Yale Institute for Nanoscience and Quantum Engineering

Friday-March 30, 2018

12:00-1:00 PM

BECTON SEMINAR ROOM
Light lunch will be served at 11:45 a.m.

Yongli Zhang
Department of Cell Biology, Yale University

"Protein Folding and Dynamics Revealed by Single-Molecule Force Spectroscopy"

Forces hold everything together and determine the structures and dynamics of macromolecules. We have broad interests and skills in measuring the intra- and inter-molecular forces and the forces generated by molecular machines as a crucial step to understand their biological functions. We combine high-resolution optical tweezers and single-molecule fluorescence spectroscopy to manipulate and visualize single molecules in real time, revealing dynamic structures of proteins inaccessible by other experimental methods. Using this new approach, we have recently elucidated the mechanistic role of Munc18-1 in SNARE assembly and membrane fusion. Munc18-1 and SNAREs constitute the core machinery for fusion involved in neurotransmission and insulin secretion. Dysfunction of the machinery has been linked to neurological disorders and diabetes. However, the mechanistic role of Munc18-1 in membrane fusion has remained enigmatic despite intensive research spanning four decades. We found that Munc18-1 acts as a non-classical protein chaperone to catalyze step-wise assembly of three SNAREs (syntaxin, VAMP2, and SNAP-25) into a four-helix bundle. The catalysis requires formation of an intermediate complex as recently hypothesized, in which Munc18-1 juxtaposes the N-terminal SNARE motifs of syntaxin and VAMP2 but keeps their C-termini separated. Next, SNAP-25 quickly binds the templated SNAREs to form a partially-zippered SNARE complex. Finally, full zippering displaces Munc18-1. Munc18-1 phosphorylation and disease mutations modulate the stability of the template complex in a way that correlates with their effects in membrane fusion, indicating that the chaperoned SNARE assembly is essential for exocytosis.

Rui Ma
Department of Molecular Biophysics and Biochemistry, Yale University

"Structural Organization and Energy Storage in Crosslinked Actin-Assemblies"

Clathrin-mediated endocytosis (CME) is a key process in membrane trafficking. During CME, a patch of flat membrane is invaginated into an Ω-shaped tubule and pinched off into a vesicle. In yeast, this membrane deformation is hindered by high turgor pressure, and actin machineries are required to produce the forces counteracting the turgor pressure. How actin filaments are organized to generate the forces remains unclear due to the small dimension (100nm) of the structure. In this talk, I will present our simulations of self-organization of rigid actin filaments in the presence of elastic crosslinkers. We found that actin filaments condensed into a disordered meshwork or an ordered bundle in free space. Around a cylinder, actin filaments formed a tensed ring-like structure that tends to constrict the cylinder. Our simulations also demonstrated that these nanometer-scale actin structures could store a large amount of elastic energy within the crosslinkers (up to 10kBT per crosslinker). This conversion of binding energy into elastic energy is the consequence of geometric constraints created by the helical pitch of the actin filaments, which results in frustrated configurations of crosslinkers attached to filaments.

Host: Professor Corey O'Hern