The neuropathogenicity of the Saffold virus in mouse models

Abstract of Doctoral Thesis

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Saffold virus (SAFV) has been isolated and/or detected in patients with diarrhea and upper respiratory tract inflammation worldwide. In addition, SAFV is occasionally detected in patients with non-polio acute flaccid paralysis, cerebellitis, and aseptic meningitis, suggesting that SAFV is possibly neurovirulent. Therefore, to elucidate the neuropathogenesis of SAFV, the pathogenicity of SAFV type 3 (SAFV-3) was determined in a mouse model.

Before establishing a method for the pathological diagnosis of SAFV infection, the polyclonal antibody raised against SAFV-3 had to be tested for the effective detection of viral antigens in paraffin-embedded tissues. The antibody only recognized SAFV antigens and did not cross-react with enteroviruses, which are a major cause of aseptic meningitis. Thus, the antibody is useful for the differential diagnosis between SAFV and enteroviruses.

Next, to elucidate the neuropathogenesis of SAFV, the pathogenesis of two clinical isolates of SAFV-3 were analyzed pathologically, virologically, and immunologically in mice. Two clinical isolates of SAFV-3, one from a patient with aseptic meningitis and the other from a patient with acute upper respiratory inflammation, were used for this study. Both clinical isolates infected glial cells in the ventricle and cerebellum, and had mild neurovirulence and neuroinvasiveness in the mouse models. However, in neonatal mice, the two isolates had different neurovirulence and tropism to epithelia.

I focused on the tropism of SAFV to the cerebellum by creating a mouse-passaged SAFV-3 strain *in vivo*. After five passages in the cerebellum

of neonatal mice, the passaged strain had higher neurovirulence and infectivity of the ventricle and cerebellum, compared to those of the original strain. Intracerebral inoculation with a high viral load of the passaged strain caused cerebellar hypoplasia in neonatal mice.

In conclusion, this study elucidated the neuropathogenesis of SAFV-3 in mice at three levels: virologically, histopathologically, and immunologically. The results reveal that SAFV-3 is a potential neurotropic pathogen. In addition, this mouse model is useful for studying the mechanisms controlling the severity of SAFV infection, for identifying antiviral factors, and for developing novel vaccines.