NORTHERN ARIZONA UNIVERSITY

Center for Bioengineering Innovation

2016 Lecture Series

Fibronectin Recycling is Involved in the Regulation of the ECM

Fibrillogenesis in Renal and Cancer Cell Hypoxia

Dr. Archana Varadaraj

Friday, November 18, 2016
1-2 p.m.
Biology (building 21), room 256

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In the last few decades it has become increasingly well accepted that the extracellular matrix (ECM) functions not just as an inert scaffold but also as an active signaling site impacting cellular response and behavior. Fibronectin is an ECM protein that affects the rigidity of the matrix by signaling through its transmembrane integrin α5β1 receptor resulting in the self-assembly of dimeric FN into polymeric fibrils–a process called fibrillogenesis. Our work demonstrates an entirely new cellular process of extracellular matrix (ECM) remodeling involving the rapid recycling of fibronectin (FN) for fibrillogenesis. We demonstrate through several biochemical, and microscopy based approaches that FN undergoes a novel trafficking route that is not linked to its degradation but instead to its incorporation into fibrils. Transforming Growth Factor β that is upregulated in many cancers, greatly enhances FN trafficking in non-cancerous mammary epithelial cells in a non-transcriptional and SMAD independent manner. Mechanistically, using a combination of proximity ligation, coimmunoprecipitation and patch/frap techniques we demonstrate an interaction between TβRII's (Transforming Growth Factor β Receptor Type II) cytoplasmic domain and integrin α5β1 and the requirement of this interaction for fibrillogenesis. This work is to our knowledge the first study demonstrating the direct trafficking and recycling of an ECM ligand and the role of a growth factor in driving this process. These findings are of broad relevance to the study of cancer invasiveness, motility and disease and provide the basis for our future studies on cancer cell hypoxia and matrix rigidity.

Dr. Archana Varadaraj completed a graduate education at the University of Cambridge, UK, where she investigated the response of PML-NDs (Promyelocytic leukemia nuclear domains) to DNA damage. Using isogenic cell lines that lacked essential genes in the damage pathway, the work was able to demonstrate the role of PML-NDs as a signaling mediator in the damage process. Her postdoctoral work at the European Oncology Institute in Milan focused on the degradation of the Von Hippel Lindau tumor suppressor protein that is often mutated or lost in renal cancers. The research showed that certain viral proteins as well as inhibitors of inflammatory cytokines degrade VHL resulting in a cellular switch towards hypoxia and an angiogenic state. Dr. Varadaraj then worked on two cellular states 1) adherent cells with an intact ECM and the molecular response to TGFβ in affecting matrix rigidity and 2) adherent cells with a propensity to metastasize and the role of growth factor GDF2 in enhancing anoikis or anchorage-dependent cell death.