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Mini Review

Tissue Highly Contagious Vaccine Efficacy that would be Enhanced by Immune Cells

Anamika Mishra*

Department of Biotechnology, University of India, India

*Corresponding Author's E-mail: mishra45@gmail.com

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Abstract

One of the major safety concerns in the development of WNV vaccines is that antibody-dependent enhancement of infection (ADE) increases the risk of vaccinated individuals becoming infected with related flaviviruses. Here we report the development of a plant-based vaccine candidate that minimizes the risk of Zika (ZIKV) and dengue virus (DENV) ADE infection while providing protective immunity against lethal his WNV-carrying mice. Notably, plant-produced virus-like particles (VLPs) containing WNV coat protein domain III (wDIII) induced both high neutralizing antibody titers and antigen-specific cellular immune responses in mice by lethal challenge of WNV infection. Surprisingly, VLP-induced antibodies did not enhance infection of Fc-γ receptor-expressing K562 cells with ZIKV or ADE with DENV. Therefore, plant-derived wDIII-presenting VLPs may induce protective immunity and induce ADE-susceptible antibodies to minimize concerns that vaccinated individuals may be susceptible to severe infection with her DENV or ZIKV.

Keywords: domain III (DIII), dengue virus (DENV), virus-like particle (VLP)

INTRODUCTION

In humans, West Nile virus (WNV) infection can lead to severe neuroinvasive diseases such as encephalitis, meningitis, and even death. The elderly and immunocompromised, or those with certain genetic factors, are at increased risk of developing life-threatening and fatal neurological disorders. . However, there is still no WNV vaccine approved for human use **(Carter CG 2001)**. WNV is a member of the Flaviviridae genus of the Flaviviridae family and is genetically closely related to dengue virus (DENV), Zika virus (ZIKV), tick-borne encephalitis virus (TBEV), and yellow fever virus (YFV). I'm here. (wDI, wDII, and wDIII) associate with other flaviviruses and mediate viral assembly, attachment to cellular receptors, and subsequent membrane fusion for viral entry **(Davis HP 1984)**. The epitope is on wDIII. Since neutralizing antibody responses have been shown to correlate with protection of licensed vaccines against YFV and TBEV, vaccine candidates against wDIII are preferred WNV vaccine candidates due to the presence of multiple neutralizing epitopes in this domain. is considered. Some antibodies induced by a particular DENV serotype during primary infection do not protect against another DENV serotype during secondary infection, but instead promote infection of Fc gamma receptor (FcγR)-expressing cells. It can increase and cause fatal shock syndrome due to ADE. Thus, WNV vaccines based on conserved epitopes among related flaviviruses promote DENV and ZIKV entry and replication in FcγR-bearing cells, resulting in severe DENV or ZIKV infection in vaccinated subjects. There is a risk of inducing reactive antibodies **(Crick FH 1958)**. Indeed, mutual enhancement between WNV and ZIKV infections has already been observed. Therefore, a human WNV vaccine should not only be effective, but also safe, with minimal risk of inducing ADE **(Haselkorn R 1973)**. Previously, he reported on his efforts to develop his WNV vaccine candidate in plants using chimeric hepatitis B core antigen (HBcAg)-wDIII virus-like particles (VLPs) (HBcAg-wDIII-VLP).HBcAg wDIII VLPs were rapidly expressed at high levels in Nicotiana benthamiana plants, suggesting that immunization with plant-produced HBcAg wDIII VLPs induced wDIII-specific antibody responses in mice. Here we report a follow-up study on the efficacy and safety of his HBcAg wDIII VLPs as a promising vaccine against WNV. We examine the neutralizing potency of

wDIII-specific antibodies, antigen-specific cellular immune responses, and the protective effect of his HBcAg-wDIII VLP immunization in mice against lethal challenge. Additionally, the risk of ADE increasing her ZIKV and DENV infections with this vaccine candidate will be assessed to address potential safety issues **(Moldave K 1985)**.

MATERIAL AND METHODS

Production in Plants

HBcAg wDIII VLPs were produced in N. Leaves were harvested 7 days after agroinfiltration (dpi) and HBcAg-wDIII VLPs were extracted and purified by sucrose gradient centrifugation as previously described. Five-week-old female BALB/c mice were used for immunization **(Lucas-Lenard JEAN 1971)**. Mice were divided into two groups (n = 6 per group), with group 1 receiving sham cells with 100 µl of PBS-saline buffer (PBS) with adjuvanted aluminum hydroxide gel (Alum, Sigma, Burlington, MA). Group 2 received 100 µl of material per dose containing 25 µg of HBcAg-wDIII VLPs in PBS adjuvanted with alum. Mice were primed with a subcutaneous injection on day 0 and boosted three times on days 21, 42, and 63 with the same dose and immunization protocol as the primary series. Retro-orbital (r.o.) blood samples were collected on day 0 before immunization (preimmune sample) and on days 14 (week 2), 35 (week 5), 56 (5 weeks) after the first immunization. A terminal blood sample was taken on day 77 (week 11) after humane sacrifice of the mice. Spleens were aseptically removed after euthanasia for in vitro splenocyte culture **(Lengyel P 1971)**.

Antibody Assay

Details of the PRNT assay are provided. Student's t-test was used to compare serum neutralization potency between different groups of mice. One-way ANOVA and two-way ANOVA were used to compare levels of cytokines between groups of mice and between samples collected at different time points. Survival of mice from at least two independent WNV challenge experiments (n=10) was analyzed by log-rank analysis (Mantel-Cox) **(Weissbach H 2012)**.

Materials

WNV has spread worldwide and is now endemic in many parts of the world. Most WNV infections cause a mild febrile illness, but the elderly and immunocompromised are at increased risk of developing fatal neuroinvasive disease with symptoms such as cognitive impairment and flaccid paralysis. As there is no approved therapy to specifically treat her WNV infection in humans, there is an urgent need to develop a vaccine to stop the WNV pandemic. Several of her WNV vaccine candidates are in development **(Loftfield RB 1972)**. These include her inactivated WNV, live chimeric viruses, DNA or protein-based subunit her vaccines containing its wE protein as the primary antigen. Studies of these vaccine candidates demonstrate that protection is mediated by vaccine-induced antibody responses by neutralizing anti-wE titers >10, which correlate with protective immunity. These promising vaccine candidates still face challenges before they are approved for human use. For example, incomplete inactivation of live her WNV, adverse host response to viral vectors, and risk factors associated with tumorigenesis due to potential insertion of DNA vaccine fragments into the host genome all contribute to safety. contribute to This gives cause for concern. Although subunit-based vaccines based on the wE protein are said to be safe compared to other candidates, their production is characterized by low yields, limited scalability and poor antigen refolding **(Andersen GR 2003)**. Suffer from endotoxin clearance. The recent outbreak of ZIKV has further complicated the development of us protein-based WNV vaccines. Based on the observation that a population previously infected with WNV was more likely to develop severe disease upon his subsequent ZIKV infection, ADE-mediated amplification of heterologous flavivirus infections (e.g., ZIKV and DENV) his WNV vaccine. have expressed concerns about the safety of To address the safety issues and challenges of vaccine manufacturing, there is a need to express wDIII, an antigen with defined neutralizing and immunopathological epitopes in the form of VLPs. I studied plant expression systems. We previously showed that high-yield production of His-HBcAg wDIII VLPs was achieved in Nicotiana benthamiana leaves within days after introduction of the target gene, ensuring that the VLPs displayed His-wDIII epitopes on their surface. The study described here aims to further demonstrate the efficacy of HBcAg wDIII VLPs in vivo and, more importantly, to address the safety issues associated with ADE. We have previously shown that HBcAg-wDIII VLPs not only induce potent production of DIII-specific antibodies, but also antibodies that compete with known protective mAbs for binding to the same epitope. This suggests that HBcAg-wDIII VLP-induced antibodies may be protective. Indeed, our current study confirms such a hypothesis, demonstrating that sera collected from mice two weeks after his first boost of HBcAg-wDIII-VLP immunization showed that at 100-fold dilution he was infected with WNV. I discovered that it showed >80. fold. This indicates that the antibody responses elicited by HBcAg-wDIII-VLP exhibit potent neutralizing activity (neutralizing titer >100) above the threshold for protective immunity (neutralizing titer >10) established by previous studies. Indicates that you have in our in vivo study, anti-HBcAg-wDIII-VLP serum protected 90% of recipient mice from lethal attack of her WNV infection, demonstrating protective effect of antibody immunity by HBcAg-wDIII-VLPs.

Taken together, these results demonstrate that protective immunity against WNV infection can be achieved by neutralizing antibody responses from HBcAg wDIII VLP immunization. Notably, both Th1 (IFN-γ and IL-2) and Th2-type (IL-6) cytokines were induced by HBcAg-wDIII VLP administration, confirming previous reports that wDIII induced both IgG1 and IgG2a responses. The ability of

HBcAg-wDIII-VLP immunization to induce cell-mediated immune responses suggests this possibility.

It not only provides immunity against future WNV infections, but also eliminates WNV infections. Most importantly, our HBcAg-wDIII VLPs did not induce the production of antibodies promoting her DENV or ZIKV infection in the immunized host. Development of a flavivirus vaccine is challenged by the risk of AD. For example, if a person has antibodies from infection or vaccination against one DENV serotype, if he is infected with another serotype, he probably develops dengue hemorrhagic fever/dengue shock syndrome (DHF/DSS) from ADE. Increased risk of developing serious symptoms. Animal model studies suggest that ADE may also occur between her WNV and ZIKV. Therefore, minimizing ADE in heterologous flavivirus infection is one of the most important considerations for WNV vaccine development. For this purpose, we chose wDIII as the main antigen for our VLP-based vaccine. Overall, DIII of the E protein is less conserved in flaviviruses than domains I and II (DI and DII), and many are neutralizing and protective.

CONCLUSIONS

In conclusion, we have shown that plant-derived VLP vaccine candidates can protect mice from WNV infection. More importantly, this vaccine candidate may have safety advantages over other vaccine candidates due to its lack of ADE activity against ZIKV and DENV infections. Therefore, our study may facilitate the development of an effective, safe, and inexpensive mass-produced her WNV vaccine.

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