BIOCHEMISTRY SEMINAR

Lipid Control of Receptor Tyrosine Kinase Assembly and Function

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Abstract: The EphA2 receptor exerts a profound influence on cancer malignancy through a bifurcated signaling behavior. EphA2 has two distinct modes of activation that have opposite effects on cancer outcomes. EphA2 acts as a tumor suppressor when it auto-phosphorylates cytoplasmic tyrosines after the binding of ephrin ligands. On the other hand, EphA2 can be activated in the absence of ligand when kinases including protein kinase A phosphorylate EphA2 at key serine residues. Under these conditions, EphA2 triggers oncogenic signaling that drives an invasive phenotype that leads to metastasis. Here, we developed a single-molecule method, SiMPull-POP, which achieves high sensitivity to quantify the oligomeric populations of membrane proteins. We applied SiMPull-POP to EphA2 to discover that cholesterol is a potent inhibitor of EphA2 assembly. Cholesterol also regulates EphA2 activity by preventing oncogenic phosphorylation of key residue Ser897. Our results additionally suggest that cholesterol controls *in trans* the activity and assembly of EphA2, by preventing b-adrenergic receptor-dependent cAMP activation of protein kinase A, which phosphorylates EphA2 serines.

EphA2 additionally impacts cancer therapeutics by facilitating resistance to EGFR therapies. We investigated lipid impact on the formation of membrane complexes between EphA2 and EGFR. We identified that the signaling lipid PIP2 promotes the formation of EphA2/EGFR complexes in cells. Taken together, our results illustrate the powerful effects that membrane lipids exert on the assembly and function of receptor tyrosine kinases that drive cancer malignancy.

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PURDUE UNIVERSITY

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About Dr. Barrera:

Dr. Francisco N. Barrera got postdoctoral training at Yale University with Donald M. Engelman. Dr. Barrera is Associate Professor (with tenure) in Biochemistry & Cellular and Molecular Biology at the University of Tennessee Knoxville, and Affiliated Faculty at the Shull Wollan Center, Oak Ridge National Laboratory. The Barrera laboratory is generally curious about membrane processes, with particular interest in receptor tyrosine kinases, lipid biophysics, membrane peptide design, pore formation, and the glycocalyx.

Dr. Barrera's service to the scientific community includes being Editorial Board Member of the Journal of Biological Chemistry, Member of the Publications Committee of the Biophysical Society, where he also served as Chair of the Membrane Structure and Function subgroup. He also organizes of the Membrane Proteins Interest Group at the Annual Meeting of the American Society for Biochemistry and Molecular Biology (ASBMB). Since 2024 he is standing member of the Macromolecular Structure and Function A (MSFA) NIH Study Section.