Tata Institute of Fundamental Research
Survey No. 36/P, Gopanpally Village, Serilingampally, Ranga Reddy Dist., Hyderabad – 500 046

Webinar

Biophysical Characterization of Structure-Function Differences in the Apolipoprotein E Isoforms

Subhrajyoti Dolai

TCIS, Hyderabad

Apolipoprotein E (apoE) is one of the major protein constituents of lipoproteins which are responsible for transportation and regulation of lipids in human body. Human apoE has three isoforms; apoE2, apoE3 and apoE4. The isoforms differ at 112th and 158th positions by Cys/Arg variations. ApoE4 (C112R) is considered as the major genetic risk factor for Alzheimer's disease (AD) whereas apoE3 (C112) is considered normal. Previously, it was hypothesized that domain interactions between N-terminal domain and C-terminal domain in apoE is the main contributing factor in AD. It is believed that ApoE4 (C112R) displays domain interactions whereas apoE3 (C112) does not. The goal of my thesis is to examine domain interaction thoroughly using multiple biophysical techniques.

The work presented in this thesis shows that the free energy of domain interactions is nearly same in apoE3 and apoE4, indicating that there is no difference between these two isoforms. However, domain interaction measured by inter-domain FRET is more stable in apoE4 than in apoE3. The apparent contradictions are resolved by investigation of intermediate or 'molten globule' (MG)-like states, by measurement of fluorescence enhancement of bis-ANS and kinetics of HDX-MS. ApoE4 is found to possess considerably higher population of MG-like state(s) even under physiological conditions. We hypothesize that MG-like state(s) are responsible for the gain of toxic function of apoE4 contributing to the progression of AD.

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