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

Seminar

Investigation of conformational heterogeneity and domain interaction in the apolipoprotein E isoforms by HDX-MS proteins

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Apolipoprotein E (apoE), the major constituent of lipoproteins in the human body is responsible for the homeostasis of triglyceride and cholesterol. ApoE3 and apoE4 differ by a single amino acid residue substitution but exhibit remarkable differences in functionality. Pathologically, ε4 allele of apoE (codes for apoE4) is considered a major genetic risk factor of Alzheimer's disease whereas apoE3 is normal. X-ray crystallography shows that structures of the N-terminal domains of the apoE isoforms are quite similar. In this work, using Hydrogen-Deuterium Exchange by Mass Spectrometry (HDX-MS) we investigated the differences in the conformational heterogeneities between the apoE4 and apoE3. The experimental results combined with the numerical simulation enabled us to characterise the conformational heterogeneity in apoE. Further, we investigated the domain interactions between the N- and C-terminal domains in full-length apoE. We find that under native conditions, apoE4 exhibits extensive conformational heterogeneity and enhanced domain-domain interaction than apoE3. Peptide level (bottom-up) HDX-MS experiments identify the regions involved in domain interactions. We speculate that the extensive conformational heterogeneity and destabilisation of the N-terminal four-helix bundle due to enhanced domain interaction in apoE4 is responsible for its poor functional outcome in vivo.

Wednesday, Mar 19th 2025

11:30 Hrs (Tea / Coffee 11:15 Hrs)

Auditorium, TIFRH