学位論文内容の要旨
Abstract of the dissertation

博士の専攻分野の名称：博士（獣医学）　　氏名：平野　港
Name

学位論文題名
The title of the doctoral dissertation

Studies on the replication and pathogenic mechanisms of tick-borne encephalitis virus in neuron

（ダニ媒介性脳炎ウイルスの神経細胞における複製および病原性発現機序の研究）

Flavivirus is a genus in the family *Flaviviridae*, and consists of positive-polarity single-strand RNA viruses. The genus *Flavivirus* contains many arthropod-borne human pathogens, such as West Nile virus, Japanese encephalitis virus, dengue virus and tick-borne encephalitis virus (TBEV). Many outbreaks have been reported, and flaviviruses are attracting global attention as emerging or re-emerging infectious diseases. Among symptoms caused by infection of flaviviruses, a neurological disease caused by TBEV is severe and is associated with high levels of mortality. However, detailed mechanisms of viral replication in the central nervous system and features of viral pathogenesis remain poorly understood. In this study, I tried to investigate the mechanism of viral replication and pathogenicity of TBEV in neuron.

In chapter I of this thesis, the neuronal replication of encephalitic flaviviruses, West Nile virus, Japanese encephalitis virus and TBEV, was analyzed by using a primary culture of mouse neuronal cells. The distribution of viral-specific antigen in the neurons varied: TBEV infection induced accumulation of viral antigen in the neuronal dendrites to a greater extent than infection with other viruses. Viral structural proteins, non-structural proteins

and double-stranded RNAs were detected in regions in which viral antigens accumulated in dendrites after TBEV replication. Replication of a TBEV replicon after infection with virus-like particles of TBEV also induced antigen accumulation, indicating that accumulated viral antigen was the result of viral RNA replication. TBEV replication induced characteristic ultrastructural membrane alterations in the dendrites. This is the first report describing viral replication in the neuronal dendrites, which may cause neuronal dysfunction by the viral infection.

To replicate within dendrites of the neurons, viral genomic RNA must be transported from the cell body to the dendrites. In chapter II of this thesis, I tried to analyze a molecular mechanism of the transport. I identified specific sequences of the 5′ untranslated region of TBEV genomic RNA that act as a *cis*-acting element for genomic RNA transport. Mutated TBEV with impaired RNA transport in dendrites caused a reduction in neurological symptoms in infected mice. I showed that neuronal granules, which regulate the transport and local translation of dendritic mRNAs, are involved in TBEV genomic RNA transport. TBEV genomic RNA bound a RNA-binding protein of neuronal granules and disturbed the transport of dendritic mRNAs. This is the first report of a neuropathogenic virus hijacking the neuronal granule system for the transport of viral genomic RNA in dendrites, resulting in severe neurological disease.

These studies demonstrate the unique mechanisms of replication of TBEV in neuron. These findings encourage further work aimed at understanding the molecular mechanisms of viral replication in the brain and the pathogenicity of neurotropic viruses. And, these findings of this unique virus–host interaction will also promote the study of neurodegenerative diseases caused by disruption of dendritic mRNA transport and the development of their treatment.

（記載例　Example）

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Studies on the ・・・・・・
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