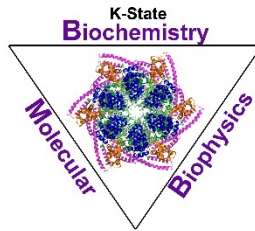


Ackert Hall, Room 120
Wednesday, November 5, 2025
4:00 P.M.



Coffee and Cookies
Chalmers Hall, Room 168
3:45 P.M.

Biochemistry

&

Molecular

Biophysics

Seminar

VCP/p97 Regulation by Cofactor Interactions and Conformational Switching

Dr. Stephanie Gates

Department of Biochemistry
University of Missouri

VCP/p97 is an essential protein unfoldase that extracts and unfolds ubiquitinated substrates in many cellular processes. p97's cellular location and function is regulated by a host of adaptor proteins, termed co-factors. The heterodimer Ufd1/Npl4 (UN) is a canonical co-factor that mediates p97's interaction with ubiquitinated substrates at the ER lumen in the process of Endoplasmic Reticulum Associated Degradation (ERAD). Dominant mutations in p97 cause the neurodegenerative disease, multisystem proteinopathy (MSP). The molecular underpinnings for the devastating defects caused by these mutants were not previously understood. We used biochemistry and structural biology to investigate the impact of MSP mutations on p97 activity and interactions with UN. We found that the mutations increased unfoldase and ATPase activity and co-factor binding affinity. Cryo-electron microscopy studies showed that the mutations caused a decoupling of the N-terminal domain conformation and nucleotide state that is observed in Wild Type, which changes the balance of how co-factors can bind and regulate p97. We have been investigating a novel p97 ERAD co-factor to understand its impact on p97 activity and substrate processing. Preliminary results indicate that the adaptor increases p97 ATPase activity and inhibits substrate processing. This study opens questions about how different co-factors interact with p97 in ERAD and their role in delivering substrates to the proteasome.