal of preventive vaccines is to prevent HSV-2 infection in uninfected populations, while therapeutic vaccines aim to reduce the severity of the disease and prevent the recurrence of HSV-related diseases in people already infected with HSV-2. According to their own characte--ristics are mainly divided into inactivated vaccine, attenuated live vaccine, subunit vaccine,replication deficiency vaccine, poly--peptide vaccine, live vector vaccine and DNA vaccine.

1. Inactivated vaccine

The study of HSV vaccine can be traced back to the 1930s. From 1940 to 1960, the virus was cultured in chicken embryo (cell culture later) and then inactivated by ultraviolet radiation, heating or chemical methods. Kern and Schiff conducted the first randomized, double-blind, placebo-controlled clinical trial of a formalin--inactivated vaccine against patients with recurrent genital herpes in 1964. The recurrence rate of the vaccine group did not decrease significantly compared with the placebo group, indicating that the vaccine was less effective[10]. Since inactivated HSV-2 vaccine has poor efficacy, low immunogenicity and may increase the risk of cancer, inactivated vaccine is no longer used as a candidate vaccine for HSV-2.

2. Attenuated live vaccine

HSV-2 attenuated live vaccine deletes virulence, latency and resuscitation--related genes, making it non-pathogenic or low pathogenicity, and theoretically more likely to successfully induce virus-specific CD8+T cell immune response. However, there is still possibility of virulence reversion.

The mutation/deletion sites of HSV-2 attenuated strain are ICP0, gD, gE, etc. The attenuated live vaccine produced by HSV-2 attenuated strain is still in the preclinical research stage. HSV-2 0ΔNLS is an ICP0 mutant virus. It shows a good balance between virulence and immuno--genicity in mice[11]. It can produce 10-100 times more protective effect than gD2 subunit vaccine in animal experiments. It is a potential candidate vaccine for HSV-2[12]. The researchers mutated 215, 222, and 223 residues of the gD protein to obtain a attenuated strain of HSV-2 gD27, which lost its ability to

interact with nectin-1 and therefore could not infect cells that only expressed nectin-1, such as neurons, and did not infect central nerve cells in a mouse model[13]. gE2-del is a deleted mutant of gE2 of HSV-2. It can not be transported from neuronal cell body to axon end. Its virulence is 5 orders of magnitude lower than that of wild-type virus. After immunized mice and guinea pigs with gE2-del as a prophylactic vaccine, it can reduce vaginal lesion, dorsal root ganglion infection and reproductive organ lesion recovery in immunized animals. Guinea pigs immunized with HSV-2 as a therapeutic vaccine can significantly reduce the recurrence rate of genital diseases[14].

3. Subunit vaccine

Subunit vaccine is the most popular HSV-2 vaccine currently in research. Most of them are HSV-2 surface glycoprotein gD and gB. gD binds to cell receptors and participates in virus invasion, whereas gB is a trans-membrane glycoprotein involved in virus penetration into host cells. Early researchers tried to produce HSV-2 vaccine from chicken embryo fibroblasts and purified HSV-2 gB, gC, gD, gE and gG glycoprotein vaccines. Clinical trials showed that the vaccines had poor immunogenicity and could not produce effective protective effects[15].

At present, HSV-2 glycoprotein vaccines mostly use recombinant HSV-2 glyco--protein, which is combined with adjuvants to enhance immune response. Two recomb--inant glycoprotein vaccines have been used as prophylactic vaccines in phase III clinical trials: gD2/gB2-MF59 vaccine containing truncated gD2 and gB2, and adjuvant M59 oil-in-water emulsion. Two randomized, double-blind, placebo-controlled trials of the vaccine were conducted in 531 subjects with partner sensation, respectively. Subjects infected with HSV-2 but with negative serum response to HSV-2 and 1,862 high-risk individuals infected with HSV-2 were tested. The results showed that the vaccine was safe and could induce neutralizing antibodies higher than those of natural infection, but failed to prevent HSV-2 infection[16]. The gD2 alum / MPL vaccine is a gD2 subunit vaccine. The adjuvant is made of aluminum hydroxide and 3-O-deacylated MPL. The vaccine has been tested in three clinical trials. The results show that the vaccine can successfully induce the specific recognition of gD2. And antibodies and CD4+ T cells, but the vaccine's protective efficacy is only 35% ~ 42%[17-18]. Thus, although the virus glycoprotein can successfully induce the body to produce specific neutralizing antibodies, but because the virus has multiple immune escape mechanisms, can resist the elimination of humoral immune response to the virus, neutralizing antibodies alone is not enough to produce sufficient protection against HSV-2 infection. Two

glycoprotein subunit vaccines were studied in patients with frequent recurrence of genital herpes by Straus et al[19]. It was found that gD2 aluminium adjuvant vaccine (dosage 100 μg gD2) significantly reduced the monthly recurrence rate, while gD2/gB2 MF59 adjuvant vaccine (dosage 10 μg each for gD2 and gB2) did not significantly reduce the monthly recurrence rate. Incidence, however, was significantly shortened in the formation of new infections and the healing time of the first relapse, suggesting the feasibility of glycoprotein vaccine as a therapeutic vaccine[20].

4. Replication deficiency vaccine

HSV-2 gH deletion vaccine is a mutant of HSV-2 deleting the gH gene. It is the only replication deficiency virus vaccine currently available in patients with frequent recurrence of genital herpes who have undergone multiple central, randomized, placebo-controlled clinical trials[21]. Due to the lack of gH gene, the virus can only proliferate in recombinant cells expressing HSV-2 gH gene. Once injected into the human body, the virus can only replicate in one round in human cells that do not express gH gene. Clinical trials have shown that the vaccine is safe, but the values of viral emissions and recurrence rates in the vaccine group are similar to those in the placebo group, indicating that the vaccine is less effective under the conditions of the titer used in the trial.

The replication-related genes UL5 and UL59 of ACAM529 virus were deleted and could only be reproduced in the cells expressing the two proteins. Mice and guinea pigs were immunized with ACAM529. After being attacked by wild-type virus, latent infection and virus emission were significantly reduced[22-23]. The UL9 of CJ2-gD virus contains a dominant mutation. Not only the mutant virus itself cannot replicate the viral DNA, but also the wild-type virus cannot replicate in the cells of the infected vaccine strain[24].

The CJ2-gD immunized mice can be vaginally attacked in HSV-2. Reduced viral emissions, genital lesions, hind limb paralysis and mortality after immuniz--ation, immune guinea pigs, can prevent acute genital lesions, hind limb paralysis after wild-type HSV-2 challenge[25], the virus emission and duration of the vaccine group is significantly lower than the control group. And the DNA load of the latent virus in the dorsal root ganglia of the vaccine group is 50 times lower than that of the control group[26].

Another potential replication deficiency virus deletes virus UL29 and expresses costimulatory molecule B7 in order to enhance the T-cell immune response of the replication deficiency virus[27]. After inoculation with the vaccine, the number of T cells producing IFN-γ increases, the virus replication in the vaginal mucosa decreases, nerves and genital lesions were

reduced, and the mortality rate was lower compared with the same type of replication deficient virus that did not express B7[28].

5. Polypeptide vaccine

HerpV is a newly developed HSV-2 polypeptide vaccine in recent years. It contains 32 kinds of 35 polypeptides synthesized by HSV-2 and is non-covalently linked to human recombinant HSP70. HerpV has good immunogenicity. It can produce both CD4+ and CD8+ T cell responses in mice and HSV-2 positive subjects. Phase I clinical trials conducted by HerpV in 2011 showed that the vaccine could successfully induce significant CD4 + and CD8+ T cell responses to HSV-2 antigen in HSV-2 seropositive subjects, and was the first candidate vaccine for HSV-2 in which HSP70 was used as an adjuvant to induce a successful immune response[29-30].

HSV-2 polypeptide vaccine can induce the production of synthetic peptides against the protective immune response of HSV-2, most of which are T cell epitopes or B cell epitopes. The first HSV-2 polypeptide vaccine to be tested in Phase I was AG-702, a non-covalent conjugate of HLA-A*0201 restricted gB2 epitopes. The adjuvant was truncated human heat shock protein 70 (HSP70) [31]. Clinical trials showed that the vaccine was safe, but no new or enhanced epitope immune response to HSV-2 CD8+ was detected in the subjects.

6. live vector vaccine

HSV-2 vaccine uses heterologous expression vectors (such as adenovirus and vaccinia virus DNA) to express HSV-2 antigen, which can effectively stimulate the body to produce immune response. It has been found that the modified vaccinia virus Ankara (MVA) vector expressing HSV-2 gD can enhance humoral and cellular immune responses[32]. In addition, recombinant Vibrio cholerae ghosts vector (rVCG) expressing both Chlamydia MOMP and HSV-2 gD can induce high levels of Chlamydia antibody and HSV-2 antibody, and induce strong Th1 immune response. However, the disadvantage of these vaccines is that antibodies produced by human body against heterologous vectors can affect the efficacy of vaccines, and the safety of carriers needs careful evaluation for heterologous vaccines[33].

7. DNA vaccine

Several recently reported DNA vaccines, such as gD2 plasmid DNA, gD2 plasmid DNA encoding UL46 and UL47, and gD2, gB2 CTL epitope DNA[34-35], can successfully induce humoral and cellular immune responses, and have strong protective effects against viral attack. In addition, Dutton et al[36] obtained a new DNA vaccine of HSV-2 by optimizing the codon of enhanced immune response. The vaccine encodes the envelope protein gD of the virus, and

contains two components: the non--ubiquitination construction of enhancing humoral immune response and the ubiquitination construction of enhancing T-cell immune response. The vaccine can be used in mouse model. Lethal dose can protect the neurons and reduce the latency of the virus in ganglion cells. The vaccine has completed phase I clinical trials, and phase II clinical trials are under way.

Expectation

HSV is extremely harmful to humans, and safe and effective vaccines are urgently needed. It is believed that with the advancement of science, a viable HSV vaccine will be developed, and effective control of HSV infection will become possible.urgently needed. It is believed that with the advancement of science, a viable HSV vaccine will be developed, and effective control of HSV infection will become possible.

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