JHU BIOLOGY DEPARMENT SPECIAL SEMINAR

Time-resolved cryo-EM visualizes snapshots of dynein's activation pathway

Guest Speaker

Aga Kendrick

Cellular & Molecular Medicine, University of California San Diego

Host: Trina Schroer

Abstract:

Regulation of cytoplasmic dynein-1 (dynein) is critical for diverse functions of eukaryotic cells, including cell division and long-range intracellular transport. Both dynein and Lis1, an essential dynein regulator, are mutated in patients with neurodevelopmental diseases and are conserved from fungi to mammals. Dynein is a dynamic molecule with activity controlled by an autoinhibited state called "Phi", in which its two motor domains interact in a way that prevents motility. Lis1 is important for promoting the formation of active dynein complexes; however, how Lis1 performs this function is unknown. Here, we use cryogenic electron microscopy (cryo-EM) and functional assays to determine the structural changes underlying dynein activation by Lis1. We capture an early intermediate step in the activation pathway, suggesting that Lis1 acts as a molecular wedge to activate dynein by breaking the autoinhibitory Phi conformation. To identify other steps in the activation pathway and account for the dynamic nature of dynein, we turn to time-resolved cryo-EM with highly heterogeneous samples. We introduce heterogeneity by adding ATP during our sample preparation, which allows dynein to go through its mechanochemical cycle. Using this approach, we capture numerous distinct dynein and dynein-Lis1 structures from the same sample and show that the presence of these different structures at different time points is regulated by Lis1. Based on our novel dynein-Lis1 structures we propose a new model for dynein activation, in which Lis1 relieves dynein autoinhibition and promotes conformations that are compatible with motility. Taken together, our approach and results highlight the importance of using time-resolved cryo-EM in studying highly dynamic processes.

Thursday, December 15th, 2022

4pm - Mudd 100