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

Seminar

Delineation of the aggregation pathways of tau protein using single-molecule fluorescence microscopy

Mahaprasad Soumitri Ranjan Sahu

TIFR, Hyderabad

Aberrant aggregation of tau protein underlies the pathology of diverse neurodegenerative diseases such as Alzheimer's disease, Pick's disease, and frontotemporal dementia with parkinsonism, yet the mechanisms of its self-assembly remains poorly understood. Here, we investigate aggregation pathways of tau, employing single-molecule fluorescence microscopy, viz., total internal fluorescence microscopy (TIRFM). We have used two isoforms of tau, viz., 4R and 3R tau. We show that in presence of RNA, tau undergoes liquid–liquid phase separation, forming condensates where nucleation occurs predominantly at the droplet surfaces. Then fibril elongation proceeds both within and outside condensates. In parallel, we identify novel tau–RNA nanoaggregates that are β-sheet-rich, yet kinetically arrested and growth-incompetent. These are distinct from the classical fibrils. Then we investigated the aggregation mechanism of 3R tau, which is involved in Pick's disease. Monitoring the growth of 3R tau fibrils revealed two distinct modes of growth. In addition to elongation, a fibrillar cloud was observed to grow around the pre-existing fibrils. The formation of these fibrillar clouds results from secondary nucleation. We conclude that the secondary nuclei are formed as a result of wetting of tau fibrils. Our findings highlight that tau aggregation occurs via heterogeneous pathways dependent on cofactors, and the solution environment. Understanding this complexity is crucial for elucidating the origins of disease-specific tau assemblies and for developing targeted therapeutic strategies.

Friday, Jul 18th 2025

14:30 Hrs (Tea / Coffee 14:15 Hrs)

Auditorium, TIFRH