

Biophysical Journal

Know the Editors



Kalina Hristova
Johns Hopkins University

Editor, Membranes

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Q: What are you working on?

We are working to uncover biophysical principles that underlie protein-membrane interactions, as well as protein-protein interactions in cellular membranes. In one project, we are developing methods to probe the stoichiometry and stability of protein complexes in biological membranes using Förster resonance energy transfer (FRET). We design our experiments such that receptor concentrations are varied over a wide range, and we measure concentrations in the plasma membranes, along with the FRET efficiencies. Thus, we can assess what type of oligomer provides the best description of the data, calculate the dimeric/oligomeric fractions, calculate the association constants in the plasma membrane, and monitor structural changes that occur due to ligand binding or pathogenic mutations. This year, we published a new methodology called Fully Quantified Spectral Imaging FRET that allows us to make such measurements in live cells. This method increases the precision of the FRET measurements by utilizing two-photon excitation and the acquisition of complete emission spectra.

We are using these methods to study the activation of receptor tyrosine kinases, which are known to transduce biochemical signals via lateral interactions in the plasma membrane. Our recent work has revealed novel mechanistic knowledge about their mode of activation in response to ligand. In the past, the ligands were believed to be absolutely required for receptor dimerization. We have shown, however, that the receptors form dimers in the absence of ligand, and that ligand binding triggers structural changes in the dimers which increase the kinase activity. Thus, the mode of

activation is more complex than originally thought. We are beginning to understand how the recognition of different ligands by a receptor is accomplished. For some receptors, the transmembrane helices sense the identity of the ligand and adopt ligand-specific dimer configurations that correlate with different activity levels.

In a different project, we are working to understand the interactions between novel classes of peptides and biological membranes. Some of these peptides have very intriguing biophysical properties, which we are characterizing. We hope that we can eventually use these peptides to deliver drugs to cells, or across the blood-brain barrier.

Q: What excites you most about your research?

It is relatively easy to acquire beautiful binding curves for soluble proteins, but it has always seemed impossible to do so for membrane proteins. My dream was to develop methodologies that make such measurements feasible for membrane proteins. Dedicated and talented lab members have now made my dream a reality. When we were finally able to analyze membrane protein interaction data from live cells, we saw that the data follow binding curves that can be predicted based on the law of mass action, yielding apparent equilibrium constants. For us, this was a discovery, and a very exciting one. The membrane proteins we study control cell growth and differentiation and are implicated in many diseases, and this discovery suggested that cellular responses in health and disease can be understood and predicted based on quantitative maps of protein interaction strengths.

Our projects focused on peptide-lipid interactions are also very exciting, as the membrane-active peptides that we work with have unique properties that are not found in nature. Some of the peptides have been discovered through high-throughput screening for specific functions. The mechanism of their action, however, is not well understood and appears very complex. Each new experiment brings new surprises, new questions, and new pursuits.