Elucidation of the pathogenesis and development of diagnostic methods of Flavivirus infection

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Control of flavivirus is an important issue in livestock and public health, because many viruses cause zoonotic diseases such as encephalitis and hemorrhagic fever in animals. Establishment of specific treatment, vaccine prevention, diagnostic method, and epidemiological studies to identify endemic areas are essential for controlling viral infection. In this study, I attempted to elucidate the mechanism of pathogenesis by producing virus-like particles (VLPs) and recombinant flaviviruses using viral gene modification technology of flavivirus, and to accumulate knowledge that lead to the development specific treatment, as well as to development of novel diagnostic and prevention methods.

The viral genome of flaviviruses encodes three structural proteins [capsid (C), pre-membrane (prM), and envelope (E)] and seven non-structural proteins. Expression of structural proteins and a subgenomic replicon that expressed the nonstructural proteins and reporter protein resulted in the production of infectious VLPs. The VLPs are unable to produce progeny particles because of lack of structural protein coding region but can infect cells as same as authentic virus particles. Examination of the production of VLPs in cells suppressed factors required for flavivirus replication indicated that intracellular vesicular trafficking and protein quality control systems such as autophagy and endoplasmic reticulum-associated degradation affected flavivirus replication[1].

Then, I established the technology to produce the recombinant flavivirus using homologous recombination in mammalian cells, and investigated the viral and host factors related to the pathogenesis of encephalitis. I found that the C protein of West Nile virus, belongs to flavivirus, bound to AMP-activated protein kinase (AMPK), one of the autophagy-inducing factors, and promoted AMPK degradation by ubiquitin-proteasome system, thereby suppressing the induction of autophagy and inducing the pathogenesis of encephalitis[2].

Establishment of virus-specific diagnostic methods is difficult because of cross-reactivity among genetically closely related flavivirus. Focusing on the antigenicity of viral particles consisting of only flavivirus prM and E proteins are almost same as authentic particles, an ELISA system that can distinguish closely related viruses were constructed. The constructed ELISA showed high specificity and were distinguishable from closely related flaviviruses, indicating that it is useful for identifying areas contaminated by flaviviruses and diagnosis for animals[3].

The results obtained in this study using viral gene modification technology will lead to form the basis of control of flavivirus infection in animals and humans, leading to develop treatment, prevention method, and diagnostic method.

References

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