ESTABLISHMENT OF HUMANIZED MICE MODEL FOR THE STUDY OF DENGUE VIRUS INFECTION AND PATHOGENESIS

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Dengue viruses (DENV) are the most important arboviral pathogens in tropical and subtropical regions throughout the world. The four serotypes of DENV are transmitted among humans by Aedes sp. mosquitoes, causing approximately 100 million infections annually leading to dengue fever (DF), and up to 500,000 cases of dengue hemorrhagic fever (DHF). A major limitation in dengue research is the lack of a small animal model that recapitulates human disease and viremia; thus, it has been a challenge to elucidate the intrinsic viral and host elements that are responsible for progression to severe dengue (DEN) disease. The objective of this work was to evaluate dengue virus infection in a humanized mouse model through natural and experimental routes of infection. Our research group has established a humanized mouse model using human fetal liver and thymus transplantation and human skin grafted onto NOD-scid IL-12Rgamma null mice, followed by human CD34+ cells injection. These mice were infected with a virulent DENV2 strain by different routes of infection. Mice were bled at several time points to assess viremia and tissues were collected to detect the presence of virus antigens. Also, the level of human reconstitution was assessed using PBMCs and lymphoid tissues harvested from each mouse. Our results showed various levels of human reconstituted cells in blood, spleen and lymph nodes. Although virus antigens were detected in the liver and kidney of animals inoculated intravenously, no viremia/virus replication was detected in mice inoculated through the different routes of infection. Taking together, our results suggest that host factors maybe involved in the susceptibility to DENV infection.