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ウイルス誘導性てんかん動物モデルと免疫系

Immune system and Theiler's virus-induced animal model for seizures/epilepsy

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【Objectives】Seizures/epilepsy have been linked to microbial infections, particularly viral infections in the central nervous system (CNS). In theory, virus infections can induce seizures either by direct virus infection of neurons in the CNS (viral pathology) or immune-mediated damage (immunopathology). To clarify the pathophysiology of virus-induced seizures/epilepsy, we have established an animal model for seizures by an experimental viral infection.

【Materials and Methods】Theiler's murine encephalomyelitis virus (TMEV) is a positive-sense single-stranded RNA virus that belongs to the genus *Cardiovirus*, family *Picornaviridae* and has been used as a murine model for virus-induced seizures/epilepsy, whose susceptibility depends on mouse strains. When susceptible C57BL/6 (B6) mice are infected with TMEV, the mice develop acute seizures and progressive hippocampal sclerosis, leading to epilepsy, although the mice can clear the virus from the CNS. In contrast, TMEV has been used as animal models for multiple sclerosis in SJL/J mice with persistent virus infection and for myocarditis in C3H mice; SJL/mice are resistant and C3H mice are intermediate susceptible to TMEV-induced seizures.

【Results and Discussion】In TMEV-infected B6 mice, seizures are observed as early as on day 3 and peaked on day 6 after intracerebral viral inoculation. TMEV infects neurons of the pyramidal cell layer in the hippocampus and induces apoptosis, the extent of which is associated with seizure incidence. In addition, innate immune responses, but not acquired immune responses, seem to contribute to seizures, as the number of infiltrating macrophages, but not lymphocytes are associated with seizures. Among molecules in the innate immune system, interleukin (IL)-6, tumor necrosis factor-α and complement component 3 have been suggested to contribute to the development of seizures, but other factors, including polymorphonuclear cells, natural killer cells, natural killer T (NKT) cells, IL-1, MyD88 or toll-like receptor (TLR) 4, are not associated with seizures. During the chronic phase, 2-7 months after infection, TMEV-infected B6 mice develop spontaneous epileptic seizures

with hippocampal atrophy.

【Conclusions】 Although further studies are required to clarify the pathomechanism of the TMEV-induced seizure model, this model is a rare viral model for seizures/epilepsy that is useful in the field of epilepsy research.