Alzheimer's amyloid proponents pinpoint precursors
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by Francesco Fiondella, BioMedNet News

After years of arguing that monstrous clumps of misfolded proteins, known as senile amyloid plaques, cause neurodegenerative diseases such as Alzheimer's (AD), proponents of the hypothesis now think that smaller, maverick precursors of these proteins may in fact be responsible, according to two papers published today.

"There have been a lot of ideas bouncing around about small clumps being the toxic entity, and these papers provide some of the first compelling evidence along those lines," said Nancy Bonini, a geneticist at the University of Pennsylvania.

Bonini, who was not involved in either study, has worked extensively on the role of protein misfolding. Her research has shown that increasing the levels of "chaperone" proteins, which help other proteins fold properly, reduces misfolding and will suppress the onset of certain human neurodegenerative diseases in transgenic fruit flies.

The papers deal with two studies of misfolding, one in vitro and the other in vivo.

In the in vitro study, an anglo-italian team chemically unfolded normally harmless bacterial and bovine proteins, and allowed them to refold. In the process of refolding, the proteins almost immediately began forming various, misfolded aggregates. After a few days, these aggregates started to develop "protofibrils," and after about 20 days, the protofibrils were replaced by mature amyloid fibrils.

The team, led by Christopher Dobson of the University of Cambridge, found that while the mature amyloids were harmless to cells, the earlier aggregates - the protofibrils - were highly toxic.

In the in vivo study, a Harvard team injected dimers and trimers of the human amyloid-beta protein into the brains of rats, and found that these much smaller aggregates "markedly" inhibited long-term potentiation (LTP), a measure of memory and learning.

Dennis Selkoe, who led the Harvard team, is a longstanding proponent of the amyloid theory; this latest report represents a significant modification of his traditional stance.

These papers, published in Nature, suggest that fibrillar amyloid is now not 'it,' or at least certainly not the only culprit, says Bonini. "It's a big step forward to have identified specific forms that are clearly showing toxicity," she told BioMedNet News.

But the work fails to convince Mark Smith of Case Western Reserve University, who believes that amyloid plaques are a consequence, not a cause of Alzheimer's.

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"In all neurodegenerative diseases characterized by accumulation of insoluble proteins - whether prion proteins in Creutzfeldt-Jacob disease or amyloids in AD - I would propose that they're there to protect the brain," he told BioMedNet News.

Smith says the studies are "interesting from a purely scientific perspective" and give insight into the importance of protein folding and cell death. He remains circumspect about their importance in the etiology of neurodegenerative disease, however. The authors show a correlation, but a correlation does not mean they have proven causality, he notes.

"First, I'm not convinced we've shown that these oligomers or protofibrils exist normally in the human brain, or are just artifacts from the process of chemical isolation," he said.

Even if they did occur in vivo, no one knows the general function of amyloid proteins, he adds, highlighting the public failure earlier this year of an AD vaccine after 15 patients developed brain inflammation and their Alzheimer's symptoms worsened. The vaccine inhibited beta-amyloid production.

Before anyone gets too excited about this latest round of findings, Smith says, amyloid proponents should first analyze the data from the patients who participated in the clinical trial.

If their oligomer levels went up and their symptoms worsened, he says, then this supports the hypothesis that oligomers may play a role in causing the disease.

"But if levels went down because of vaccination therapy, and this would be expected [since the vaccine should have decreased amyloid production], then they should abandon this theory," he said.

Picture caption:
Beta-amyloid formation, courtesy National Center for Biotechnology Information.

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