BMC Proceedings

BioMed Central

Oral presentation

Dengue neurovirulence in mice: identification of molecular signatures in the E and NS3 helicase domains

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from Infectious diseases of the nervous system: pathogenesis and worldwide impact
Paris, France. 10–13 September 2008

Published: 23 September 2008

BMC Proceedings 2008, **2**(Suppl 1):S39

This abstract is available from: http://www.biomedcentral.com/1753-6561/2/S1/S39

Dengue virus (DV), a member of the *Flavivirus* genus (family *Flaviviridae*), is an arthropod-borne, which cause severe disease in humans. The spectrum of illness ranges from a self-limiting fever (DF) to severe hemorrhagic (DHF), which can progress to dengue shock syndrome (DSS) and death. However, recent observations indicate that the clinical profile of DV infection is changing and that neurological manifestations are becoming frequent. The neuro-pathogenesis of dengue and the contribution of viral and host factors to the disease are not well understood. To better understand dengue neuropathology and to map putative molecular markers of neurovirulence in mice we used a murine model of dengue encephalitis to adapt a human isolate of DENV-1 virus strain FGA/89 by serial passage in mouse brains. A new neuroadapted variant (FGA/NA P6) was generated and characterized in vivo and the amino acid substitutions in the viral genome detected during the process were mapped and compared with other neurovirulent DENV-1 strains previously obtained (FGA/NA a5c). Only three amino acid substitutions were identified in the neurovirulent strains, in comparison with the parental strain, mapping in the envelope E protein and nonstructural NS3 helicase domain. These mutations enhanced the ability of neuroadapted viral strains to replicate and to produce virus particle in the CNS of infected mice, causing irreversible damage in CNS cells with extensive leptomeningitis and encephalitis. These mutations had been inserted in an infectious clone and the viral phenotypes are being evaluated in vitro and in vivo. The characterization of substitutions in the viral genome of neurovirulent strains can be useful as potential biomarkers, and may be used to elucidate novel mechanisms behind the neuropathology of dengue infection.

Financial support
CNPq/Fiocruz/Fundação Araucária e Fundo Paraná.