Joint Condensed Matter
and Center for Soft Matter and
Biological Physics Seminar

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"A Mitochondrial Throttle: Lipid-Mediated Protein Complexes at the Mitochondrial surface"

Monday, October 5, 2020

4:00pm-5:00pm

Virtual Meeting:

Zoom Link: https://virginiatech.zoom.us/j/84402156548

Mitochondria are organelles found in virtually all eukaryotic cells. Mitochondria are not only "the powerhouse of the cell" but are also involved in multiple crucial cellular functions. Mitochondrial dysfunction plays a central role in a wide range of age-related disorders, neurodegenerations, and cancer. Mitochondria are composed of two membranes. The inner membrane plays a prominent role in power production via oxidative phosphorylation, while the mitochondrial outer membrane (MOM) acts as a "throttle", controlling the access of metabolites to the inner membrane and thus the rate of energy production. A significant portion of the control functions is carried on by the voltage-dependent anion channel (VDAC), a passive transport channel which allows water soluble metabolites and ions to cross MOM. Recent findings uncover an efficient regulatory mechanism of this channel through its interactions with cytosolic proteins. One such regulator is α-synuclein (αSyn), the intrinsically disordered neuronal protein highly expressed in nervous system and associated with Parkinson's Disease pathology. αSyn is directly involved in mitochondrial dysfunction in neurodegeneration. Probing the interactions of αSyn with VDAC nanopore by single-channel recordings we showed that αSyn induces transient blockages of the ionic current through the channel; identified as the insertion and escape of the unstructured charged C-terminal tail of αSyn into the channel in response to a transmembrane potential. The discovery of this novel regulatory mechanism of mitochondrial respiration has raised several fundamental biophysical questions, including a mechanism of αSyn transient blockage of the VDAC nanopore and translocation through it, and what role mitochondrial lipids assume in mediating the αSyn-VDAC interaction. In this talk, I will discuss of how we answer these questions by using a combination of single-molecule electrophysiology, theoretical modeling, and macroscopic biophysical studies of αSyn binding to planar and liposome membranes. The VDAC nanopore thus proves to be extremely sensitive single-molecule probe for peripheral membrane protein interaction with integral membrane proteins of mitochondria. This study could be important for the structure-inspired design of mitochondria-targeting agents.