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

博士の専攻分野の名称：博士（獣医学）　　氏名：板倉 友香里
Name

学位論文題名
The title of the doctoral dissertation

Studies on mechanisms of rabies virus infection, proliferation, and pathogenesis

（狂犬病ウイルスの感染増殖および病態発現機構に関する研究）

Rabies is a viral zoonosis of international public health importance that needs to be addressed. There are many questions about the mechanism of RABV infection, propagation, and pathological manifestation, and it is required to accumulate sufficient knowledge to develop effective therapeutics.

In Chapter I, the attenuation mechanism dependent on the 333rd amino acid residue of the G protein (G333) of HEP strain, an attenuated vaccine strain of RABV, was investigated. The vaccine strain HEP with Glu at G333 does not exhibit pathogenicity in mice, but the HEP^{333}R strain in which G333 is replaced with Arg becomes lethally pathogenic in mice. Underlying this pathogenetic difference, the HEP strain had a higher astrocyte infection efficiency and a higher level of IFN production in astrocytes than the HEP^{333}R strain. Strong relationship between the accelerated IFN response and pathogenesis associated with astrocyte infection was confirmed by lethal phenotype of HEP strain in type I and type II IFN receptor-deficient mice (AG129 mice). Thus, it is shown that the IFN response in infected astrocytes is important for elimination of HEP strains resulting in attenuation.

Chapter II focused on the virus-host interaction, which is essential for understanding the viral infection cycle, and analyzed the role of ESCRT proteins generally involved in lipid membrane modeling. In this chapter, the ESCRT-I component TSG101 was revealed to interact with the M protein *via* the L-domain and contributes to RABV budding and particle formation. Suppression of TSG101 expression or impaired RABV mutant binding to TSG101 showed common abnormalities such as intracellular aggregation of viral proteins and disruption of the bullet-like shape of virions. Furthermore, this RABV mutant reduced proliferation in cells and virulence in mice. These results suggest that the RABV budding and bullet-shaped virion formation are highly dependent on TSG101, and that the RABV M-TSG101 interaction *via* the L-domain is important for this process and efficient virus replication.

Finally, in this study, new mechanisms for virulence manifestation/attenuation and a molecular mechanism for budding and bullet-shaped particle formation of RABV was proposed. Understanding pathogenicity and attenuation mechanisms is important for the development and improvement of live attenuated vaccines, which is a key to control rabies in wild animals. Also, clarifying virus-host interactions is essential to understand the host-dependent viral infection cycle. I hope these findings will encourage further research to understand the molecular mechanisms of RABV infection and virulence, and future research will expand the potential therapeutic targets for rabies.