Scientists identify most lethal known species of prion protein

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This is Scripps research professor Corinne Lasmézas. Credit: Photo by Randy Smith, courtesy of the Scripps Research Institute

Scientists from the Florida campus of The Scripps Research Institute have identified a single prion protein that causes neuronal death similar to that seen in "mad cow" disease, but is at least 10 times more lethal than larger prion species. This toxic single molecule or "monomer" challenges the prevailing concept that neuronal damage is linked to the toxicity of prion protein aggregates called "oligomers."

The study was published this week in an advance, online edition of the journal Proceedings of the National Academy of Sciences.

"By identifying a single molecule as the most toxic species of prion proteins, we've opened a new chapter in understanding how prion-induced neurodegeneration occurs," said Scripps Florida Professor Corinne Lasmézas, who led the new study. "We didn't think we would find neuronal death from this toxic monomer so close to what normally happens in the disease state. Now we have a powerful tool to explore the mechanisms of neurodegeneration."

In the study, the newly identified toxic form of abnormal prion protein, known as TPrP, caused several forms of neuronal damage ranging from apoptosis (programmed cell death) to autophagy, the self-eating of cellular components, as well as molecular signatures remarkably similar to that observed in the brains of prion-infected animals. The study found the most toxic form of prion protein was a specific structure known as alpha-helical.

New Paths to Explore

In addition to the insights it offers into prion diseases such as "mad cow" and a rare human form Creutzfeldt-Jakob disease, the study opens the possibility that similar neurotoxic proteins might be involved in neurodegenerative disorders such as Alzheimer's and Parkinson diseases.

In prion disease, infectious prions (short for proteinaceous infectious particles), thought to be composed solely of protein, have the ability to reproduce, despite the fact that they lack DNA and RNA. Mammalian cells normally produce what is known as cellular prion protein or PrP; during infection with a prion disease, the abnormal or misfolded protein converts the normal host prion protein into its disease form.

Lasmézas explains that prion diseases are similar to Alzheimer's and other protein misfolding diseases in that they are caused by the toxicity of a misfolded host protein. Recent work, as reported in The New York

Times, also found that diseases such as Alzheimer's resemble prion diseases by spreading from cell to cell.

The new study adds another twist. "Until now, it was thought that oligomers of proteins are toxic in all these diseases," Lasmézas said. "Since we found for the first time that an abnormally folded monomer is highly toxic, it opens up the possibility that this might be true also for some other protein misfolding diseases as well."

More information: The first author of the study, "Highly Neurotoxic Monomeric α-Helical Prion Protein," is Minghai Zhou of Scripps Research. Other authors include Gregory Ottenberg and Gian Franco Sferrazza also of Scripps Research. For more information on the study, see www.pnas.org/content/early/201 … /1118090109.abstract

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