CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Award ID:
R1216

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

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

Principal Investigator:
Jaqaman, Khuloud

Entity:
The University of Texas Southwestern Medical Center

Lay Summary:

I obtained my B. Sc. degree in physics from Birzeit University in the West Bank in 1998, where I had the honor of being the graduation commencement valedictorian. As I was always fascinated by scientific discovery but research opportunities were scarce in the West Bank, I started graduate school right after finishing my undergraduate education. I went to Indiana University Bloomington and worked toward a Ph. D. in biophysics under the mentorship of Prof. Peter Ortoleva. My research was in the field of molecular dynamics, where I devised efficient methods for the computational modeling of protein folding. I obtained my Ph. D. degree in 2003.

For my postdoctoral training, I decided to work at the interface between experimental cell biology and mathematical modeling; I had reached the conviction that the two approaches combined were much more powerful than each in isolation for advancing our understanding of cell biological systems. Thus I joined the group of Gaudenz Danuser at the Scripps Research Institute, funded in part by a Helen Hay Whitney postdoctoral fellowship award.

When I first joined the Danuser lab, I was very interested in questions of cell division. In collaborations primarily with the Sorger (HMS) and Swedlow (U. Dundee) labs, I developed quantitative live-cell imaging approaches and statistical time series analysis methods that allowed us to elucidate the molecular factors that regulate kinetochore microtubule dynamics to ensure accurate chromosome segregation. As I immersed myself in the world of cell biology, my interests shifted and I became fascinated by questions of receptor organization in the plasma membrane and its role in transmembrane signal transduction. Thus, in collaboration with the Grinstein lab (Hospital for Sick Children, Toronto), I did a single molecule study to determine what factors regulate the dynamics, clustering and consequently function of the cell-surface scavenger receptor CD36 in macrophages. For this I developed an image analysis algorithm that can track densely-labeled receptors and capture their clustering events, a challenge in single molecule imaging. With the help of the analytical tools that I developed, we found that CD36 dynamics in the plasma membrane are regulated by the cytoskeleton in a manner that enhances unligated receptor clustering, thus priming macrophages to respond when exposed to ligand.

Building on these technological developments and discoveries, the goal of my research program is to understand the spatiotemporal organization of receptors in the plasma

membrane at the single- molecule level, as a means to elucidate the critical first steps in signal transduction. There is increasing evidence that cell surface receptors are highly organized within the plasma membrane through complex networks of inter-molecular interactions, yet how this receptor organization is achieved, how it influences transmembrane signal transduction in normal physiology, and how it is altered in cancer pathophysiology are questions of fundamental importance that remain largely unanswered. I am particularly interested in the signaling pathways that regulate angiogenesis, the process of sprouting new blood vessels from the existing vasculature. During cancer progression, these pathways are disrupted to promote angiogenesis, thus supporting tumor growth and producing tortuous and leaky blood vessels that can facilitate cancer cell metastasis.

Advancing our understanding of the mechanisms of transmembrane signal transduction might suggest design principles for new classes of therapeutic agents that target the interactions between cell- surface receptors to initiate, modulate or inhibit intracellular signaling. In the specific case of tumor- associated angiogenesis, it might reveal new strategies to inhibit and/or normalize angiogenesis based on the cellular mechanisms that keep angiogenesis properly balanced in normal physiology.

In autumn of 2009, I took an instructor position in the Department of Systems Biology at Harvard Medical School, sponsored by Peter Sorger. Through this position, I have started a single molecule study of the anti-angiogenic signaling of the extracellular matrix protein thrombospondin-1 via two of its receptors, CD36 and ß1-integrin. Going forward, I plan to expand this research to study the interactions between various other critical pro- and anti-angiogenic receptors. My goal is to establish how these interactions initiate intra-cellular signals, what molecular and cellular factors regulate them, and how they are altered within the tumor microenvironment to promote angiogenesis.