Mechanobiology provides insight into disease and healing processes

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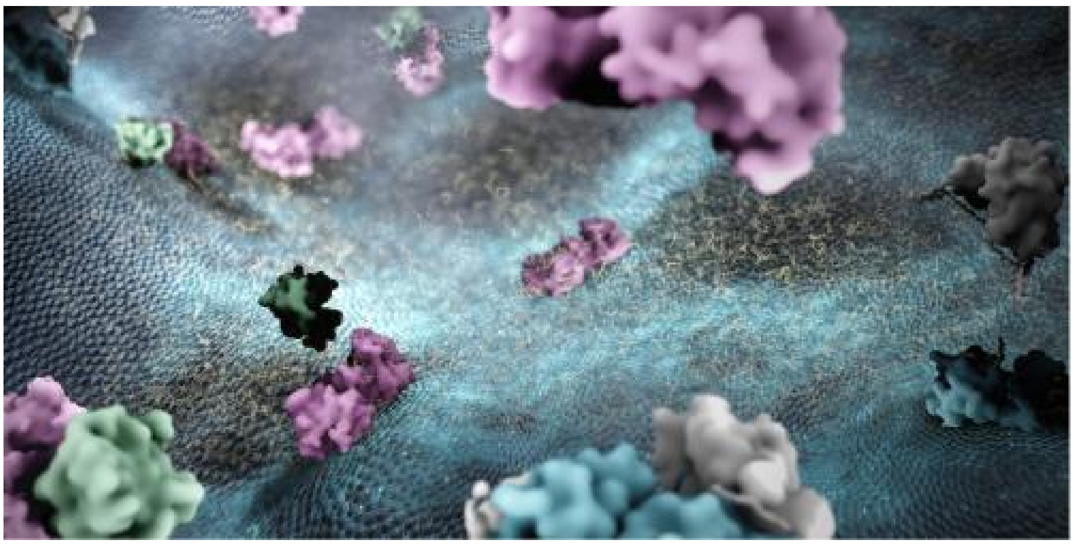

Credit: Dr Larisa Bulavina

Researchers in Singapore are gaining further insight into how the mechanical environment of cells drives fundamental cellular processes such as motility, growth and survival. These processes are integral to many clinical challenges, from cancer prognosis to wound healing and skin repair.

Cells are constantly exposed to mechanical stimuli such as compressive or elastic forces, or the push or pull between neighbouring cells. How a cell responds to these forces is determined by the presence of molecular mechanoreceptors and mechanotransducers. These include stretchable

proteins located at the cell membrane as well as a dynamic network of contractile filaments, known as the cytoskeleton. Since mechanical signals are integrated into biochemical signalling pathways, mechanotransduction mechanisms influence basic cellular processes, right down to nuclear dynamics
and gene transcription.

With these principles in mind, researchers from the Mechanobiology Institute (MBI) at the National University of Singapore are exploring the interplay between cell mechanics and biochemical pathways. They hope to gain insight into its contribution to physiological functions and disease progression.

Controlling cell proliferation

In one study led by Professor Jay Groves, MBI researchers examined the regulation of "Ras" (a protein involved in cell proliferation) at a level never before achieved. Using an innovative device developed at MBI called the MembraneChipTM, the team visualised for the first time the activity of individual SOS proteins, which are key regulators of Ras. The team found that when SOS proteins adopt a rare but highly active conformation or shape, a single SOS molecule could activate thousands of Ras molecules. This finding could have important implications given that the Ras protein plays a key role in cancer progression.

In another study, led by Professor Low Boon Chuan, MBI researchers discovered that an interaction between Ras and a second protein called Rho, which is involved in cytoskeleton regulation, can slow the growth of certain Ras-induced liver cancers in zebrafish. Specifically, they found that the concurrent expression of two particular forms of these proteins can slow tumour growth and increase survival rates. Since the tumours they studied closely resembled the most common type of human liver cancer, this finding may lead to new therapies to help suppress the spread of this disease.

Harnessing cell motility

Another area of interest to MBI researchers is cell motility (the movement of cells), which is essential for wound healing and skin repair. Here, cytoskeletal dynamics generate the forces required to initiate and maintain cell movement. Cell-to-cell adhesions allow these forces to be transferred between cells and enable cells to move together in a process known as collective cell migration.

By growing cells on tiny pillars and controlled substrates, MBI researchers can simulate wound healing and measure the forces the cells generate. In one study, a team headed by Professor Chwee Teck Lim and Professor Benoit Ladoux observed the formation of epithelial cell bridges, which were supported almost entirely by adhesive forces between individual cells. In a second study, Professor Ladoux and his colleagues identified a novel mechanism involved in wound healing, whereby contractile protein filaments made by individual cells join together and compress the material under the wound to help speed up the repair process.

Next steps

MBI researchers are continuing to explore the role of mechanical stimuli and physical forces on cellular processes such as motility, cell invasion, differentiation and cytoskeleton dynamics. The institute's major focuses include how mechanical signals influence nuclear dynamics and gene expression, how mechanical signals translate into biochemical signals, and the dynamics of cell adhesion.

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