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

Webinar

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

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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 the strongest genetic risk factor of Alzheimer's disease whereas apoE3 is normal. X-ray crystallography studies show that structures of the N-terminal domains of the isoforms of apoE are quite similar. In this work, we employed Hydrogen-Deuterium Exchange by Mass Spectrometry (HDX-MS) together with numerical simulation to investigate the structural heterogeneities between apoE4 and apoE3. We characterised the conformational heterogeneity of apoE and further examined the domain interactions between its N- and C-terminal domains in full-length protein. 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 or influenced by domain-domain interactions. The extensive conformational heterogeneity and destabilisation of the N-terminal four-helix bundle due to enhanced domain interaction in apoE4 may attribute to its poor functional outcome in vivo. We also developed a novel HDX-MS–based methodology for screening structure-corrector drug molecules that can potentially convert apoE4 into a disease-neutral, apoE3-like form. This approach may serve as a foundation for the development of effective therapeutics to combat Alzheimer's disease.

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11:00 Hrs