

First atomic-level look at a protein that causes brain disease

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For the first time, researchers have peered deeply at the atomic level into the protein that causes hereditary cerebral amyloid angiopathy (CAA) -- a disease thought to cause stroke and dementia. The study pinpointed a tiny portion of the protein molecule that is key to the formation of plaques in blood vessels in the brain.

Ohio State University chemist Christopher Jaroniec and his colleagues report their results this week in the online edition of the *Proceedings of the National Academy of Sciences*.

Researchers worldwide are working to understand how certain kinds of proteins, called prions, cause degenerative brain diseases such as CAA. More common prion diseases include bovine spongiform encephalopathy (mad cow disease), and Creutzfeldt-Jakob disease in humans. All are incurable and fatal.

Jaroniec understands that any discovery related to prions could raise people's hopes for a cure, but he emphasized that his study is only a first step towards understanding the structure of the prion for CAA.

"This is a very basic study of the structure of the protein, and hopefully it will give other researchers the information they need to perform further studies, and improve our understanding of CAA," he said.

His team partnered with biochemists from Case Western Reserve University, who took a fragment of the human prion protein for CAA

and tagged it with chemical markers.

Jaroniec explained that, while the prion protein used in the study is associated with the development of hereditary CAA, it is not infectious.

After the researchers tagged the molecule, they created the right chemical conditions for it to fold into macromolecules called amyloid fibrils.

Researchers know that in the body, these fibrils form plaques that lodge in blood vessel walls in the brain. But nobody has been able to closely examine the molecular structure of CAA fibrils until now.

“These fibrils are very large and complex, and so traditional biochemical techniques won’t reveal their structure in detail,” Jaroniec said.

The assistant professor of chemistry at Ohio State is an expert in a technique that can reveal the structure of such large molecules: solid-state nuclear magnetic resonance (NMR) spectroscopy.

NMR works by tuning into the radio waves emitted by atoms within materials. Every atom emits radio waves at a particular frequency, depending on the types of atoms that surround it.

The NMR technique the chemists used, called “magic angle spinning,” involves spinning materials at a certain angle with respect to the NMR’s magnetic field in order to remove radio interference among the atoms. It offers researchers a clear view of which atoms make up a particular molecule, and how those atoms are arranged.

So after the researchers let the prion proteins fold into amyloid fibrils, they used magic angle spinning NMR to study the fibrils’ structure.

They searched the NMR signals for the chemical tags that had been planted in the prions. In that way, they were able to determine what parts of the original prion protein were contained within the fibrils.

They found, to their surprise, that some 80 percent of the original prion protein molecule was not present in the fibrils. The fibrils consisted exclusively of the remaining 20 percent -- approximately 29 amino acids, of which two appear to be especially critical to the structure of the molecule.

Other studies have suggested that these two amino acids, numbered 138 and 139, were key to the formation of the CAA fibrils, Jaroniec said. But this study is the first to confirm their importance by studying them at the atomic level.

The researchers are continuing this work, and plan to examine the structure of the fibrils in more detail, as well as other strains of the CAA prion protein.

Source: Ohio State University

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