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SCIENTISTS FOCUS ON PRECURSORS TO AMYLOID PLAQUE IN ALZHEIMER DISEASE

[TOWARD A BETTER UNDERSTANDING OF THE PATHOPHYSIOLOGY]

Carroll, Linda

Using solid-state NMR spectroscopy, scientists have imaged precursors of the amyloid plaques that accumulate in the brains of Alzheimer patients, according to a new report in the *Journal of the American Chemical Society* (2005;127:13472–13473).

While studies have shown that mature plaques are toxic to neurons, there is mounting evidence to suggest that much of the damage to the brain is being caused by smaller clumps of misfolded protein. Because of this, some researchers have turned their attention to the earlier stage aggregates as a potential target for Alzheimer therapies.

"These intermediary species are between 10 and 20 nanometers in diameter," said study co-author Yoshitaka Ishii, PhD, Assistant Professor in the Department of Chemistry at the University of Illinois at Chicago. "They are a precursor to the plaques and are thought to be even more toxic than the plaques themselves. So people are starting to pay a lot of attention to them."

FREEZING THE PLAQUE

In the new study, Dr. Ishii focused on amyloid-beta (1–40). "Amyloid fibrils of Alzheimer's beta-amyloid peptides ranging from 39 to 43 residues are the primary components of senile plaque of Alzheimer disease," he noted.

In the past, researchers have had trouble teasing out the structure of the early stage aggregates because these forms tend to be unstable, Dr. Ishii explained. To get around this problem, the researchers used a quick freezing technique of samples at autopsy to halt aggregate development at an early stage.

Before starting the freezing process, Dr. Ishii and his colleague, graduate student Sandra Chimon, applied thioflavin – a florescent dye commonly used to stain senile amyloid plaques – to the sample. Once the samples were prepared and frozen, they could be imaged with a solid-state spectroscope.

FINDING A BETA-SHEET STRUCTURE

Experts have assumed that plaque, in the early stages of development, had a chaotic structure, Dr. Ishii said. "But contrary to expectations, we found that it already had a beta-sheet structure," he added. "That was quite a surprise."

To better describe the amyloid beta- sheet structure, Alzheimer disease expert Gail V.W. Johnson, PhD, likens it to the Middle Eastern dessert baklava.

"A lot of proteins take on this structure," said Dr. Johnson, Professor of Psychiatry at the University of Alabama at Birmingham. "It's a secondary structure in which the proteins fold back on themselves and form kind of a flat sheet."

When amyloid beta is folded this way it tends to stack up like the layers of pastry in baklava, Dr. Johnson said. “You get very compact layering,” she added. “And that's what it looks like is happening here.”

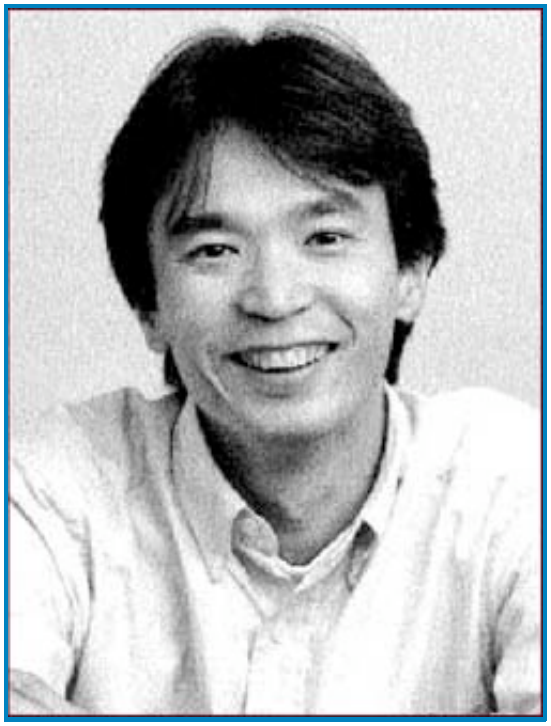

Figure. Dr. Yoshitaka Ishii: “By finding out more about the detailed structure of the plaque precursors we should learn more about how these proteins misfold, and this may allow us to find a way to prevent them from misfolding into plaque.”

The new results may help researchers who are looking for therapies to halt the disease process, Dr. Ishii said.

“Before this, we knew something about the beginning and the end of the process,” he added. “But nothing was known about the middle. By finding out more about the detailed structure of the plaque precursors we should learn more about how these proteins misfold, and this may allow us to find a way to prevent them from misfolding into plaque.”

Dr. Ischii said the new technique could be valuable to researchers looking for therapies for other neurodegenerative diseases, such as Parkinson disease and Creutzfeldt-Jakob disease.

You want to be able to design molecules that will interact with the small chemical subunits and prevent the disease from progressing, he said. That's been difficult in the past. Now we may have new clues, he added.

MIXED RESPONSE FROM EXPERTS

Alzheimer disease experts were mixed in their opinions of the new study. “This is a nice little study,” Dr. Johnson said. “We didn't realize that there was so much order to the precursors. It's surprising to see that they take a more organized structure so early in the process.” This kind of information could aid in the development of therapies, she added.

Gal Bitan, PhD, Assistant Professor in Residence in the Department of Neurology at the David Geffen

School of Medicine of the University of California-Los Angeles, agreed. Knowing the structure of the precursors may help drug designers come up with better, more targeted medications, said Dr. Bitan.

"It suggests that drugs that target this particular conformation may act on the disease at an earlier stage," he added. But, Dr. Bitan cautioned, this isn't the first study to scrutinize the structure of amyloid-beta plaque precursors.

"Earlier studies did not find this beta sheet conformation until later stages of plaque development," he said. "Depending on the particular stage of the aggregation process, the earlier studies didn't show any ordered conformation or find other secondary structure.

"There is a big question," Dr. Bitan said, "regarding the relevance of the new findings to Alzheimer disease. The authors used amyloid-beta (1–40) for their study. The most current data show that the longer form of the protein, 1–42, likely is the actual culprit causing the disease."

In Dr. Bitan's experience, "amyloid-beta (1–40) is easier to study because it's much more soluble than amyloid-beta (1–42)."

Further, Dr. Bitan said, "the new study looked at the peptide in a concentration that are orders of magnitude higher than those found in biological samples. So, the fact that in the test tube these concentrations of amyloid-beta (1–40) form these assemblies may or may not be relevant to Alzheimer disease." Another possible caveat of the new study, according to Dr. Bitan, is that the researchers have not formally proven that the material they studied were precursors and not fully mature fibrils.

Figure. Dr. Gal Bitan said that knowing the structure of the precursors [to amyloid plaque] may help drug designers come up with better, more targeted medications.

"Their control experiments do not positively show that the data they presented are not for amyloid-beta fibrils," he said. "A formal proof could have been given using electron microscopy to identify the morphologies of the samples studied by NMR," he added.

"It's possible that while the researchers were processing the samples to view with NMR spectroscopy,

the precursors developed into fibrils," Dr. Bitan said. "If, indeed, there are no fibrils there, then the NMR data becomes a lot stronger," he added. "I would like to see formal proof that these are oligomers and not mature fibrils."

Dr. Bitan also would like to see the study redone with amyloid-beta (1–42).

"If they showed the same thing for that version of the peptide, I would be very excited," he said. "It is possible to do that, and I think people will try."

The new study was supported by the Alzheimer's Association and the National Science Foundation.

ARTICLE IN BRIEF

[check mark] A new study has unearthed information about the earlier stage development of amyloid plaque implicated in Alzheimer disease, providing insight into the disorder's pathophysiology and potential targets for therapy.

REFERENCE

Chimon S, Ishii Y. Capturing intermediate structures of Alzheimer's beta-amyloid, Abeta (1–40) by solid-state NMR spectroscopy. *J Am Chem Soc* 2005;127:13472–13473. **Full Text** | **Bibliographic Links** | **Library Holdings** |

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