Role of DENV Vaccine-Induced Antibodies And T Cells In Protection Against Heterologous DENV2 Infection

LAM Jian Hang

Abstract
Dengue virus (DENV) is the etiological agent of dengue fever, a major public health problem worldwide with an estimated 100 million cases of symptomatic infections each year. Several live attenuated vaccine candidates are in various stages of clinical development and the prospect of a human-approved vaccine is high. Subneutralising levels of maternal dengue antibodies are implicated in the development of severe dengue disease in children through the mechanism of antibody dependent enhancement (ADE) of infection. Therefore, one area of concern is the outcome of a primary dengue infection in children born to vaccinated mothers. PDK53 is a live attenuated dengue 2 virus (DENV2) developed by the Mahidol University. It is well tolerated by human subjects and highly immunogenic. To study the immune response to PDK53, we used the A129 mouse model, which is IFNa/β R⁻/⁻ and hence more susceptible to DENV. Five weeks old female mice inoculated with a single 10⁶ PFU dose of PDK53 developed strong neutralising titres against parental DENV2 strain 16681. However, immune sera from vaccinated mice were poorly neutralising towards a heterologous DENV2 strain (D2Y98P-PP1), indicating limited cross-protection. Pups born to PDK53-vaccinated dams acquired maternal antibodies and exhibited strong neutralising titres against homologous strain 16681 at three weeks of age. Nevertheless, sera from these pups remained poorly neutralising towards strain D2Y98P-PP1 and the mice remained susceptible to D2Y98P-PP1 infection. When these pups were vaccinated with PDK53, seroconversion was not detected three weeks after – a phenomenon known as maternal antibody interference. Nevertheless, vaccinated pups were fully protected against lethal D2Y98P-PP1 infection, suggesting a protective role for T cells. Consistently, strong NS4B-specific CD8⁺ T cell activity was present in the vaccinated pups. CD8⁺ T cells depletion experiments are being performed to confirm their role in protection from D2Y98P-PP1.

Biography
Lam Jian Hang received his Ph.D. in Microbiology from the National University of Singapore in 2015 under the supervision of A/Prof. Sylvie Alonso and has remained as a Research Fellow. His work involves developing a mouse model to study dengue vaccines and understand the relative contributions of B and T cells to dengue immunity.

Antiviral Discovery And Strategies For Human Enterovirus 71 That Causes Hand, Foot And Mouth Diseases

Jialei SUN

Abstract
Enterovirus 71 (EV71) causes hand-foot-and-mouth diseases in young children. Interferon (IFN) can inhibit the replication of many viruses with low cytotoxic effects. Previously, an adenovirus vectored mouse interferon-α (DEF201) was generated to prolong the half-life of IFN. In this study, the antiviral effects of DEF201 against EV71 were evaluated in a murine model. Our study showed that pre-treatment of mice with single dose of 10⁶ PFU of DEF201 offered full protection of the mice against EV71 infection compared with the empty vector control. In addition, virus load in EV71-infected mice muscle tissue was significantly decreased upon DEF201 treatment. Histopathology analysis further revealed that DEF201 significantly prevented mice from developing severe tissue damage and decreased viral antigen in muscle tissue. Post-treatment assay at 6h instead of 12h, offered full protection indicating that DEF201 could be used as an anti-EV71 therapeutic agent in early stage of EV71 infection. In addition, DEF201 enhanced the production of specific anti-EV71 neutralizing antibodies in EV71-vaccinated mice. Furthermore, microarray analysis revealed that DEF201 induced robust expression of immune system related genes in mice tissues. In conclusion, single dose of DEF201 is highly efficacious as a prophylactic and therapeutic agent against EV71 infection in vivo.

Biography
Jialei graduated with a Bachelor’s degree with honours in Life Sciences from Nankai University, China. He is currently a PhD student in the Laboratory of Molecular RNA Virology and Antiviral Strategies under the mentorship of Assistant Professor Justin Chu in the National University of Singapore. His current research interest is focused on the discovery of antivirals against enteroviruses.