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Title of research project	Quantitative assessment of Atypical Bovine spongiform encephalopathy infectivity to human with humanized genetically-modified mice
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【Abstract】

Atypical form of bovine spongiform encephalopathy (BSE) agent shows different characteristics from classical form (C-BSE) that causes variant Creutz-feldt-Jakob disease by infection to human via meat consumption. Atypical BSE has 2 different forms, L-BSE and H-BSE, and has no evidence to infect to human, but suggests its possibility by animal experiments. In this study, the aim is to evaluate infectivity of BSE agents to human by animal experiments with humanized gene-modified mice expressing with prion protein gene of human. The humanized mice were inoculated via intracerebral, intraperitoneal or oral routes with cattle brain homogenates for each BSE agent.

L-BSE and H-BSE agents were not transmitted via any route to the humanized mice, while C-BSE agent was transmitted via intracerebral and intraperitoneal routes to two types of humanized mice with Methionine homozygote at codon 129: one was with glutamine homozygote at codon 219 and the other was with Lysine homozygote at codon 219. Based on the evidence that the vCJD patients also had these polymorphism, the humanized mice can be useful to identify the risk factor of BSE infection in human. Our results suggest that the risk of L-BSE and H-BSE infection in human might be smaller than one of C-BSE.

Any agents of BSE were not transmitted into the humanized mice via oral route. Animal experiments with the bovinized mice gene-modified with the bovine prion protein gene showed that the agents of L-BSE and C-BSE were transmitted via oral route, but not H-BSE agent. Compared to the results for titration assay via intracerebral route, the BSE infectivity via oral route reduce at 1/10,000 lower than via intracerebral route. Titration assay via oral route showed infection level of L-BSE was lower at 1/10 than one of the C-BSE agent, and one of H-BSE was at 1/100 and lower, suggesting that oral transmissibility of atypical BSE might be lower than one of C-BSE.

The infectivity of L-BSE and H-BSE agents decreased below the detection limit by two treatments with the digestion process, simulated in the human gastric and pancreatic juices, and with heating at 100 ºC for 10 min. However, the infectivity in C-BSE agent had resistance to the process of digestion and heating under same condition. The results show that atypical BSE agents are unstable and easier to inactive than C-BSE.

These studies demonstrate that the human PrP gene polymorphisms of Lysine at codon 219 and Methionine at codon 129 implicate in the risk factor of BSE infection from cattle to human and suggest that infectivity of atypical BSEs to human is lower than C-BSE, but not in quantitative evaluation.