ANTIBODY-DEPENDENT DENGUE VIRUS INFECTION MODULATES CELL INTRINSIC RESPONSES FOR ENHANCED INFECTION

(1,2) Chan CYY, (3) Gan ES, (3) Ong EZ, (1) Zhang SLX, (1) Tan HC, (4) Chai XR, (4) Ghosh S, (1,5,6) Ooi EE, (1) Chan KR

(1) Emerging Infectious Diseases Program, Duke-NUS Medical School, Singapore
(2) Singapore General Hospital, Department of Infectious Diseases, Singapore
(3) Viral Research & Experimental Medicine Center @ SingHealth / Duke-NUS (ViREMiCS), Singapore
(4) Program in Cardiovascular & Metabolic Disorders and Centre for Computational Biology, Duke-NUS Medical School, Singapore
(5) Department of Microbiology and Immunology, Yong Loo Lin School of Medicine, National University of Singapore, Singapore
(6) Saw Swee Hock School of Public Health, National University of Singapore, Singapore

Aims: Dengue is caused by infection with dengue viruses (DENV), and the risk of severe disease appears to be increased by baseline seropositivity from prior DENV infection. DENV opsonised with non- or sub-neutralising antibodies, through engagement of activating Fc gamma-receptor (FcR) pathways result in enhanced replication compared to entry through canonical receptor-mediated endocytosis in target cells. However, whether the enhanced replication is due to more efficient portal of virus entry or through differential expression of host factors that favours DENV replication remains unclear. The study aims to clarify if the early host responses to DENV infection could be modified by the portal of virus entry.

Methods: Primary human monocytes were infected fluorescent-labelled DENV opsonised with antibody and without antibody. Mock infection and heat-inactivated DENV opsonised with antibody served as experimental controls. To control for the amount of infection, human monocytes that display a specific window of fluorescence intensity were sorted by fluorescence-activated cell sorting. The early global host gene expression profiles of sorted cells were analysed by RNAseq.

Results: Herein, we demonstrated that despite controlling for the amount of infection, cells infected with antibody-opsonised DENV display a transcriptome that is fundamentally different to those infected with DENV only. Specifically, antibody-opsonised DENV infection resulted in enrichment of genes related to RNA splicing, endocytic trafficking and ubiquitination where have previously been shown to be host factors for DENV replication. We also found that this differential gene expression is influenced by, but not exclusively dependent on FcR signalling. Rather, our results showed that host responses to DENV infection depend on the complex and dynamic interplay between viral entry, compartmentalisation, trafficking, and replication.

Conclusion: Collectively, our findings suggest that besides facilitating virus uptake, antibodies can alter viral trafficking and compartmentalisation, which in turn enhances DENV infection in human monocytes by modulating host cellular and immune responses that promote virus survival, replication and egress. Our findings support the notion that host responses to DENV infection needs to be defined in the context of its pathway of infection.