Tata Institute of Fundamental Research
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Seminar

Probabilistic origin of Alzheimer's Disease: A real time nanoscale molecular perspective

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Alzheimer's Disease (AD) is a complex neurodegenerative disorder characterised by the presence of neurofibrillary tangles and amyloid plaques. The Amyloid Cascade Hypothesis has been extensively studied to gain insights into the disease, but the initial mechanisms that lead to the excessive generation of toxic amyloids or the inability of the system to clear them from the brain remain unclear. Recently, the Probabilistic model of AD has emerged, which suggests that an altered penetrance and weight of the Amyloid pathophysiological cascade, combined with stochastic factors such as environmental exposures and lower-risk genes, contribute to the complex pathology of the disease. While most research focuses on the risk factors that control the formation of various proteoforms like amyloid beta, little attention has been given to the association of full-length Amyloid Precursor Protein (APP) and its variants with synaptic proteins or different risk factors, and how this association affects the local generation of different proteoforms. Although extensive investigations have been conducted into the role of APP proteoforms in health and disease, the mechanisms by which the stochastic real-time molecular organisation of APP's proteolytic machinery contributes to long-term deficits in Alzheimer's disease are not yet fully understood. The retention of Amyloid Precursor Protein in the local cellular environment can determine whether it undergoes an amyloidogenic or non-amyloidogenic processing pathway, which is one of the pathological hallmarks of Alzheimer's disease. The activity of secretases, as well as the spatial and temporal localisation and trafficking of APP and secretases in different subcellular organelles, regulates the propensity of amyloid-beta generation. Recent research has revealed insights into how molecules are organised into functional domains of a few hundred nanometres, contributing to the heterogeneity of localisation, retention, and trafficking of synaptic molecules and amyloidogenic machinery in synaptic sub compartments. Here, we present a unique data-driven quantitative model for synaptic amyloidogenic processing. We identify a set of novel molecular determinants that decide the fate of APP proteolysis at single synapses using super resolution imaging combined with reaction-diffusion models. Super resolution imaging and quantitative analysis are employed to pin down a nanoscale chemical map of the localisation of APP, β-secretase, and γ-secretase in functional zones of synapses such as postsynaptic density and endocytic zone. Additionally, we evaluate the association of these nanodomains of β-secretase and γ-secretase between themselves and with APP, revealing a heterogeneity in their nanoscale association and molecular content in both compartments. Furthermore, with the aid of reaction-diffusion models of unitary vesicles that arise from the endocytic zone, we demonstrate that even minor alterations in the molecular fingerprints of this synaptic nano-organisation can yield significant changes in the local product formation through amyloidogenic processing in single synapses. Finally, we confirm the competency of this model using AD-transgenic mouse models and post-mortem human brain tissues. Additionally, we show how divergent pathways could contribute to the generation of amyloid betas, where the presence of autosomally dominant mutations of APP is nucleated differentially at the nanoscale than the environmental risk factor. Our observations are consistent with a stochastic origin where the molecular organisation into functional domains of a few hundred nanometres is variable with subsynaptic compartments and controlled by Brownian diffusion of components and the copy number of the molecules of amyloidogenic machinery. By gaining additional insights into the molecular mechanisms that control the heterogeneity of APP localisation, we can better understand the molecular pathology underlying the onset of AD and how local changes in the rates of amyloid beta production. Altogether, these observations provide valuable insights into the heterogeneity in the local product formation at individual synapses.

Tuesday, May 2nd 2023

11:30 AM (Tea / Coffee 11.15 AM)

Auditorium, TIFR-H