Scientists devise accelerated method to determine infectious prion strains

May 29 2009

Current tests to identify specific strains of infectious prions, which cause a range of transmissible diseases (such as mad cow) in animals and humans, can take anywhere from six months to a year to yield results - a time-lag that may put human populations at risk.

Now, a group of scientists from The Scripps Research Institute's Florida campus have developed a new method that cuts this critical time lag by several months.

The new research was published in the open-access journal PLoS ONE on May 29, 2009.

"Because some prion strains are pathogenic for humans and some are not, it's vital that we know the difference when we find them in the field and when we study them in the laboratory," said Corinne Lasmézas, a professor in the Department of Infectology at Scripps Florida who led the study. "Currently, the identification process for mouse-adapted strains takes between six and eight months and can take as long as a year, depending on the strain. Our accelerated method reduces that time to around four months."

The new method for distinguishing among various strains combines a transgenic mouse model with a rapid and sensitive cell-based procedure, the Cell Panel Assay developed by Scripps Florida's Charles Weissmann (chair of the Department of Infectology) and Sukhvir Mahal (senior staff scientist), also investigators on the new study.

"There are about 20 prion strains known in mouse models," Lasmézas said. "We still don't understand what determines the difference among strains even though it's very important, especially for any potential therapeutic development. Our new method should help quicken the pace of research."

The Mysteries of Prions

Prion diseases, also called spongiform encephalopathies, are a group of closely related, fatal neurodegenerative disorders that affect mammals, including cows, sheep, and deer, as well as humans. Different strains of the infectious agent, called a prion, cause mad cow disease, chronic wasting disease, and different forms of scrapie and human Creutzfeldt-Jacob disease.

Mad cow disease has had devastating consequences for bovine livestock populations, particularly in Europe, and for humans who have consumed contaminated beef products.

To date, there have been more than 200 recorded human fatalities worldwide due to mad cow disease. Creutzfeldt-Jacob disease, a low-incidence but always fatal disease, affects humans in all countries.

Prions consist mainly or entirely of an abnormal form of a normal cellular protein. They multiply by converting their normal counterparts into a likeness of themselves, which may aggregate to form deposits called amyloid. Accumulation of different kinds of amyloid plays a role in a wide range of neurodegenerative diseases, including Alzheimer's and Parkinson's diseases.

Currently, different varieties of prion strains are identified in mouse models according to incubation time, clinical symptoms, and localization of brain lesions.

Accelerated Incubation

In the new test developed by Lasmézas and Weissmann, a transgenic mouse line called Tga20 plays an important role, because it succumbs rapidly to prion disease.

"The prions primarily target the brainstem and the thalamus of this transgenic mouse, explaining why these animals have a shorter incubation time than their normal counterparts," Lasmézas said. "The prion aggregates also don't spread evenly to other brain regions, and their distribution is characteristic for different strains."

Importantly, the brain tissue can be subjected to the Cell Panel Assay, which unlike the current histological method, doesn't require time intensive examination of brain lesions and can be completed within two weeks, Lasmézas added. The test has been partially automated.

Development of the method provided the scientists with the opportunity to make the observation that there was, in some brain regions, little relationship between the amount of abnormal prion protein deposition and the amount of normal prion protein. This was something of a surprise, Lasmézas said, but not totally unexpected.

"We and others believe that the prion protein may not be the sole player in these diseases," she said. "Perhaps there is a co-factor, or perhaps the protein structure differs somewhat from one brain region to the next. We don't know. Just like we don't really know the reason for the different behavior of the various prion strains—is this cause or effect? Our new method should help accelerate the process of discovery."

More information: The first authors of the study, "Prion Strain Discrimination Based on Rapid in Vivo Amplification and Analysis by the Cell Panel Assay," are Yervand E. Karapetyan and Paula Saá of The

Scripps Research Institute. Other authors include Sukhvir P. Mahal, Gian Franco Sferrazza, Alexandra Sherman and Nicole Salčs, also of Scripps Research. For more information, see dx.plos.org/10.1371/journal.pone.0005730 .

Source: The Scripps Research Institute (news : web)