□대한내과학회 연구비 결과보고□

Expression of ICAM-1 and VCAM-1 on the Hantaan Virus Infected Human Umbilical Vein Endothelial Cells

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Hantavirus and related viruses are the causative agents of Hemorrhagic Fever with Renal Syndrome and Hantavirus Pulmonary Syndrome(HFRS/HPS). Despite of extensive studies on etiologic virus and epidemiology, there is no consensus on the pathogenesis of HFRS and HPS. In HFRS/HPS, the major manifestations depend on the vascular change. The change might be the result of the infection of endothelial cells with Hantaan virus, but it is not known to what extent changes in endothelial function are from virus infection or from immune response to virus infection.

Clinically, there is a various degree of disseminated intravascular coagulation (DIC) which was evident in the early phase of illness. We had reported the possible role of the endotheial cells in the development of HFRS. We were able to localize viral antigens in the endothelial cells and demonstrated the changes of anti-coagulant characteristics of endothelial cell membrane after Hantaan virus infection.

We believed that the vascular endothelial cells would express various kinds of adhesion molecules when they got infected with Hantaan virus and these molecules would play a key role in the establishment of inflammatory lesions in HFRS.

This study investigated the role of adhesion molecule in pathogenesis of Hantaan virus related disease. The expression of ICAM-1 antigen on the cell membrane of human umbilical vein endothelial cells (HUVECs) was assessed by immunohistochemistry and ICAM-1 mRNA in the endothelial cells was assessed by in situ hybridization after Hantaan virus infection

We used the virus stock of which the infectivity was calculated as usual and it was 2.6×10^4 PFU/ mL by the classical plaque assay.

By the immunohistochemistry against Hantaan antigen, we could not find any positive cells when we had inoculated radiation sterilized virus solution.

With Hantaan virus inoculation, we could find small number of scattered positive cells through the cell layer after 12 hours. After 24 hours the positive islands against Hantaan antigen increased in number and started to distribute all over the monolayer. Three days after inoculation, the positive cells increased markedly in their number and distribution. On day 7, almost all cells were demonstrated to have Hantaan antigen by immunohistochmestry.

Hantaan virus inoculation expressed ICAM-1 antigen after 6 hour and ICAM-1 expression increased with time. ICAM-1 antigen expressed high between 12 hours and 24 hours of postinoculation. The percentage of positive cells is between 5% and 10%. After day 1, the expression decreased abruptly and barely seen in day 4.

When Hantaan virus was inoculated, we could observe positive reaction after 2 hours which increased in intensity and extent along the course by in situ hybridization. The positive reaction was evident between day 1 and day 2 and tended to decrease.

In conclusion, the human umbilical vein cells (HUVECs) infected with Hantaan virus express specific adhesion molecules for circulating inflammatory mononuclear cells, and the expression may contribute organ specific inflammatory processes including kidney, heart and CNS in HFRS.