Tata Institute of Fundamental Research
Survey No. 36/P, Gopanpally Village, Serilingampally, Ranga Reddy Dist., Hyderabad - 500107

Students' Annual Seminar

Biophysical characterization of the interactions between Apolipoprotein E and Amyloid-β peptide

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Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by extracellular deposition of amyloid β (Aβ) peptides in the brain. Apolipoprotein E (ApoE) is a 299 residues lipoprotein that plays important roles in regulating metabolism of lipids and cholesterol. There are three major isoforms of ApoE namely: ApoE2 (Cys 112, Cys 158), ApoE3 (Cys 112, Arg 158), and ApoE4 (Arg 112, Arg 158). While ApoE is an important functional protein, ApoE4 is a major risk factor for Alzheimer's disease. Here we investigate the molecular mechanism of ApoE-Aβ interactions by comparing the effects of the different domains of ApoE on Aβ. Kinetics of aggregation of Aβ1-42 is delayed dramatically in presence of substoichiometric, nanomolar concentrations of N-terminal fragment (NTF), C-terminal fragment (CTF) and full-length ApoE. However, interactions between ApoE and Aβ measured by intermolecular Forster Resonance Energy Transfer (FRET) is found to be minimal at t = 0 but it increases in a time dependent manner. Thus, ApoE must interact with the one or more 'intermediates' rather than the monomers of Aβ. Kinetics of FRET between full-length ApoE4 labeled with EDANS at position 62 or 139 or 210 or 247 or 276, and tetramethylrhodamine labeled Aβ (TMR-Aβ), further support involvement of all the three domains of ApoE in the interactions. A competitive binding assay examining the effects of unlabeled fragments or full-length ApoE on the FRET between EDANS-ApoE and TMR-Aβ show that binding affinity of the full-length ApoE to Aβ is much higher than that of the fragments. Taken together, we hypothesize that high affinity of the ApoE-Aβ interaction is achieved due to multivalent binding mediated by multiple interactions between oligomeric Aβ and full-length ApoE.

Friday, Feb 8th 2019

10:30 AM (Tea/Coffee at 10:15 AM)

Seminar Hall, TIFR-H