Infectious, test tube-produced prions can jump the 'species barrier'

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Researchers have shown that they can create entirely new strains of infectious proteins known as prions in the laboratory by simply mixing infectious prions from one species with the normal prion proteins of another species. The findings are reported in the September 5th issue of the journal *Cell*.

Prion diseases, also known as transmissible spongiform encephalopathies (TSEs), are infectious neurodegenerative diseases affecting the brain of several species of mammals including humans. Creutzfeldt-Jakob disease (CJD) is the most common prion disease in humans, along with scrapie in sheep, bovine spongiform encephalopathy (BSE, aka mad cow) in cattle, and chronic wasting disease (CWD) in deer and other cervids.

Unlike conventional infectious microorganisms, the infectious agent in the case of prion diseases consists exclusively of a misfolded form of the prion protein, earlier studies showed.

The researchers now find that prion strains produced by combining normal hamster proteins with infectious mouse proteins can infect hamsters and vice versa. Although they are both rodents, prions from one of the two species normally don't readily infect the other, a common phenomenon amongst prions known as a species barrier, the researchers explained.

The novel prions they produced not only look different, but they also

produce symptoms in the animals that differ from any known strain found in nature, they report.

" We are forcing the system by putting everything together, but this suggests that the variety of possible prions is really very large," said Claudio Soto of the University of Texas Medical Branch. "We shouldn't be surprised if new barriers are crossed and new prions arise. There is the potential for a large variety of new infectious prions—some of which may have dramatic effects."

"The infectous agent is nothing like what we're used to," Soto said. "It's just a protein with a different shape from the normal protein we all have." Those misfolded and misshapen proteins can spread by causing normal protein to change their shape. Those aberrant forms band together, forming fibrils.

Soto's team recently reported the generation of infectious prions by amplification of prion misfolding in the test tube. In those experiments, they used a technology called protein misfolding cyclic amplification (PMCA) that mimics some of the fundamental steps involved in the replication of infectious prions in living animals, but at an accelerated rate. The method involves placing small quantities of infectious prions with large quantities of the normal protein from the same species together, allowing the infectious form to imprint on the normal form and thereby replicate itself.

Now, they show that the same method can generate new strains when infectious prions from one species are mixed with normal prion proteins from another species. The finding provides conclusive evidence that the imprinting of disease-causing prions on normal forms can overcome species barriers, and doesn't require any other infectious agent.

This new insight has profound implications for public health, according

to the researchers.

" One of the scariest medical problems of the last decades has been the emergence of a new and fatal human prion disease--variant CJD--originated by cross-species transmission of BSE from cattle," the researchers said. BSE has also spread to other animals, including exotic cats, other primates and domestic cats, after they ate feed derived from diseased cows.

The new method might provide insight into the risk that other prion diseases could spread from one species to another, Soto said. For instance, scientists don't know whether chronic wasting disease, a condition now on the rise amongst deer in some parts of the U.S., can be transmitted to humans or not.

Test tube studies like this one might help answer that question, and-- in the case that the deer prions can make the leap—such studies may inform scientists about what those prions might look like, he said. By studying any new prion strains created in mice with the human prion protein, scientists might also gain insight into the potential symptoms associated with those diseases.

" The data demonstrate that PMCA is a valuable tool for the investigation of the strength of the barrier between diverse species, its molecular determinants, and the expected features of the new infectious material produced," the researchers concluded. "Finally, our findings suggest that the universe of possible prions is not restricted to those currently known but that likely many unique infectious foldings of the prion protein may be produced and that one of the sources for this is cross-species transmission."

Source: Cell Press