WPI CHEMISTRY & BIOCHEMISTRY

Department of Chemistry and Biochemistry
Worcester Polytechnic Institute

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12:00 PM
Gateway Park 1002

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"Floppy Proteins and Fuzzy Complexes: A Single Molecule Approach to Dynamic Structural Biology in the Postsynaptic Density"

Scaffold proteins allow for co-localization of signaling proteins lacking a direct interaction. Their evolution produced different combinations of binding modules that rewired signal transduction pathways. The synaptic Membrane-Associated Guanylate Kinase (MAGuK) scaffold proteins share the same highly-conserved binding domains connected by divergent linkers, which generates functional differences in learning and memory. We combine biophysical and single-molecule experiments with DMD simulations to describe the supertertiary structure and function of these dynamic proteins. MAGuKs are targets for tyrosine phosphorylation by Src kinase, but the extent and impacts of phosphorylation are poorly understood. We characterized the in vitro phosphorylation with mass spectroscopy, which revealed multisite phosphorylation. Phosphorylation elicited opposite responses by MAGuKs in the recruitment of key synaptic clients into supercomplexes. Surprisingly, phosphorylation affected biomolecular condensation in ways disconnected from changes in binding affinity. Phosphorylation sites were primarily in linkers rather than binding domains yet impacted function. To better understand the role of disordered linkers, we altered linker and surface properties and measured the impact on structure and activity. This revealed an enthalpic and entropic tug-of-war that controls supertertiary structure and dynamics. Changes in the linker alone were enough to alter biomolecular condensation without altering binding affinities. Our results suggest that the affinity of protein interactions is disconnected from the thermodynamics of phase separation.

Host: Suzanne Scarlata