

CORRELATION BETWEEN OLIGOMER CONFORMATION AND PATHOLOGICAL VARIATIONS IN ALZHEIMER'S DISEASE

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Widespread phenotypic differences observed among Alzheimer's disease (AD) patients are one of the diverse clinical manifestations in all neurodegenerative diseases. Deciphering the molecular mechanisms that underpin such differences especially for an idiopathic disease is rather challenging. Aggregation of amyloid- β ($A\beta$) peptides has long been known as the key trigger in AD pathology. Polymorphism observed within the aggregation end products of $A\beta$ fibrils seem to correlate with clinically observed pathologic variations, which has in part, corroborated the hypothesis that conformeric strains of $A\beta$ aggregates could manifest in distinct phenotypic outcomes. In our lab, we propose to understand this phenomenon in the context of whether and how the strains of low molecular weight oligomers could propagate their structure faithfully towards morphologically distinct fibrils with conspicuous pathological phenotypes. By biophysical investigations, we recently demonstrated that an $A\beta_{42}$ dodecamer called large fatty acid derived oligomers (LFAOs) is able to quantitatively replicate at low concentrations and at elevated concentrations, propagate their mesoscopic structure faithfully towards morphologically unique fibrils containing the discrete LFAO units. Furthermore, LFAO-seeded aggregates were able to selectively induce massive amounts of cerebral amyloid angiopathy (CAA) in transgenic CRND8 mice as opposed to unseeded or fibril seeded aggregates, which induced more parenchymal deposits. Results based on our model oligomer demonstrate that certain oligomeric strains could faithfully propagate their structure towards distinct fibrils and induce selective pathological phenotypes in the brain. Overall, these results bring forth important mechanistic insights into strain specific propagation of oligomers that have remained elusive thus far.

Biography

Vijay Rangachari has completed his PhD from All India Institute of Medical Sciences (AIIMS), New Delhi and Postdoctoral Studies from Florida State University and Mayo Clinic School of Medicine. He is currently the Chair of the Chemistry and Biochemistry Department at University of Southern Mississippi, a premier research and teaching institution. He has published more than 35 papers in reputed journals and has been serving many publication houses.

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