



# HOKKAIDO UNIVERSITY

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Studies on the cellular responses of duck cells to Duck Tembusu virus and Japanese encephalitis virus infection and the effect of minocycline on Duck Tembusu virus-infected neurons

アヒルテンブスウイルスおよび日本脳炎ウイルス感染に対するアヒル細胞の応答ならびにアヒルテンブスウイルス感染神経細胞に対するミノサイクリンの効果に関する研究

DTMUV and JEV are a member of mosquito-borne flavivirus. Similar to other neurotropic flaviviruses, DTMUV causes severe neurological signs in several birds. Birds also serve as reservoir and amplifier hosts for JEV. In contrast to DTMUV, JEV-infected birds do not show a noticeable clinical sign. Factors responsible for the difference in neuropathogenicity between DTMUV and JEV infection have not been investigated yet. Due to the limitation of avian neuronal cell culture model, mechanisms of virus-induced neuronal cell death as well as neuron-specific innate immune responses in DTMUV- and JEV-infected birds have not been well-investigated. Therefore, the purpose of this study was to examine the difference in neuropathogenicity between DTMUV and JEV infection using primary cultured duck neurons (DNs). For the development of possible anti-DTMUV treatment, the efficacy of minocycline treatment in DTMUV-infected DNs was also

analyzed.

**In Chapter I**, the responses of DNs and duck fibroblasts (DFs) to DTMUV and JEV infection, particularly on apoptosis and innate immune responses, were investigated. Both DNs and DFs were susceptible to DTMUV and JEV infection and replication. DTMUV induced higher degree of caspase-3-dependent apoptosis in DNs and DFs than JEV did. Moreover, DTMUV infection induced stronger mRNA expression of various innate immune-related genes in DNs and DFs than JEV infection. Nevertheless, higher levels of innate immune gene expression presented in DTMUV-infected DNs and DFs did not result in the suppression of viral replication and cell death. The difference in the level of neuronal apoptosis between DTMUV and JEV infection might be involved in the difference of neuropathogenicity of these viruses in birds. This comparative study provided basic information for understanding the mechanisms of neuropathogenesis in DTMUV and JEV in birds. Also, DNs established in the recent study will be a valuable and reproducible model for investigating the mechanisms of various events occur in the neuron of birds infected with DTMUV and JEV.

**In Chapter II**, the neuroprotective effects of minocycline on DTMUV-infected DNs were investigated because of no approved vaccines and effective therapeutics for DTMUV infection. Several studies reported that minocycline had anti-apoptotic and anti-inflammatory properties. It has been widely used for treating neurological diseases including viral encephalitis. Minocycline protected DNs from cell death triggered by DTMUV infection; however, it did not suppress DTMUV replication in treated DNs. These

results present that minocycline exhibits neuroprotective function against DTMUV infection via the inhibition of apoptosis rather than the inhibition of viral replication.

These studies provide insight on cell death mechanisms and innate immune responses to DTMUV and JEV infection in ducks, and further demonstrate the neuroprotective effects of minocycline on DTMUV infection. Minocycline seems to be a candidate drug for DTMUV treatment in birds.