BIOCHEMISTRY SEMINAR SERIES

Midstream Presentation - Fall 2020

“Investigating the atomic structures of prion-like assemblies formed by CPEB3”

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Prions are proteins capable of self-templating and self-propagating and are typically associated with neurodegenerative diseases. Yet, functional prion-like proteins are now known to be involved in a variety of biological functions ranging from controlling flowering time in plants to immune inflammatory responses in mammals. By nature of their structural transitions and beta-sheet rich amyloid conformation, they appear as an anomaly in the delicate framework of neurons. However, the molecular basis of memory formation requires a form of biological memory relying solely on self-replicating information as opposed to the traditional roles taken on by nucleic acids. This mechanism's endurance must be robust enough to withstand molecular turnover and sporadic environments within neuronal synapses. The Cytoplasmic Polyadenylation Element Binding Protein (CPEB) has been shown to form functional and robust puncta-like assemblies in activated synapses, promoting translation of proteins critical for synaptic plasticity. Previous experiments show that endogenously purified CPEB from Drosophila fly brain form reversible yet stable amyloid filaments. Here, I present my biochemical evaluation of a mammalian CPEB, CPEB3. I investigate its ability to form reversible, amyloid-like structures in-vitro, present two atomic resolution MicroED structures of CPEB3 segments and preliminary reconstructions of the CPEB3 prion-like domain determined by single particle cryo-EM.

“Structural Characterization of LECT2 Systemic Amyloidosis”

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Over 50 amyloid related diseases have been identified in humans to date. All of these are characterized by protein misfolding events leading to protein aggregation by fibrillization into a β -sheet rich structural form. These diseases occur in tissues throughout the body ranging from neurodegenerative diseases, such as Alzheimer's Disease, to systemic diseases like Type II Diabetes. One poorly understood amyloid disease is ALECT2. ALECT2 was only recently acknowledged as an amyloid disease and is characterized by the aggregation of the LECT2 signal protein in the kidneys ultimately leading to renal failure. To date, there has been no structural characterization of the amyloid state of the LECT2 protein, limiting our ability to design effective aggregation inhibitors or other treatments. We aim to characterize the amyloid state of LECT2 through structural studies of peptide segments and full-length fibrils using X-Ray crystallography, MicroED, and single particle Cryo-EM. Further, to address current limitations in phasing our electron diffraction data, we are working to develop new phasing methodologies. Specifically, we use the structure solution program ARCIMBOLDO, which uses secondary structure fragments as search models for PHASER and SHELXE analysis, to achieve fragment-based phasing of MicroED datasets which otherwise could not be determined.

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via Zoom

4:00 pm

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