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

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Pathological studies on hantavirus using hemorrhagic fever with　renal syndrome mouse model and development of a novel serodiagnosis method for shrew-borne hantaviruses

(腎症候性出血熱マウスモデルを用いたハンタウイルスの病原性解析及び新規トガリネズミ由来ハンタウイルスの血清診断法開発)

HFRS is a zoonotic disease caused by several hantaviruses. It encompasses several diseases, such as Korean hemorrhagic fever (KHF), nephropathia epidemica, and epidemic hemorrhagic fever. HFRS has become a major epidemic problem in Asian and European countries, but pathological studies are lacking due to the lack of animal models. As rodents are the natural hosts of hantaviruses, the inoculation of Hantaan virus to immunocompetent laboratory rodents causes no symptomatic infection. However, Shimizu *et al*, 2017 reported that laboratory mice inoculated with Hantaan virus strain KHF showed renal hemorrhage. In this study, two KHF viruses were used to analyze hantavirus pathogenesis, the virulent strain KHF5, and the avirulent variant KHF4, which have a single amino acid alteration in envelope glycoprotein at 417 from E to K. By comparing the characterization of the two strains in vitro and in vivo, hantavirus pathogenesis was investigated.

The avirulent strain KHF4 showed higher viral antigen accumulation in cells but lower virus titer in culture supernatant. Epitope profiling with monoclonal antibodies, cell fusion assay, and pseudotype virus production found no significant difference between the characteristics of two glycoproteins. In vivo analysis showed higher and earlier virus production in KHF5 inoculated mice lung tissue, which may cause severe pneumonia and edema. Interestingly, KHF5 showed lower infectivity to cultivated lung tissue, suggesting that KHF5 only targets the lungs in vivo. KHF5 inoculation caused hepatitis and renal hemorrhage; monocyte infiltration and neutrophil activation were found in the lungs and liver together with viral antigens. Shimizu *et al*.　previously reported that CD8+ T cells are important for development of renal hemorrhage. In this study, increased transcription indicating CD8+ T-cell activation was detected in the liver. These data suggest that the immune response plays an essential role in pathogenesis in KHF5 infected mice. However, to support the hypothesis of cytokine storms combined in HFRS, more evidence is required. In this

HFRS model, massive replication of KHF5 virus in the lungs in the early phase seems essential for pneumonia, severe hepatitis, and renal hemorrhage.

Chronic kidney disease with unknown etiology (CKDu) has become a public health problem in the past three decades in Sri Lanka. Since 50% of patients with CKDu were seropositive for Thailand orthohantavirus, rodent-borne hantavirus infection was considered to be a risk factor for CKDu. However, shrew-borne hantavirus infectivity to humans has not been examined. Serological detection methods were established for Asama, Thottapalayam, Alatai, and Seewis viruses and a total of 375 samples from the CKDu endemic area were screened. One Alatai virus seropositive result was detected from a patient with CKDu as well as two Thottapaayam virus seropositives from a healthy control group, however, the relationship between the seroprevalence of shrew-borne hantaviruses and CKDu was not shown. More investigation is needed from various perspectives to solve this problem.