World Academy of Science, Engineering and Technology
International Journal of Medical and Health Sciences
Vol:19, No:04, 2025

Dengue Virus Serotype-specific Inhibition of T Cell Responses Is Due to a Single Amino Acid Polymorphism in the Envelope Protein

Authors : Xiang Jinhua, Mclinden James, Chang Qing, Fosdick Micaela, Ploss Alexander, Bhattarai Nirjal, Houtman Jon, Stapleton Jack

Abstract : Background: Clinical outcomes differ among dengue virus (DENV) serotypes though few serotype-specific differences are identified. We previously found that ZIKV and DENV-2 envelope proteins do not inhibit T cell receptor (TCR) signaling. Here, we investigated the effect of DENV-1-4 infection and env expression on T cell functions. Methods: DENV-1 though 4 were added to PBMCs or Jurkat T cells prior to TCR stimulation. Signaling was measured by IL-2 release. The effect of DENV env (1-4) expression in primary and Jurkat T cells on TCR was measured. DENV env regions required for TCR inhibition were mapped by chimera, deletions, and point mutagenesis. Results were confirmed by reverse genetics using replication competent DENV generated by CPER. Results: DENV-1-4 caused abortive infection in T cells, yet DENV-1 and -4 inhibited TCR signaling measured by IL-2 release in primary and transformed T cells while DENV-2 and -3 did not. This was not due to differences in binding, entry or RNA production. DENV-1 and -4 env expression in Jurkat or exposure in primary T cells recapitulated TCR inhibition. The Env sequences in volved were mapped and mutation of Env a.a V55 to the T present in DENV-2 and -3 abolished TCR inhibition in replicating viruses. Substituting the DENV-1 55V into DENV 2, 3 led to partial TCR inhibition; however, addition T66S into the V55T DENV-2 and -3 rescued the TCR inhibition found in DENV-1 and -4. Preliminary data suggest that the envelope substitutions may reduce replication kinetics in different mammalian or insect cells, and this is under further study. Conclusions: Epidemiological data suggest that DENV 2 and 3 are more often associated with severe dengue including hemorrhagic fever and shock. Since DENV-1 and -4 interfere with TCR, it is possible that this TCR effect blunts host immunologic responses during infection, mitigating immune-mediated pathogenic effects of DENV. Recombinant viruses demonstrate that DENV1 V55T substitution is sufficient to remove the TCR inhibitory phenotype, and that changing DENV-2, -3 aa 55 and 66 to that seen in DENV-1 mimics TCR inhibition observed in DENV-1 and -4. These findings may provide an approach to safer live-attenuated DENV vaccines.

Keywords : dengue Viruses, TCR signaling, CPER, dengue viral envelope protein
Conference Title : ICVID 2025 : International Conference on Virology and Infectious Diseases
Conference Location : Chengdu, China
Conference Dates : April 10-11, 2025