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

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学位論文題名
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Identification and functional analysis of disease-associated microglia in West Nile virus-infected mice
(ウエストナイルウイルス感染マウスにおける疾病関連ミクログリアの同定と機能解析)

West Nile virus (WNV) is a mosquito-borne flavivirus that has emerged as a significant cause of viral encephalitis worldwide. Despite its threat to public health, there are still no specific treatments or human approved vaccines for WNV infection, because the detailed mechanisms of its pathogenesis are not fully understood. Microglia are the resident immune cells of the central nervous system and play a crucial role in the early defense against viral infections, including WNV. However, their functions and responses during WNV infection are not yet fully understood. A deeper understanding of microglia responses is essential to advance the development of microglia-targeted therapeutic strategies for viral encephalitis.

In this study, the diversity of microglia phenotypes was examined from WNV-infected mice through the expression analysis of different microglia markers, including general marker such as ionized calcium-binding adapter molecule 1 (Iba1), purinergic receptor P2Y12 (P2RY12), or transmembrane protein 119 (TMEM119). A variety of activated microglia phenotypes were identified in WNV-infected mice. Among these, disease-associated microglia (DAM), positive for integrin alpha X (CD11c), and weakly positive for TMEM119, were frequently observed near WNV-infected cells. In addition, DAM were increased in WNV infection which may be related to the pathogenesis of WNV infection.

The function of DAM was further investigated by the induction method. Ligands of the Colony stimulating factor-1 receptor (CSF1R), namely colony-stimulating factor-1 (CSF-1) and interleukin-34 (IL-34), were used to induce DAM. Only IL-34 treatment significantly reduced mortality rate, viral titers, and number of neuronal apoptosis in mice

infected with WNV. Furthermore, IL-34 treatment increased the number of CD11c-positive microglia with reduced TMEM119 expression, which were located near WNV-infected cells in the brains of infected mice. Therefore, IL-34 may promote the induction of DAM and contribute to neuroprotection in WNV infection.

These findings indicate that DAM were observed in WNV infection and may contribute to a protective response. Furthermore, IL-34 known as a potential immunomodulatory factor promotes the induction of DAM during WNV infection. Continued research in this field may help fill the current knowledge gap and support the development of microglia-targeted therapeutic strategies for viral encephalitis.