



HOKKAIDO UNIVERSITY

Title	Studies on prion propagation in neurons and neurons vulnerable to prion infection [an abstract of dissertation and a summary of dissertation review]
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Degree Grantor	北海道大学
Degree Name	博士(感染症学)
Dissertation Number	甲第16474号
Issue Date	2025-03-25
Doc URL	https://hdl.handle.net/2115/95507
Rights(URL)	https://creativecommons.org/licenses/by/4.0/
Type	doctoral thesis
File Information	Temuulen_Erdenebat_abstract.pdf, 論文内容の要旨



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（感染症学）

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学位論文題名
The title of the doctoral dissertation

Studies on prion propagation in neurons and neurons vulnerable to prion infection

(神経細胞におけるプリオンの増殖とプリオン感染に脆弱性を示す神経細胞に関する研究)

Prion diseases are fatal neurodegenerative disorders caused by the misfolding of PrP^C into PrP^{Sc}. The generation and accumulation of PrP^{Sc}, which is synchronous with prion propagation, in the brain, varies across brain regions in prion-infected animals. However, mechanisms for the uneven distribution of PrP^{Sc} and their involvement in neurodegeneration remain poorly understood. Elucidation of the mechanisms underlying region-dependent prion propagation will contribute to the understanding of prion disease neuropathobiology. Thus, brain region-dependent prion propagation and neuronal death were investigated using *in vivo* and *ex vivo* experiments. Additionally, the utility of primary neuronal and neural cultures for analyzing prion propagation was investigated.

In Chapter I, prion propagation and neuronal death were analyzed using mice and primary neuronal cultures infected with the prion 22L strain. PrP^{Sc} accumulation was less intense in the striatum, where GABAergic inhibitory neurons predominate, compared to the cerebral cortex and thalamus, where glutamatergic excitatory neurons are predominant, in mice intracerebrally or intraperitoneally inoculated with the 22L strain. PrP^{Sc} stains were observed along the needle track after stereotaxic injection into the striatum, whereas they were also observed away from the needle track in the thalamus. Consistent with inefficient prion propagation in the striatum, the 22L prion propagated more efficiently in glutamatergic neurons than GABAergic neurons in primary neuronal cultures. RNAscope *in situ* hybridization revealed a decrease in *Vglut1*- and *Vglut2*-expressing neurons in the ventral posterolateral nuclei of the thalamus in 22L strain-infected mice, whereas no decrease in *Vgat*-expressing neurons was observed in the adjacent reticular nucleus, mainly composed of *Vgat*-expressing interneurons. These results demonstrate that the prion 22L strain propagates more efficiently in excitatory neurons than inhibitory neurons and excitatory neurons in the thalamus are vulnerable to prion infection.

In Chapter II, remarkable differences were observed in the localization and staining patterns of PrP^{Sc} in primary neuronal and astrocytic cultures; PrP^{Sc} was detected on the surface of primary neurons as string-like stains. In contrast, intracellular granular PrP^{Sc} stains were mainly detected in primary astrocytes. Treatment of prion-infected primary neurons with anti-PrP mAb 31C6, which binds to PrP^C on the cell surface and inhibits PrP^{Sc} formation in prion-infected neuroblastoma cells, inhibited the formation of string-like PrP^{Sc} stains on the surface of primary neurons. Treatment of prion-infected primary astrocytes

with mAb 31C6 reduced the size of granular PrP^{Sc} stains. Although the localization of PrP^{Sc} in primary neurons and astrocytes is quite different, these results suggest that blocking PrP^C on the cell surface affects PrP^{Sc} formation both in primary neurons and astrocytes. These findings suggest that primary neuronal and astrocytic cultures are useful models for studying prion propagation, transmission, and the evaluation of anti-prion therapeutics, as a model closer to the brain.

This doctoral dissertation demonstrated the excitatory neuron-prone prion propagation and the vulnerability of thalamic excitatory neurons to prion infection. Furthermore, this dissertation revealed the potential of primary neuronal and neural cultures for analyzing prion propagation and neurodegeneration. This study will provide new insights into future research addressing the mechanism of neuropathobiology of prion diseases.