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GEN News Highlights : Oct 2, 2014

Most Dangerous Aggregates in Alzheimer's Identified

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Beta amyloid, the peptide long associated with Alzheimer's disease, embodies a diabolical version of the Goldilocks principle. For beta amyloid, "just right," when it comes to killing neurons, means forming aggregates of intermediate size—specifically, aggregates of 20 to 100 units. Neither smaller aggregates nor amyloid fibrils, which can contain up to 3,000 peptide units, are as toxic.

This finding, from scientists based at the Institute for Research in Biomedicine (IRB Barcelona), squarely faces one of the key uncertainties in Alzheimer's research, namely, the lack of unequivocal proof that beta amyloid causes the onset and development of the disease. Beta amyloid in isolation is not harmful. And, while beta amyloid aggregates are associated with Alzheimer's, it has been unclear which aggregates might actually be harmful.

"We are not dealing with a single target, beta amyloid alone, but with multiple ones because each aggregate of peptide, which can go from two units to 3,000, is a potential target," explained Natàlia Carulla, Ph.D., a research associate at IRB Barcelona. "Determining the aggregate responsible for neuronal death is extremely complex and is one of the key issues for confirming or rejecting the hypothesis regarding beta amyloid."

Dr. Carulla and colleagues developed a technique that distinguishes between the different types of beta amyloid aggregates that form during aggregation and in parallel to establish which is most toxic. Aggregates of different types could be distinguished, said the researchers, by means of pulse-labeled hydrogen-deuterium exchange (PL-HDX), in combination with electrospray ionization mass spectrometry (ESI-MS).

The researchers, who used this technique to observe how aggregation proceeded in cultures of mouse neurons, were especially alert to correlations between neuronal cell death and phases in aggregate growth. These correlations were reported September 29 in ACS Chemical Biology, in an article entitled, "Hydrogen/Deuterium Exchange-Protected Oligomers Populated during Aβ Fibril Formation Correlate with Neuronal Cell Death."

"The ensembles populated at different stages of the aggregation process have a surprisingly consistent

average degree of exchange, indicating that there are definite structural transitions between the different stages of aggregation," wrote the authors. "The results of [PL-HDX-ESI-MS experiments with parallel measurements of the neurotoxicity] show that the maximum toxicity correlates with the ensemble comprising HDX-protected oligomers, indicating that development of persistent structure within Aβ oligomers is a determinant of neurotoxicity."

The researchers also noted that their observations would not have been possible by means of conventional assays such at Thioflavin T. "[Our technique] allows us to detect how the structure within these aggregates increases, that is to say, how the aggregates take shape and how they get organized," Dr. Carulla asserted. "We observed that maximum toxicity occurs when they have acquired a given degree of structure, a certain rigid part in the aggregate."

By characterizing the shifting patterns of beta amyloid structures, the researchers hope to advance the search for and design of therapeutic molecules. They also anticipate that the tools that they developed to study beta amyloid aggregation could be used to examine the aggregation of other proteins that are associated with conditions such as Parkinson's disease, Huntington's disease, and type 2 diabetes.

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