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

Seminar

The critical role of the variable domain in driving proteotoxicity and aggregation in full-length light chains associated with AL amyloidosis

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Light chain (AL) amyloidosis is the most common systemic amyloid disease caused by deposited amyloid fibrils derived from immunoglobulin light chains (LCs). Both full-length (FL) LCs and their isolated variable (VL) and constant (CL) domains contribute to amyloid deposits in multiple organs, with the VL domain predominantly forming the fibril core. However, the interplay of these domains in amyloidogenic behaviour and toxicity is not well understood. Using a patient-derived amyloidogenic λ6-LC AL55, this work explores the roles of both FL and isolated domains in aggregation and soluble toxicity. Biophysical analyses reveal that the isolated VL domain is partially folded, unstable, highly dynamic, proteolysis-sensitive, and slightly toxic. In contrast, the isolated CL domain is stable, proteolysis-resistant, and non-toxic, indicating that neither domain alone is the primary pathogenic factor in AL amyloidosis. FL AL55, on the other hand, forms well-defined dimeric structures with intermediate stability to isolated VL and CL domains. X-ray crystallographic analysis shows that its VL domains adopt unique open dimeric conformations, where two VL are virtually monomeric, a prerequisite to initiating protein aggregation. Slow refolding kinetic of FL confirms the unfolded VL domain as a kinetic trap and shifts the equilibrium towards misfolding and aggregation. Moreover, VL's open and misfolded conformation may aberrantly interact with cellular components in the crowding microenvironment, contributing to aggregation and soluble toxicity.

Monday, Dec 30th 2024

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

Auditorium, TIFRH