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The valosin-containing protein is implicated in West Nile virus replication and an examination of the pathogenicity of novel WNV strain isolated in Zambia

(ウエストナイルウイルスの複製に関与するバロシン含有タンパク質に関する研究と

ザンビアで単離されたウエストナイルウイルスの病原性の検索)

West Nile virus (WNV) is a zoonotic pathogen can cause West Nile virus fever and encephalitis in human and several kinds of mammals such as horses and dogs. WNV belongs to the genus *Flavivirus* in the family *Flaviviridae*, and has approximately 11 kb of positive sense single-stranded genomic RNA. The genomic RNA of WNV encodes ten proteins, including three structural proteins and seven non-structural proteins. This virus is transmitted by mosquito bite, especially *Culex* spp., and widely spread to many countries. Wild birds play an important role as a primary vertebrate reservoir of WNV.

WNV was firstly isolated in 1937, the virus has been continuing a problem in public health in both developed and developing countries. In 1999, at New York, United States of America (USA), there was major outbreak of WNV strain, NY99 which is a cause of endemic in USA until now. Approved WNV vaccine for human is not available yet. Control of WNV is still difficult issue because this virus is mosquito-borne disease.

Understanding of WNV in several aspects, including pathogenicity, host-virus interaction, host immunological responses and epidemiology would provide the valuable knowledge for development of vaccine and therapeutic agents to prevent and cure for WNV infection.

This thesis consists of two chapters. The first chapter contains the investigation of the role of valosin-containing protein (VCP) in the replication of WNV. The second chapter represents examination of pathogenicity of a novel strain of WNV isolated from captured mosquitoes in the Republic of Zambia.

In chapter I, the role of VCP in WNV infection was investigated. It is suggested that VCP is important for WNV infection. Perturbation of VCP significantly suppressed WNV replication through inhibition of WNV genomic

RNA replication and early steps of WNV intracellular replication cycle. The VCP might be promising target for development of WNV infection by targeting multiple stages of WNV life cycle.

In chapter II, the virulence of a novel strain of WNV was evaluated. This novel strain was isolated from mosquitoes captured in Zambia. The virulence of the Zambian isolate was compared to high-pathogenic strain, NY99 6-LP and low-pathogenic strain, Eg101. According to the obtained results, Zambian isolate caused relatively high morbidity and mortality in C57BL/6 mice after IP inoculation. The mechanism of Zambian isolate caused fatality in mice is now under investigation. This virus should be concerned as one of the causes of febrile diseases and encephalitis in human and other animals in Zambia and neighbor countries.