Chemists characterize Alzheimer's neurotoxin structure

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Amyloid plaques, the hallmark of Alzheimer's disease, are clumps of fiber-like misfolded proteins which many experts think cause this devastating neurodegenerative disease.

While effective treatment remains an elusive goal, new research by University of Illinois at Chicago chemists suggests a possible new approach.

Yoshitaka Ishii, associate professor of chemistry, and his students managed to capture and characterize a crucial intermediate step in the formation of amyloid plaque fibers, or fibrils, showing tiny spheres averaging 20 nanometers in diameter assembling into sheet-like structures comparable to that seen in formation of fibrils.

Fibrils made of small proteins called amyloid-beta are toxic to nerve cells, but intermediate spheres, including those identified by Ishii's group, are more than 10 times as poisonous. That has made the spherical intermediates a new suspect for causing Alzheimer's disease.

"The problem with studying the structure of this intermediate form is that it's so unstable," said Ishii. His team's approach, he said, was to 'freeze-trap' the fleeting intermediate form, then use solid-state nuclear magnetic resonance to determine its structure and electron microscopes to study its morphology, or shape.

Ishii and his coworkers confirmed that the intermediate spherical stage

of amyloid is more toxic than the final-form fibrils. Their findings are the first to pinpoint sheet formation at the toxic intermediate stage in the misfolding of the Alzheimer's amyloid protein and support the notion that the process of forming the layered sheet structure might be what triggers toxicity and kills nerve cells.

"Our method characterized the detailed molecular structure of this unstable, intermediate species," Ishii said. "To the best of our knowledge, this is the first characterization of detailed molecular structures for toxic amyloid intermediates. We found that the structure was very similar to the final (fibril) form, which wasn't expected at all."

Ishii said a complete determination of the intermediate structure remains to be done, but he is confident his lab will be able to do that. Once completed, the findings may provide pharmaceutical manufacturers with the information they need to create drugs that will prevent interaction between the toxic molecules and nerve cells.

Ishii said the method can also be applied to structural studies of proteins associate with other neurodegenerative diseases, including Parkinson's, and prion diseases, such as Creutzfeldt-Jakob.

"We're also interested in applying our technique in the nanoscience field to examine the formation process of peptide-based nano-assemblies," he said.

The findings were reported online yesterday in *Nature Structural & Molecular Biology*.

Source: University of Illinois at Chicago