COMBATTING FUTURE BIOLOGICAL THREATS – HOST-DIRECTED INTERVENTIONS TO EMERGING THREATS FOR RAPID RESPONSE

Characterization Of Neurological Sequelae Induced By Venezuelan Equine Encephalitis Virus

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Venezuelan equine encephalitis virus (VEEV) is a neuroinvasive virus which can be transmitted via aerosol or bite of an infected mosquito. VEEV infections in humans result in a relatively low mortality rate (<1%); however, the progression to neurological deficits is significant with <14% of cases progressing to neurological signs with a higher incidence in children, elderly, and immune compromised people. Chronic manifestations of VEEV in animal models are relatively poorly understood, but some animal models display similar neurological deficits to human infections including seizure, behavioral, and emotional changes. Unfortunately, there are currently no publicly available antiviral treatments for VEEV, or neuroprotective drugs to combat the long-term neurological deficits, which result in significant population health problems, increased health costs, and negative impacts on civilian and military personnel worldwide. To this end, we characterize the pathology, behavior, and transcriptomic changes caused by VEEV infection in C57BL/6 mice. Mice were intranasally infected with a sublethal dose of VEEV TC-83 (~80% survival), weighed, and monitored for clinical scores for 90 days post infection. By Day 9, 65% of mice displayed signs of neurological illness including circling, head tilt, head pressing, and altered gait or imbalance. Interestingly, mice which displayed neurological signs in the acute phase of infection have significantly more weight loss and slower recovery in comparison to mice without neurological signs. At both acute (Day 2 and 7), and chronic (Day 90) days post-infection (DPI), mice were sacrificed to look at pathology as well as immunohistochemistry analysis (IHC) for neuronal and microglia activation. At 7 DPI, VEEV infected mice displayed decreased NeuN staining in the dentate gyrus of the hippocampus indicating reduced hilar interneuron levels. VEEV infected mice also had reduced expression of total Reelin and Reelin-expressing interneurons at 7dpi compared to mock controls. At 30, 60, and 90 DPI the behavior of the mice was assessed via Novel object Recognition and Y-Maze (memory), Elevated Plus maze (anxiety), and a modified SHIRPA (neuromuscular). Mice appear to have hyperexcitability, anxiety, and memory changes at 60 and 90 DPI with few signs of neurological disease at 30 DPI. Finally, we performed single-cell RNA sequencing to identify potential drug targets. Transcriptomic analysis highlighted neuroinflammation, driven by proinflammatory markers IL-6 and TNF, as well as other potential drug targets such as apoptosis/TP53 activation, and Focal Adhesion Kinase (FAK) which may mediate neurological damage caused by VEEV. Ongoing experiments are designed to evaluate drug efficacy and target specificity in vitro and in vivo against VEEV infection with future potential evaluation against other neuropathologies.

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