Vaccine developed for human herpesvirus 6B

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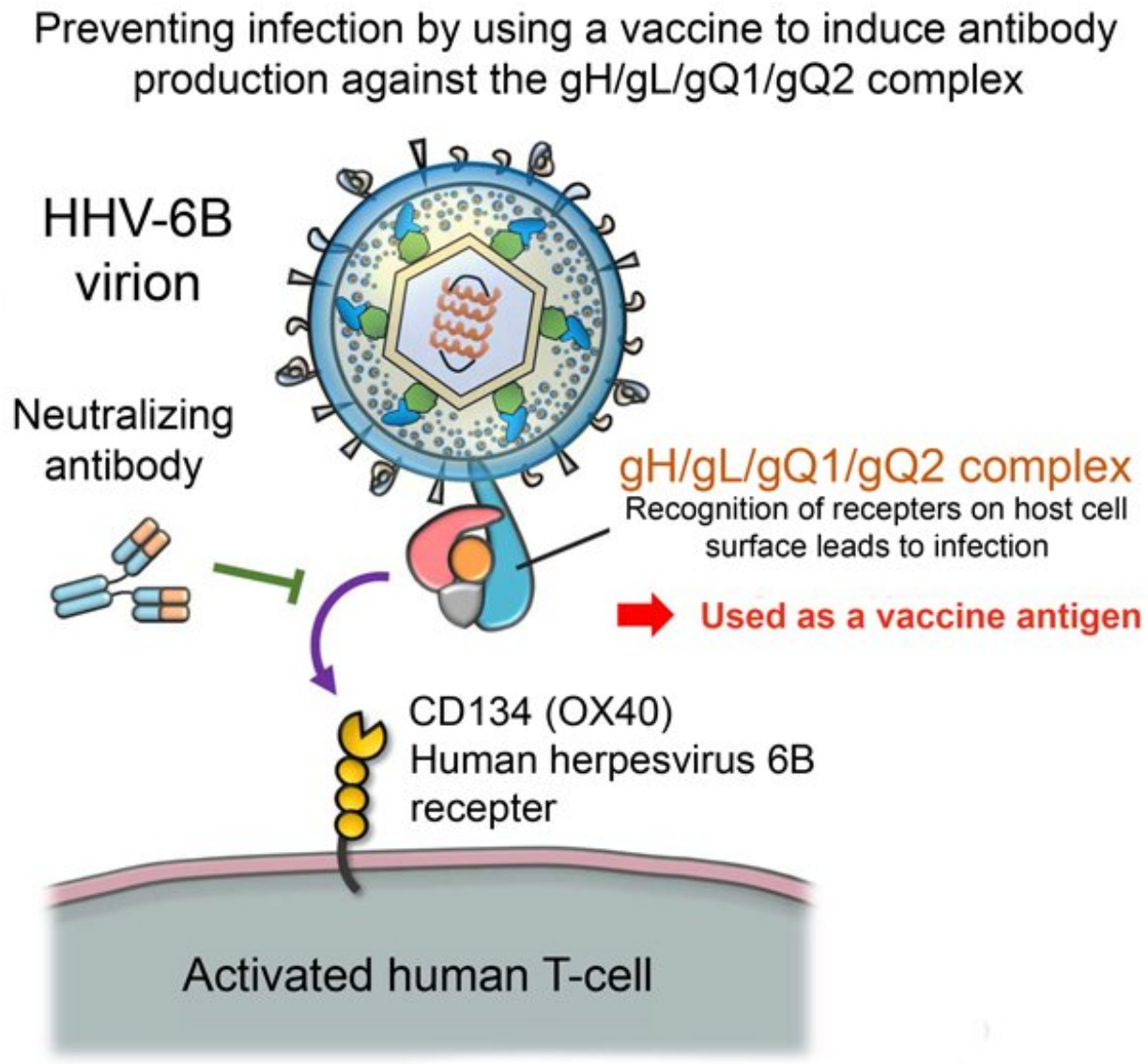


The mechanism by which HHV-6B infects human cells is the target of this research. Credit: Kobe University

A research group led by Professor Mori Yasuko (of the Division of Clinical Virology, Center for Infectious Diseases, Kobe University Graduate School of Medicine) has revealed that the HHV-6B glycoprotein complex gH/gL/gQ1/gQ2 is an effective vaccine candidate for human herpesvirus 6B (HHV-6B). There are still no methods to treat or prevent HHV-6B infection, and this study represents the first attempt in the world at developing a vaccine. The results were published online in the American scientific journal *PLOS Pathogens* on July 23.

Main Points

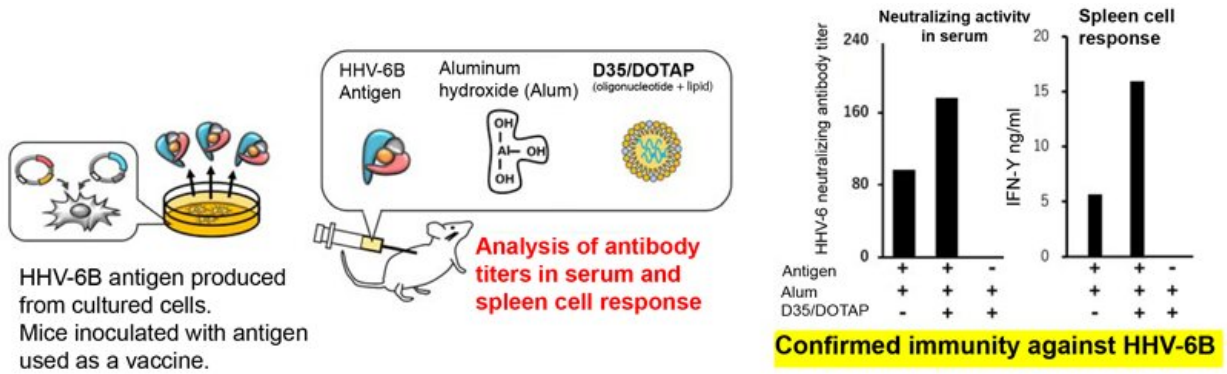
- Human herpesvirus 6B (HHV-6B) is a pathogen that infects the vast majority of people when they are infants. It not only causes exanthem subitum, with symptoms of a fever followed by a skin rash (roseola) but can also trigger severe complications with lasting after-effects such as febrile convulsions, encephalitis (brain inflammation) and encephalopathy.
- Methods to effectively prevent or treat HHV-6B infection have yet to be established. The infection rate is extremely high and great risks are posed by HHV-6B. It is hoped that the realization of a vaccine would enable infants to be inoculated against HHV-6B, resulting in widespread prevention of this virus.
- This research group previously discovered a HHV-6B glycoprotein complex that is an essential factor in HHV-6B infection. In this study, they utilized this complex as a vaccine antigen and analyzed its effectiveness.
- The research group inoculated mice with the purified virus antigen combined with immunostimulants known as adjuvants, demonstrating that this induced effective immunity against HHV-6B. Furthermore, the combination with the adjuvants was also shown to induce cellular immunity.
- These successful results are a big step towards the realization of a safe and effective vaccine for HHV-6B. It is hoped that this

research can proceed to clinical trials.

Research Background

Human herpesvirus 6B (HHV-6B) is passed on to infants via the saliva of family members etc., causing exanthem subitum which has symptoms of a fever over 38°C followed by a rash all over the body (roseola). The overwhelming majority of people are infected with HHV-6B. The infection period is between 6 months and 2 years of age; this coincides with the diminishment of antibodies received from the mother.

In most cases, infants recover without experiencing any serious symptoms, however severe complications can occur. For example, it has been reported that in Japan, around 150 infants a year suffer encephalitis or encephalopathy, resulting in lasting aftereffects in around half of this number. Therefore, it is essential to develop a vaccine to protect infants from HHV-6B infection, as there is currently no established treatment nor preventative measures against the virus.



Immunity induction in mice inoculated against HHV-6B gH/gL/gQ1/gQ2 complex. Credit: Kobe University

Previously, Professor Mori's research group discovered the glycoprotein complex gH/gL/gQ1/gQ2, which is expressed on the HHV-6B virus's surface. They also revealed that the interaction between this complex and CD314 (OX40), which is expressed on stimulated T-cells, is the key to infection. An antibody that targets the gH/gL/gQ1/gQ2 complex would be able to prevent HHV-6B infection. Therefore, the group is also conducting research into generating antibodies that can be used on humans from mice antibodies.

From this accumulated knowledge and experience came the following idea: an efficient immune response against HHV-6B infection could be achieved if inoculation with the gH/gl/gQ1/gQ2 complex induced immunity against the complex.

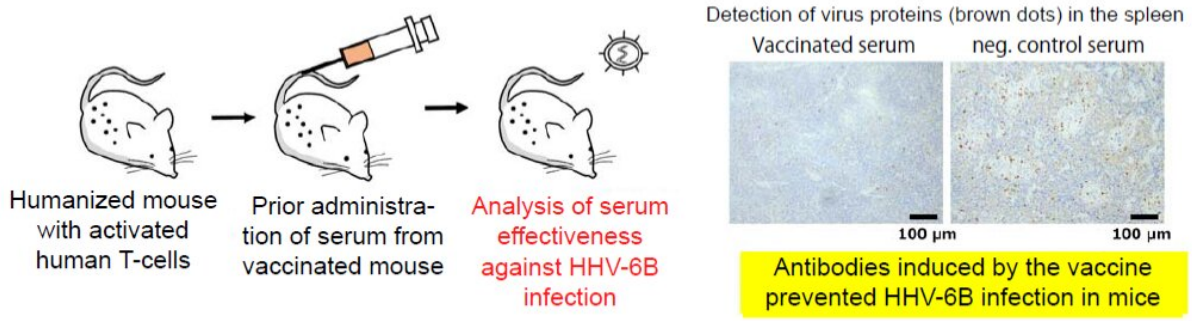
Research Findings

The researchers developed a vaccine based on the HHV-6B gH/gL/gQ1/gQ2 complex. (A Patent Application for the vaccine has been filed by the BIKEN Foundation and Kobe University (Patent Application No. 2017-509816)). They generated the gH/gL/gQ1/gQ2 complex via genetic modification techniques. This complex was utilized as the vaccine antigen and mice were inoculated with this in combination with an adjuvant, and immunity induction was analyzed.

The HHV-6B gH/gL/gQ1/gQ2 complex is a complicated molecule constructed in a cell with four types of protein. A method was developed to grow this complex in a cultivated cell in which all the proteins are expressed at the same time. It was confirmed that the HHV-6B gH/gL/gQ1/gQ2 complexes generated using this method still retained their function of binding to their target receptor molecule, CD134 (OX40).

The complex was combined with the adjuvant aluminum hydroxide

(abbreviated to Alum), which is widely used in current vaccines, and administered to mice in several doses. The immune response was analyzed; the results confirmed there were vaccine induced antibodies against the gH/gL/gQ1/gQ2 complex in the serum of the mice, and their serum had actually prevented HHV-6B from infecting the cells. Furthermore, it was shown that the glycoprotein complex itself had activated dendritic cells, inducing innate immunity.



Vaccine trials using the animal model of HHV-6B infection. Credit: Professor Mori Yasuko/Kobe University

Furthermore, a vaccine with a combination of oligonucleotide D35 (which can induce cellular immunity) and its transporter, the DOTAP lipid, as adjuvants in addition to Alum was developed. This vaccine was demonstrated to induce an even stronger antibody response. Spleen cells were extracted from mice after the immunity experiments and the immune cell responses to the gH/gL/gQ1/gQ2 complex were investigated. The results showed a stronger response to the antigen in the group inoculated with the Alum/D35/DOTAP combination and

confirmed that cellular immunity was induced. Additional analysis results revealed that CD4 T-cells were the main responders to the antigen.

The researchers also investigated whether or not the induction of serum antibodies via inoculation with the gH/gL/gQ1/gQ2 complex actually prevented HHV-6B infection in animals. This experiment utilized immune cell-humanized mice to develop an animal model of HHV-6B infection. As a negative control, humanized mice were administered with serum from mice that had been given a vaccine containing only the adjuvant. The humanized mice were then injected with HHV-6B. The virus proliferated internally and many virus antigens were detected in the spleens of the negative control group.

On the other hand, the virus did not proliferate in humanized mice that received prior administration of serum from mice who were inoculated with the vaccine containing the gH/gL/gQ1/gQ2 complex. Also, there were hardly any virus antigens in the spleens of these humanized mice. This demonstrates that the induced immunity from the vaccine is efficient against HHV-6B infection in mice.

Further Developments

Effective treatment and preventative methods for HHV-6B infection have yet to be established despite the latent risks that it poses to the health of all infants. The results of this research represent a huge step towards the efficient prevention of HHV-6B infection with a vaccine. It was demonstrated that this vaccine, which used the gH/gL/gQ1/gQ2 complex as an antigen, efficiently induced an immune system response. Also, the vaccine is promising from a safety aspect as it is a subunit vaccine that does not contain other virus-derived molecules, aside from the complex. Currently, many infants are given a combined inoculation against four diseases called the DPT-IPV vaccine (D: Diphtheria, P:

pertussis, T: tetanus and IPV: inactivated polio virus) at 3 months of age. It is hoped that HHV-6B inoculation could be added to this vaccine to prevent infants from contracting it.

After infection, HHV-6B remains latent inside its host for their entire life. It can be reactivated by conditions such as drug-induced hypersensitivity syndrome or a decline in immunity, and has been reported to trigger various illnesses. In particular, this as a problem when hematopoietic stem cell transplants are used to treat leukemia, leading to a high frequency of HHV-6B reactivation which can cause life-threatening encephalitis. The vaccine developed by this study, when combined with adjuvants, not only grants humoral immunity but can also induce cellular immunity. In other words, this vaccine can induce a strong immune response to HHV-6B. It is believed that it could also be used to suppress the HHV-6B infection in those undergoing hematopoietic stem cell transplants.

Next, the researchers will build upon these results, collect data on the effectiveness and safety of the vaccine and then proceed to clinical trials. They aim to bring a pioneering HHV-6B vaccine developed in Japan to the world.

More information: Bochao Wang et al, Tetrameric glycoprotein complex gH/gL/gQ1/gQ2 is a promising vaccine candidate for human herpesvirus 6B, *PLOS Pathogens* (2020). DOI: 10.1371/journal.ppat.1008609

Provided by Kobe University