CHEMISTRY & CHEMICAL BIOLOGY COLLOQUIUM:

The Function and Mechanisms of UBQLN2-mediated Phase Transitions in Protein Quality Control and

Carlos A. Castaneda
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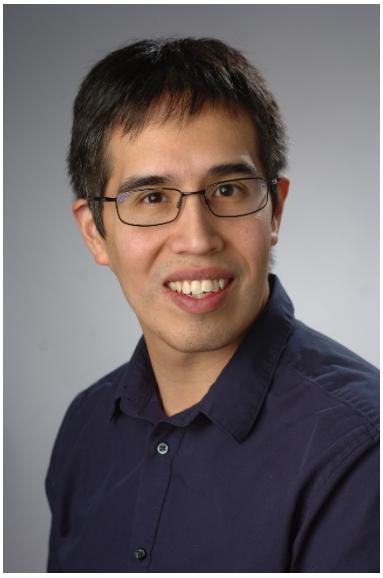
Date:
12/11/2020

Time:
1:30 PM - 2:50 PM

Link:
https://ucmerced.zoom.us/j/93194925460?pwd=L1NLaDhMUzNJa1VvTGhqT3kyYkU0UT09

About The Speaker:



Carlos A. Castañeda is an assistant professor of Biology and Chemistry at Syracuse University. He received his PhD in Molecular Biophysics from Johns Hopkins University working with Dr. Bertrand García-Moreno on the electrostatic energies of proteins. He completed his postdoctoral work with David Fushman at the University of Maryland-College Park. There, he entered the ubiquitin field studying the structure and function of all polyubiquitin chain types using NMR spectroscopy and small angle scattering techniques. There he published new methodologies to assemble all-natural polyubiquitin chains using unnatural amino acid incorporation. He received a NSF Postdoctoral fellowship while at UMD. Since starting at Syracuse University in 2014, Carlos began investigating the role of ubiquilin (UBQLN) proteins in protein quality control mechanisms in cells, particularly UBQLN2, an ALS-linked protein. His lab recently discovered that UBQLN2 undergoes liquid-liquid phase separation and is recruited to stress-induced puncta in cells. He has received two grants from the ALS Association, a CAREER award from NSF in 2018, as well as a NIH R01 in 2020. Some of his lab's recent work has been published in Molecular Cell, Structure, and J. Phys Chem B.

Abstract:

Liquid-liquid phase separation (LLPS) has recently emerged as a possible mechanism that enables ubiquitin (Ub)-binding shuttle proteins to form biomolecular condensates to facilitate the degradation of ubiquitinated substrates. Shuttle protein LLPS is modulated by multivalent interactions among their various domains as well as heterotypic interactions with polyubiquitin (polyUb) chains. We recently showed that the Ub-binding shuttle protein UBQLN2 colocalizes with stress granules in cells, undergoes LLPS in vitro and specific interactions with monoUb drive disassembly of UBQLN2-rich droplets.

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CHEMISTRY & CHEMICAL BIOLOGY COLLOQUIUM: Electronic Dynamics Underlying Molecular & Nanoplasmonic Light Harvesting Studied by X-Ray Spectroscopy

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Abstract (cont.):

UBQLN2 LLPS behavior is modulated by multivalent interactions involving its folded domains as well as the intrinsically-disordered STI1-II and proline-rich (Pxx) regions. For example, ALS-linked mutations in the Pxx region disrupt UBQLN2 LLPS by promoting liquid-to-solid phase transitions. We hypothesize that monoUb binding to the UBQLN2 UBA reduces the number of multivalent “stickers” that are important for promoting UBQLN2 LLPS. However, the effects of polyUb chains on UBQLN2 LLPS is not known. In this presentation, we show that UBQLN2 exhibits reentrant phase behavior in the presence of long polyUb chains, which stabilize and destabilize UBQLN2 LLPS at low and high polyUb to UBQLN2 ratios, respectively. Intriguingly, different types of polyUb chains affect UBQLN2 LLPS differently. The compact K48-linked polyUb chains moderately enhance UBQLN2 LLPS whereas the extended K63-linked chains substantially stabilize UBQLN2 phase separation over a wide range of polyUb to UBQLN2 ratios. These differences can stem from the preference of UBQLN2 for one type of polyUb chain over another, the conformational change in UBQLN2 upon binding to different chains, and polyUb chain conformations whereby extended chains might serve as better multivalent crosslinkers to drive UBQLN2 LLPS. These results have significant implications for the cellular functions of UBQLN2, which could modulate stress granule disassembly and/or dynamics through interactions with different polyUb chains. Moreover, UBQLN2 is involved in both proteasomal degradation and autophagy, which are typically, but not exclusively, signaled by K48- and K63-linked chains, respectively, as well as the oligomeric states of shuttle proteins. These observations provide mechanistic insights to how UBQLN2 could differentiate between proteasomal degradation and autophagy pathways via LLPS.

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