University of Cyprus
Department of Biological Sciences

Ph.D. Thesis Defense

Student Presentation

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""Roles of tension driven ligand independent integrin activation in physiological cellular processes""

Integrin receptors mediate cell adhesion through their interactions with extracellular matrix (ECM) components and the formation of focal adhesions (FAs), linking the ECM with the actin cytoskeleton. Integrins exist in different conformations, which correspond to different states of activation and affinity for ligand binding. Interaction with a ligand is necessary for full activation of the receptor; however, it has been shown that ligand independent activation of integrins is possible. Previous work from our group showed that integrins can be activated by plasma membrane (PM) tension at the cortex of mitotic cells, leading to the recruitment of FA proteins and formation of the cortical mechanosensory complex (CMC). The CMC is established on the lateral cortex, at a distance from the substrate and is essential for spindle responses to external mechanical stimuli. In this study, we show that, on cadherin substrates, integrin activation takes place at the cortex of the cell in the absence of integrin ligands and cell-ECM interactions. Integrins at the cortex acquire the extended closed headpiece conformation in agreement with the absence of ligands. We show directly that retraction fibres (RFs) exert forces on the cortex of metaphase cells, and that force sensing is only required for spindle orientation when mitotic cells fully round up and display no shape anisotropy. We show specifically that a core member of the CMC, the focal adhesion kinase (FAK), is only required for correct spindle orientation in cells that do not maintain shape anisotropy. We go on to show that PM tension driven, ligand independent activation of integrins also takes place at adherens junctions (AJs). AJs spatially guide the clustering and activation of integrin receptors in a ligand independent fashion, again promoting the acquisition of the extended with closed headpiece conformation. Integrin activation at AJs promotes the recruitment of several FA proteins, leading to the formation of hybrid adhesions (HAs), in which FA and AJ components are spatially segregated but co-exist in a single adhesive unit. AJ associated integrin clustering and activation depend on actomyosin generated tension, and promote AJ disassembly in a caveolar endocytosis and microtubule network dependent manner. Finally, we show that AJs spatially influence integrin ligand binding on the cell surface by guiding the distribution of high ligand affinity integrin receptors. Collectively, we demonstrate two different contexts in which ligand independent integrin activation takes place through PM tension, impacting intracellular processes such as spindle orientation, AJ dynamics and BM formation.