

MAE Seminar SERIES

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ROLE OF MECHANOSENSITIVE PIEZO1 PROTEINS IN MECHANOTRANSDUCTION OF ADHERENT CELLS

ABSTRACT

Cells experience a range of forces from their surroundings that modify their development, behavior and fate. Two prominent forces acting on adherent cells are fluid shear stress at the apical surface and extracellular matrix (ECM) cues from the underlying basement membrane. Previous work showed that these forces caused cell remodeling, however, how cells sense the forces and formulate the response is unclear. In recent years, mechanosensitive Piezo1 ion channels have shown evidence as flow sensors in endothelial cells and as ECM force sensors in neurons and epithelial cells. In our study, we investigated the role of Piezo1 channels in sensing and transducing these two prominent forces in adherent cells, particularly in epithelia. Using MDCK cells as our model, we studied the underlying mechanisms of cell remodeling under fluid shear stress. We show that shear stress causes nuclear shrinkage through Piezo1 mediated Ca^{2+} uptake. Contrary to the popular opinion, that, external forces reach nucleus through cytoskeleton network, we found that fluid shear stress causes the nuclei to shrink through a Ca^{2+} dependent signaling pathway. Piezo1 inhibition blocked the nuclear shrinkage and the activation of piezo1, triggered the shrinkage without shear stress. Piezo1 knockdown with silencing RNA also minimized nuclear shrinkage, suggesting that Piezo1 channel is a key element for transmitting shear force input to nuclei. The cells sensory on ECM mechanical cues was studied by micropatterning the substrates with adhesive proteins and by modifying the stiffness of the substrates. We show that Piezo1 activity is required for cells to follow a patterned substrate. A knockout of Piezo1 eliminated elongation. Furthermore, inhibiting Piezo1 conductance produces different results than a knockout so that Piezo1 may have effects beyond its role as an ion channel. In comparison, MDCK cells respond to substrate stiffness variations with profound cytoskeletal reorganization with minimal changes in their size and shape. Cells on hard substrates show abundant F-actin bundles that are reorganized to peripheral actin rings on soft substrates. Inhibition or knockdown of Piezo1 induces an actin reorganization on hard substrates. These results suggest that cell's response to ECM mechanical properties is coupled by Piezo1 mediated Ca^{2+} signaling. Rho-ROCK pathway is involved in both processes. In conclusion, our study demonstrates that Piezo1 is a primary force sensor in epithelial cells, which mediates the cell response to changes in local mechanical environments.

BIO SKETCH

Deekshitha Jetta is a Postdoctoral Fellow at the Hospital for Sick Children affiliated with University of Toronto. She recently received her PhD in Mechanical and Aerospace Engineering, with a specialization in Bioengineering at University at Buffalo. Her research focuses on using microfluidic technologies to build in vitro assays for studying the mechanosensitivity of cells. She is interested in developing a 3D model mimicking the brain architecture to study how the tissue folding, curvature influences brain tumor initiation, growth, and therapy response.



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