

JUNE 28, 2006

Brittle Prions Are More Infectious

Brittleness is often seen as a sign of fragility. But in the case of infectious proteins called prions, brittleness makes for a tougher, more menacing pathogen. Howard Hughes Medical Institute researchers have discovered that brittle prion particles break more readily into new “seeds,” which spread infection much more quickly.

The discovery boosts basic understanding of prion infections, and could provide scientists with new ideas for designing drugs that discourage or prevent prion seeding, said the study's senior author Jonathan Weissman, a Howard Hughes Medical Institute investigator at the University of California, San Francisco (UCSF).

Weissman and colleagues from UCSF reported their findings on June 28, 2006, in an advance online publication in *Nature*.

"From a therapeutic point of view, our findings suggest that effective treatment strategies for prion diseases might aim at stabilizing prion aggregates. By preventing the aggregates from being broken up to smaller seeds, their propagation can be reduced."

- Jonathan S. Weissman

The scientists studied yeast prions, which are similar to mammalian prions in that they act as infectious proteins. In recent years, mammalian prions have gained increasing notoriety for their roles in such fatal brain-destroying human diseases as Creutzfeldt-Jakob disease and kuru, and in the animal diseases, bovine spongiform encephalopathy (“mad cow” disease) and scrapie.

Yeast and mammalian prions are proteins that transmit their unique characteristics via interactions in which an abnormally shaped prion protein influences a normal protein to assume an abnormal shape. In mammalian

prion infections, these abnormal shapes trigger protein clumping that can kill brain cells. In yeast cells, the insoluble prion protein is not deadly; it merely alters a cell's metabolism. Prions propagate themselves by division of the insoluble clumps to create "seeds" that can continue to grow by causing aggregation of more proteins.

In earlier studies, Weissman and his colleagues had discovered that the same prion can exist in different strains and have different infectious properties. These strains arise from different misfoldings of the prion protein that result in different conformations. A similar strain phenomenon has been described for mammalian prions. More generally, even in noninfectious diseases involving protein misfolding, like Alzheimer's and Parkinson's diseases, the same protein can misfold into more than one shape with some forms being toxic and others benign. However, Weissman said, it was not understood how different conformations cause different physiological effects.

As part of the studies published in *Nature*, the researchers created a mathematical model that enabled them to describe the growth and replication of prions according to the physical properties of the prion protein. To validate that model in yeast, they then created in a test tube, infectious forms of the prion protein in three different conformations and introduced them into yeast cells. They then correlated the strength of infectivity of each prion with its physical properties and compared their results to those predicted by their mathematical model.

According to Weissman, the researchers found that the slowest-growing conformation seemed to have the strongest effect in producing protein aggregates inside cells. "But we knew from our model that growth was only half of the equation," said Weissman. "The other key feature was how easy it was to break up the prion and create new seeds, and this propensity to seed could be an important determinant of the prion's physiological impact. And that is what we found experimentally -- that the slower growth of that conformation was more than compensated for by an increased brittleness that promotes fragmentation."

According to Weissman, the importance of a prion's brittleness, or "frangibility," to its physiological effects has both basic research and clinical implications. "Investigators trying to develop synthetic prions as a research model for mammalian prions have had a very hard time getting a high degree of activity," he said. "Part of the reason may be that they were trying to create forms that were very stable. But that might have been exactly the wrong thing to do, because prions that are too stable may be the ones that are not very infectious because the aggregates are hard to break up.

"And from a therapeutic point of view, our findings suggest that effective treatment strategies for prion diseases might aim at stabilizing prion aggregates. By preventing the aggregates from being broken up to smaller seeds, their propagation can be reduced. In contrast, most such strategies now aim at preventing the aggregates from forming in the first place," he said.

In future studies, Weissman and his colleagues plan to expand their analytical model to describe in more detail how prions' physical properties lead to different physiological effects. They also plan more detailed analyses to examine how the molecular structure of a prion protein gives rise to its physical properties.