Tata Institute of Fundamental Research
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Seminar

Role of RNA interactions in phase separation driven cellular compartmentalization and neurodegeneration

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Phase separation of RNA and RNA binding proteins (RBPs) underlie formation of dynamic membrane-less compartments (MLCs) such as stress granules and processing bodies in the cytoplasm or paraspeckles and Cajal bodies in the nucleus. These dynamic liquid-like MLCs convert to solid-like aggregates in neurodegenerative diseases- Amyotropic Lateral Sclerosis (ALS) and Frontotemporal Dementia (FTD). The defining features of the phase separation prone RBPs is the low complexity sequences which drive liquid droplet formation through multivalent promiscuous self-interactions. How do cells use these non-specific interactions to form specific MLCs and what prevents the transition from dynamic liquid-like assemblies to solid-like aggregates? To answer these questions, I used in vitro reconstitution approaches along with live cell imaging to characterize the phase behavior of the prion-like proteins FUS, TAF15, EWSR1, hnRNPA1 and TDP43. I found that RNA interactions control the phase behavior of these proteins in cells. My studies revealed that high concentration of nuclear RNA inhibits phase separation of prion-like RBPs but keep them in a poised state which facilitated nucleation of assemblies by long specific scaffold RNA. I also found that RNA interactions can delay the phase transition of the RBP assemblies to a solid-like state. This explained why mislocalization of RBPs to RNA poor cytoplasm in ALS and FTD results in formation of cytoplasmic aggregates. Based on these findings, I propose that RNA interactions have a broader implication for cellular compartmentalization and disease. In future, I will probe into effect of different RNA species and its properties on phase behavior of prion-like RBPs and its implication for neurodegeneration. I will also focus on the cellular mechanisms which control RNA metabolism and hence RNA interaction led cellular compartmentalization.

Monday, Jan 27th 2020

4:00 PM (Tea/Coffee at 3:30 PM)

Seminar Hall, TIFR-H