Award ID:
R1215

Project Title:
Recruitment of First-Time, Tenure-Track Faculty Members

Award Mechanism:
Recruitment of First-Time, Tenure-Track Faculty Members

Principal Investigator:
Levental, Ilya

Entity:
The University of Texas Health Science Center at Houston

Lay Summary:

I received a BS in Chemical Engineering at Georgia Tech while doing two years of undergraduate research on nanobiotechnology under Dr. Gang Bao, which yielded a platform presentation at the National Biomedical Engineering Society Meeting in 2006. I went on to a PhD from the Department of Bioengineering at the University of Pennsylvania, where my interest in the molecular mechanisms and biological role of membrane structure developed during my doctoral thesis in the laboratory of Dr. Paul Janmey. My investigations of purified lipids revealed an interplay of electrostatic repulsion and hydrogen bonding that results in microdomains enriched in polyphosphoinositides (PPIs), central signaling lipids in eukaryotes. Most significantly, these microdomains are modulated by pH and [Ca2+], suggesting mechanisms by which signaling through PPIs (e.g. PIP2) could be regulated by intracellular factors which modulate lipid structure.

Also in my thesis work, I collaborated with Dr. Tobias Baumgart on a novel and exciting tool to study functional phase separation in biological membranes – i.e. lipid rafts. We discovered factors that regulate phase separation of isolated plasma membranes and their modulation by cholesterol. My postdoctoral research has focused on the structural factors determining protein partitioning between coexisting domains in isolated plasma membranes and represents my greatest scientific success to date. I conceived the ideas for this project independently, and applied for postdoctoral funding through the Humboldt Foundation. I received this prestigious grant and undertook the work in Kai Simons' lab at the Max Planck Institute of Molecular Cell Biology and Genetics. There, I developed the first quantitative assay for raft association and showed that the length of a protein transmembrane domain (TMD) determines raft partitioning, with longer TMDs preferring thicker, more ordered raft domains. This partitioning is regulated by palmitoylation (a dynamically reversible post-translational fatty acylation) for the majority of integral membrane proteins. Importantly, raft partitioning correlates with protein sorting to lysosomes, establishing a functional link between microdomains and protein degradation. The experience of leading a project from conception, through funding and execution, to publication has convinced me of my potential for success in academic research.

My future aims are to use classical cell biology, biophysics, synthetic biology and computational modeling to characterize the role of membrane structure in the regulation of cell function, specifically in the context of oncogene addiction in breast cancer cell signaling. I intend to elucidate the microdomain-dependent functions of oncogenic

growth factor receptors and associated downstream second messengers. A related aim is to establish quantitative tools to measure post-translational protein modification by lipids, which is a central mechanism for regulation of membrane association and sorting. These tools will then be used to define the dynamics of protein lipidation in aberrant signaling of transformed epithelial cells. The ultimate goal of these research aims will be to develop small molecule agents to modulate microdomain association and post-translation lipidation of proteins involved in proliferative and anti-apoptotic signaling for therapeutic intervention in breast carcinomas.