ME PhD Thesis Colloquium

Mechanobiology of cell-substrate interaction

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ABSTRACT

Cells attachment to substrates is a complex process facilitated by focal adhesion complexes (FA) that help them perform vital cellular functions like migration, growth, and division. Cells probe their mechanical milieu through contractile stresses generated *via* cross-bridge cycling between actin and myosin. These stresses induce an exquisite feedback between the substrate and acto-myosin stress fibers, resulting in remodeling of the cytoskeleton and FA. A repertoire of signaling molecules, including calcium and a mechanosensitive protein, talin, in FA complexes, facilitate these interactions. How do tractions change along the cell length? Do cells remodel under dynamic mechanical loads in tissues such as arteries? How do individual components of the FA regulate cell adhesions? I use numerical methods to address these questions on cell-substrate interaction.

As a first study, I quantified the cell tractions using micropatterned pillar array detectors (mPAD) created using soft lithography. Results from our study show that mPAD topography resulted in persistent migration of fibroblasts. I used image analysis to quantify the micropillar deflection and computed tractions using a neo-Hookean constitutive model to report variations in tractions along the cell length. We next developed a multi-scale computational cell model, incorporating stress fiber, calcium signaling, and FA dynamics, to investigate the effects of cyclic stretch and substrate stiffness on cell-substrate interactions. We used the modified Hill model and reaction-diffusion equations to model stress fiber contractility in the presence of calcium. The attachment of adaptor proteins, representing FA, was simulated using a stochastic Gillespie algorithm in tandem with finite element analysis. The model shows that adhesions and tractions vary along the cell length under static and cyclic stretch conditions; the maxima occurred at behind the cell edge. Cell tractions and adhesion increased initially with substrate stiffness and ligand density but decreased beyond an optimum substrate stiffness. Cyclic stretch enhanced tractions and adhesions on compliant substrates; in contrast, these were reduced on stiff substrates.

We quantified the influence of mechanosensitivity of talin to substrate stiffness and corresponding traction development at various locations in the cell. Talin orchestrates FA formation and aids in force transfer to cytoskeletal actin in the presence of vinculin. We simulated the force response of talin using a composite worm-like chain model. We show that the talin-vinculin assembly is mechanosensitive to substrate stiffness and extension rate. Talin extension on stiffer substrates resulted in higher tension and vinculin recruitment. A lower talin extension rate was accompanied by the delayed unfolding of the helical domains and corresponding lower tractions. As a final study, I incorporated the talin model into the multi-scale cell model to explore talin's role at different spatial locations during cell adhesion. We demonstrate that the talin force was lower at the cell edge and was dependent on actin flow compared to regions located away from the edge. Together, these studies show the importance of adaptor protein mechanics in substrate sensing during adhesion and in response to mechanical stimuli.

ABOUT THE SPEAKER

Siddhartha Jaddivada is a Ph.D. student in the Dept. of Mechanical Engineering, IISc. His research interests include biomechanics, solid mechanics, finite element methods, and microfabrication. He works with Prof. Namrata Gundiah in the Biomechanics Lab, IISc.

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