Mutant Proteins Result in Infectious Prion Disease in Mice

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A worldwide group of scientists has created an infectious prion disease in a mouse model, in a step that may help unravel the mystery of this progressive disease that affects the nervous system in humans and animals. The research team, including Christina J. Sigurdson, D.V.M., Ph.D., assistant professor of pathology at the University of California, San Diego School of Medicine, also discovered that changing the structure of the prion protein by altering just two nucleic acids leads to a fatal neurological disorder in mice. Their findings will be published on line in *Proceedings of the National Academy of Sciences (PNAS)* the week of December 1.

The study, led by Professor Dr. Adriano Aguzzi of the Institute of Neuropathology at the University of Zurich in Switzerland, was designed to investigate the specific changes in the prion protein that may contribute to chronic wasting disease (CWD). CWD is a highly infectious prion disease found in free-ranging deer and elk that is similar to bovine spongiform encephalopathy (BSE, or "mad cow disease") in cattle and Creutzfeldt-Jakob disease in humans. Prion diseases are thought to be a result of a misfolded form of the prion protein that induces formation of amyloid plaques in the brain – changes that are also seen in patients with Alzheimer's disease.

By altering two nucleic acids in the prion gene, the researchers developed a transgenic mouse model that expressed the mutant prion protein. These changes resulted in a "loop" in the protein structure of the mice that was rigid – similar to the structure of the elk prion protein, and unlike the flexible "loop" found in normal mouse or human prion proteins. Aging mice with the "rigid loop" prion protein accumulated plaques in the brain and developed symptoms of neurological disease that are features of prion-related disorders.

"It could be that this 'loop' region of the protein can promote the formation of amyloid plaques in the brain," said Sigurdson. "We also found that by transferring brain tissue from mice with the mutant protein into mice expressing the normal mouse prion protein, we could transmit the neurologic disease between the two groups of animals."

According to Sigurdson, the discovery that an infectious disease can be generated through just two mutations in the prion gene is of particular interest. "Some forms of prion disease in humans caused by genetic mutations have also been shown to be infectious," she said. "This new mouse model of the disease may be useful in our understanding of how the misfolded protein leads to neurodegeneration and for testing new therapies against prion disease."

Additional contributors to the study include K. Peter R. Nilsson, Mathias Heikenwälder, Giuseppe Manco, Petra Schwarz, David Ott, Christian Julius and Jeppe Falsig of the University of Zurich; Simone Hornemann, ETH Zürich; Thomas Rülicke, Austria University of Veterinary Medicine, Vienna; Pawel Liberski, Medical University Lodz, Poland; Lothar Stitz, Friedrich-Loeffler-Institute, Tübingen, Germany; and Kurt Wüthrich, The Scripps Research Institute, La Jolla, CA.

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