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Alzheimer's Disease and Protein Aggregation: Biophysical Properties Predict Cellular Pathogenesis

By

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Alzheimer's disease (AD), the leading cause of dementia in the elderly, is characterized by the presence of amyloid plaques in the brain parenchyma and cerebrovasculature. These deposits are comprised primarily of aggregated amyloid-β protein (Aβ). Despite observations that Aβ aggregates elicit a number of physiological responses, ranging from alteration of protein expression to cell death, the Aβ specie(s) accountable for these responses remains uncertain. Thus, it is important to characterize the physiological activity elicited by different Aβ aggregate species. We have paired biophysical characterization techniques for Aβ aggregates with different of cell culture systems to explore this relationship.

An endothelial cell culture assay, designed to mimic physiological responses observed in the cerebrovasculature of AD brain, was used to show that isolated soluble $A\beta_{1\text{-}40}$ aggregates, but not monomer or mature fibril, selectively stimulate physiological response via NF-κB signaling pathways. Correlations between average Aβ aggregate size and observed increases in physiological response illustrate that smaller soluble aggregates are the most potent activators of endothelium.

A neuronal cell culture assay was used explore how Aβ oligomer conformation can influence Aβ-induced cell signaling pathways associated with neuronal death. These studies reveal that an unexpected inverse dose-response results from the formation of less active conformations at higher concentrations. In addition, experiments show that while dietary polyphenols are capable of modulating oligomer size and structure, it is their antioxidant activity that more readily influences Aβ-induced cell signaling.

To further characterize interactions between Aβ aggregates and cells, we explored the manner in which phospholipid bilayer composition can influence Aβ aggregation. These studies were motivated by epidemiological evidence suggesting an inverse relationship between polyunsaturated fatty acids levels and the risk of AD. We employed a quartz crystal microbalance (QCM) to show that phospholipid bilayers containing a higher content of unsaturated fatty acids are less capable of supporting Aβ aggregate growth and can influence the effect of aggregation inhibitors.

Together, this work reveals an important interplay between Aβ aggregates and their physiological environment and demonstrates that therapeutic and dietary interventions could work synergistically.

Bio: Dr. Moss received her doctorate in Chemical Engineering from the University of Kentucky and completed postdoctoral training at the Mayo Clinic. She joined the Chemical Engineering faculty at South Carolina in 2004, where she now serves as Director of the Biomedical Engineering Program. She has published more than 35 peer-reviewed manuscripts, with a current research focus in the area of amyloid protein aggregation in Alzheimer's disease. Dr. Moss was an NSF Graduate Research Fellow and an AHA Postdoctoral Fellow. As a faculty member, she has been the recipient of an NSF CAREER Award, a New Investigator Research Award from the Alzheimer's Association, and a Beginning Grant-In-Aid from AHA and has been part of an NIH-funded COBRE center. Dr. Moss is currently funded by NSF-BBE to study the evolution of early amyloid protein aggregates, by NSF-DMR to investigate rational design of nanoparticle as aggregation inhibitors, and by the NIH to investigate the propagation of Aβ oligomers. Dr. Moss received the 2012 Governor's Young Scientist Award and was named a 2010 Rising Star by the University. In addition, she has received a Mortar Board Excellence in Teaching Award, a Gibbons Distinguished Teaching Award, a Distinguished Undergraduate Research Mentor Award, the Ada B. Thomas Outstanding Faculty Advisor Award, and the Joseph M. Biedenbach Service Award.

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