Venezuelan equine encephalitis virus (VEEV) is an emerging infectious agent and a CDC category B priority pathogen. VEEV has caused periodic outbreaks involving several hundred thousands of equine and human cases. VEEV may also cause severe to fatal encephalitic disease in young and old subjects with underdeveloped or weak immune system. Inflammation in brain following VEEV infection is multifocal and believed to play a key role in the pathogenesis of VEEV. However, the underlying molecular mechanisms of VEEV encephalitis are poorly understood.

Molecular characterization of VEEV encephalitis and its kinetics were evaluated by gene expression profiling of VEEV infected mice brain using whole genome and pathway specific toll-like receptors (TLR) and extracellular matrix and adhesion molecule gene microarrays. Localized expression of translation products was evaluated by immunohistochemistry in the brain tissues.

VEEV infection of mice brain resulted in the differential modulation of several immune pathways such as antigen presentation, inflammation, apoptosis and response to virus. Specifically, VEEV infection up regulated Toll like receptor signaling pathways components and revealed a MyD88 biased TLR signaling. Comparative host gene expression analysis of mice infected with either neuroinvasive or non-neuroinvasive strains of VEEV identified signaling pathways specific to neurovirulent VEEV infection. A gene expression signature that was common to both the neuroinvasive and non-neuroinvasive strain of VEEV was also identified.

Cell to cell adhesion molecules and extracellular matrix protein genes such as ICAM-1, VCAM-1 and MMPs were also differentially regulated in the mouse brain after VEEV infection. Studies in ICAM1 knockout mice infected with VEEV demonstrated a delay in initiation of disease accompanied with reduced inflammation in the brain early in the infection. A twenty percent reduction in the mortality following VEEV infection was also observed in ICAM-1 knockout mice.

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anuj.sharma@usuhs.edu