



V 2 Pathogenesis of neurotropic flaviviruses and its control using modern approaches

Alexander G. Pletnev

Laboratory of Infectious Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland, USA

Two diverse properties characterize the neuropathogenesis of tick-borne encephalitis viruses (TBEV): neuroinvasiveness and neurovirulence. To elucidate the mechanisms of TBEV neuroinvasiveness, we tracked sites of virus replication, spread, and invasion into CNS of mice infected with Langkat virus (LGT) using immunohistochemistry, histopathology, and virology. Initially, LGT replicated in draining lymph nodes and spleen, then spread into nasopharynx and digestive tract, and utilized the axonal transport via olfactory and peripheral nerves to access brain and spinal cord. Multifocal, widely dispersed LGT infection observed in the brain suggests that viral invasion also occurs by a hematogenous route. In the CNS, neurons are the principle targets of LGT or chimeric TBEV/dengue virus (TBEV/DEN4) that contains structural protein genes of highly virulent TBEV. We developed computerized image analysis to quantitatively assess the inflammatory response and neurodegeneration in the CNS of monkeys infected with neurotropic flaviviruses. We found that the kinetics, spatial pattern and magnitude of microglial activation, trafficking of T and B cells, and changes in T-cell subsets within the CNS define a unique phenotypic signature of virus. Balanced T and B cell response within the CNS likely plays an important role in recovery from viral infection.

Modern DNA technology and discovery of microRNAs, which regulate expression of cellular genes, have enabled a novel strategy to control virus pathogenesis. We explored the ability of microRNAs expressed in the CNS to restrict the TBEV/DEN4 neurotropism. Inclusion into the viral genome of a single target copy for brain-expressed microRNAs prevents the development of otherwise lethal encephalitis in mice. Viruses bearing microRNA targets were highly restricted in replication in primary neurons, had limited access into the CNS of immunodeficient mice, and induced a strong immune response in monkeys. This work suggests that microRNA-targeting to control flavivirus pathogenesis might represent a rational approach for virus attenuation and vaccine development.