



Title	Analysis of immune response and pathogenesis in mice infected with hantavirus
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other countries. Furthermore, virus isolations were conducted from ticks and rodents in the study area.

Results are summarized as follows.

1. Oshima-5-10 showed high degree of identity with Russian spring summer encephalitis (RSSE) virus strain Sofjin; 95.7% in nucleotide sequence and 99.0% in amino acid. Phylogenetic analysis identified Oshima-5-10 as RSSE type virus.

2. Two virus strains were isolated from 600 *I. ovatus* ticks collected in April and May, 1996. The minimum field infection rate of *I. ovatus* was calculated as 0.33%(2/600).

3. Virus strains were isolated from *A. speciosus* trapped in 1995 and *C. rufocanus* trapped in 1996.

4. Virus isolates from *I. ovatus*, *A. speciosus* and *C. rufocanus*, were identified as TBE virus by indirect immunofluorescent antibody test using monoclonal antibodies. Furthermore, these virus isolates were identified as RSSE type virus by phylogenetic analysis of the E protein genes of each isolates.

5. The sequence size of 3'-noncoding region (3'NCR) of Oshima-5-10 was different from RSSE virus strain Sofjin.

Analysis of immune response and pathogenesis in mice infected with hantavirus

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Hantavirus is maintained various murine groups as a reservoir in the nature, and humans become hantavirus infection by contacting with the infected animal. A part of the infected animals holds a virus for a long time, and becomes the persistently infected animals which excrete the virus in the discharges. Therefore, these persistently infected animals is very important as not only the maintenance of the virus in the murine groups, but also the animals which transmit this virus to humans. However, all infected animals doesn't become persistent infection, and it seems that various factors is related to establish the persistent infection of this virus. So in this thesis, two viral strains which differ from pathogenesis were inoculated to the suckling mice and the adult mice, and it was examined how influence the establish of the persistent infection by a degree of maturity of the immune system

and a difference in the viral strains. Further, the preparation of the antigen presentation cell was tried for the measurement of cytotoxic activity to viral antigen.

The results were summarized as follows.

1. In the inoculated adult BALB/c mice, the virus wasn't detected in 4 and 8 weeks after infection and then it seems that the virus was excluded from mice. On the other hand, in the inoculated suckling BALB/c mice, the virus was detected until 8 weeks after infection. These result showed that suckling BALB/c mice inoculated with hantavirus was the model of persistent infection.

2. In the inoculated both suckling mice and adult mice, maximum level of IgG and neutralizing antibody was detected in 4 to 8 weeks after infection, and kept until 12 weeks after infection. On the other hand, IgM antibody was detected in

4 and 8 weeks after infection in the inoculated suckling mice, but in only 4 weeks after infection in the inoculated adult mice. The detection period of the IgM antibody by both mice may be different because the suckling mice were caused persistent infection by the virus and were continuously stimulated by viral antigens.

3. Con A responses of splenic cells from the suckling BALB/c mice which persistently infected confidently reduced as compared with uninfected BALB/c mice. In contrast, Con A responses of splenic cells from the adult mice which transiently infected were similar to uninfected BALB/c mice. These results indicated that cellular immune response was important to eliminate hantavirus

from mice.

4. P388D1 cells which were inoculated hantavirus by antidody-dependent enhancement were infectious rate of only 1 to 2% at first, but until 12 days post inoculation viral antigens were able to detected almost 100% of cells. Further, these cells could be cultured for a long time. Then, P388D1 cells inoculated hantavirus may be useful to measure the cytotoxic activity to viral antigen.

5. Nucleocapsid protein gene of hantavirus inserted into eukaryotic expression vector was transfected to P815 cell. As a result, mRNA of Nucleocapsid protein was detected in some of clone.

Apoptosis and intracellular signal transduction induced in X-irradiated MOLT-4 cells

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Ionizing radiation is widely utilized for a tumor therapy. Recently, it has been reported that ionizing radiation as well as Fas-antigen, NGF, anticancer drug, UV and reactive oxygen species induce apoptotic cell death in various tumor cells. The signal transduction leading to apoptosis was wellknown to be related to the *p53* tumor suppressor gene. However, many tumors have been reported to exhibit unfunctional *p53* mutations. Therefore, considering the radiation treatment of *p53*-independent tumors, it is important to study the mechanism of radiation-induced *p53*-independent apoptosis. This study was performed to clarify the relationship between the activation of *p53*-independent signal pathway (the increase of intracellular calcium ion $[Ca^{2+}]_i$, the activation of stress-activated protein kinase/

c-Jun N-terminal kinase (SAPK/JNK) and interleukin-1 β -converting enzyme (caspase)) and apoptosis in X-irradiated human leukemia cell line, MOLT-4.

First, to check whether *p53* accumulated in X-irradiated MOLT-4 was functional, the cell-cycle distribution of MOLT-4 was examined after X irradiation by flowcytometry. No *p53*-dependent G_1 arrest was observed after X irradiation, but G_2 arrest and sub- G_1 fraction showing apoptosis were detected. This result indicated that *p53* induced in X-irradiated MOLT-4 cells failed to function well, and, therefore, X-ray-induced apoptosis occurred by the *p53*-independent manner. As a *p53*-independent pathway to apoptosis, the ceramide-SAPK/JNK-caspase pathway has been shown in the NGF- or