NUS National University of Singapore | Infectious Diseases Translational Research Programme
Yong Loo Lin School of Medicine

Zika Virus Evolution in the Presence of Pre-Existing Anti-Dengue Immunity and Dendritic Cell Response to Zika Virus

Associate Professor Sujan Shresta
Center for Infectious Disease and Vaccine Research
La Jolla Institute for Immunology

Date/Time:
WEDNESDAY
11 August 2021
11AM-12PM

Registration required.
To register scan QR code or click on ZOOM icon. Please send your enquiry to idtrp@nus.edu.sg.

Abstract

At present, little is known about the evolution of flaviviruses in individuals with prior exposure to related flaviviruses, including the nature of acquired mutations and their impact on virulence and pathogenicity. We sought to address this question by mimicking Zika virus (ZIKV) evolution through the natural transmission cycle; namely, by repeated passaging through cultured mosquito cells and either naïve or dengue virus (DENV)-immune mice. We then determined the impact of the resulting ZIKV sequence mutations on infectivity, transmissibility, and pathogenicity. As the mammalian host, we employed IFN-α/β receptor-deficient (*Ifnar*$^{-/-}$) mice, a well-studied model of flavivirus infection. We identified ZIKV mutations that were induced by passage in either naïve and DENV-immune mice or were selectively induced by exposure to pre-existing DENV immunity. Moreover, we found that single substitutions in the NS2B and E proteins enabled enhanced ZIKV infectivity, transmissibility, and pathogenicity in mosquitoes, naïve *Ifnar*$^{-/-}$ mice, and/or DENV-immune non-pregnant and pregnant *Ifnar*$^{-/-}$ mice. Importantly, we identified naturally occurring ZIKV clinical isolates that harbored the same or homologous mutations, suggesting that our findings have clinical relevance for DENV-immune individuals at risk for ZIKV infection.

Dendritic cells are key targets for flavivirus infection. To identify host pathways manipulated by flaviviruses in dendritic cells, we developed a system that enables characterization of genome-wide transcriptional and epigenetic changes in ZIKV-infected and neighboring, uninfected primary human dendritic cells. ZIKV upregulated a small number of transcripts that are highly enriched for lipid metabolism genes but suppressed inflammatory gene expression. Infection of dendritic cells by ZIKV increased recruitment of sterol regulatory element binding proteins (SREBPs) to lipid gene promoters and increased transcriptional initiation of these genes. Pharmacologic inhibition or gene silencing of SREBP2 suppressed ZIKV infection in dendritic cells. Thus, SREBP2 activation is a major transcriptional mechanism that is utilized by ZIKV to infect human dendritic cells, and can be pharmacologically targeted.

Biography

Dr. Sujan Shresta is an Associate Professor in the Center for Infectious Disease and Vaccine Research at La Jolla Institute for Immunology. Dr. Shresta is an internationally recognized expert on dengue and Zika viruses. Her team developed a variety of mouse models of dengue and Zika infections that mimic epidemiological scenarios, allowing scientists to learn how these viruses spread, how the immune system reacts, and most importantly, to test vaccine and drug candidates that can treat diseases caused by these viruses. Dr. Shresta obtained her B.A. in Biological Sciences from Smith College and Ph.D. in Immunology from Washington University in St. Louis, and completed her post-doctoral training in Virology at the University of California, Berkeley, before joining LJI in 2005.