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Editorial

Special Issue: Experiments and Modeling in Micro- and Nano-Biomechanics

The field of biomechanics is experiencing a rapid growth in the area of mechanical analyses of biological systems at micro- and nano-scales. Research in this area involves quantitative analyses of mechanical properties of macromolecules, organelles, and cells, mechanisms of molecular interactions within a cell, between different cells, or between cell and its microenvironment, and mechanisms of cellular responses to mechanical cues. These studies have led to better integration between biomechanics and modern biology, and allowed biomedical engineers to stay in the forefront in addressing fundamental issues in biology.

Advance in micro- and nano-biomechanics research has been accelerated by recent developments in biomaterials and enabling technologies as well as discoveries in molecular biology, genomics, and systems biology. New technologies, such as atomic force microscope, optical and magnetic tweezers, and modern optical microscopes, have allowed better control or more precise measurements of forces and deformation at micro- and nano-scales; novel biomaterials have led to creation of better microenvironment or substrates of cells that can closely mimic those observed in tissues; and new biomarkers and molecular sensors have greatly improved sensitivity in detection of cellular responses to mechanical and chemical stimuli.

Micro- and nano-biomechanics is an active research field around the world. This Special Issue aims to show some of the significant contributions by investigators from Asian countries. The invited papers are divided into two groups: computational and experimental. In experimental studies, Matsumoto *et al*. demonstrated that hypertension-induced hypertrophy of smooth muscle in aorta was accompanied by a decrease in actin filaments, which could lead to reduction in cell stiffness and cause cell transformation from contractile to synthetic phenotype. Results from this study provided a direct connection between hypertension-induced changes in morphology and contractility of smooth muscle cells (SMCs). SMC contraction may cause changes in focal adhesions (FAs) that are demonstrated in the study by Nagayama and Matsumoto. They quantified dynamic changes in traction forces at FAs and morphological changes of FAs during cell contraction. The data showed that serotonin stimulated cell contraction increased both traction forces and FA size in the direction of cell major axis. The size increase was initially due to the growth of FAs but involved merging of FAs along actin stress fibers at a later stage. These observations suggested that cell contraction could strengthen cell adhesion to extracellular matrix (ECM), which in turn facilitated transmission of contraction forces to ECM. In addition to active contraction, SMCs can be deformed passively in aorta due to oscillation in systemic blood pressure. The deformation may cause cell damage or trigger apoptosis. Qi *et al*. investigated apoptosis of vascular SMCs induced by cyclic stretch. The data showed that the induction of apoptosis could be blocked by inhibiting RACK1 expression and the subsequent Src activity. Huang *et al*. studied an alternative signaling pathway, which originated from intercellular junctions but did not involve the well-known FAK, in the regulation of FA redistribution during orientation of endothelial cells in a confluent monolayer under cyclic stretch. They found that the blockage of intercellular junctions via inhibiting SHP-2 reduced redistribution of paxillin but not beta-1 integrin.

Primary cilium has been considered as a mechanosensor in bone cells. It can sense fluid shear stress and release signals to induce osteogenic responses. Jeon *et al*. investigated the responses of osteoblasts to shear stress, in terms of COX-2 production and PGE2 release. The data showed that the cellular responses required the presence of primary cilia, activation of FA kinase (FAK), and phosphorylation of Akt. This information could be used in future studies on specific intracellular signaling pathways involved in cellular response to mechanical stimuli.

Focal adhesion is a more common mechanosensor for structures and properties of cellular substrate that can modulate various cell behaviors. Okeyo *et al*. investigated the coordination between cell adhesion to substrate and lamellipodia protrusion during migration of fish epidermal keratocytes seeded on fibronectin coated, rectangular areas separated with adhesion-suppressed gaps of varying widths. The suppression of cell adhesion to substrate inhibited lamellipodia protrusion into the gap region. To overcome the adhesion

barrier, actomyosin contractility was upregulated by treating cells with calyculin, which enhanced actin cytoskeleton integrity and increased the width of lamellipodia. As a result, cells could protrude lamellipodia to cross bigger gaps. Koo *et al*. investigated responses of human keratocytes to topographical and mechanical cues from the substrate by culturing cells on chitosan or polydimethylsiloxane surface patterned with different gratings. The responses were quantified in terms of cell alignment and elongation, alignment of type I collagen deposited by cells on the substrate, and aldehyde-3-dehydrogenase expression. It was observed that the cellular responses were more sensitive to differences in topographical cues than in substrate stiffness. Additionally, the extent of responses was higher on the surface with nanogratings than microgratings.

Mendoz and Lim developed an experimental method for investigation of collective migration of cells in monolayers. It combined a modified ring cell migration assay with single cell tracking technique to determine the dependence of collective spreading of cell monolayer on motility of individual cells. This method was used to demonstrate the correlation between morphological changes in lamellipods, intercellular adhesion, and collective migratory behaviors of benign and malignant breast tumor cells cultured on different substrates. The study revealed that the benign cells exhibited more coordinated movement compared to the malignant ones, and this difference in cell migration could be attributed to unique phenotypes of these cell lines, in terms of lamellipod formation and cell-cell adhesion.

Three theoretical studies are included in this Special Issue. Fu *et al*. developed a kinetic model that combined a two-body collision theory with the probabilistic modeling of binding kinetics. The model was used to predict aggregation dynamics of blood cells mediated by interacting molecular pairs under shear flow. Results from numerical simulations fitted well to the measured heterotypic or homotypic aggregation. The model also predicted the underlying kinetic and biophysical parameters. In the second study, Zhong *et al*. developed a multiscale mathematical model to simulate dynamics of disassembly of focal adhesions and formation of stress fibers in cells on a cyclically stretched substrate. The model considered coupled mechano-chemical interactions at cellular, subcellular and molecular levels. Results from the simulation demonstrated that substrate stretching could induce cell reorientation that depended on competition between two processes: collapse of focal adhesions and formation of stress fibers. The former could be modulated by stretch frequency whereas the latter was less dependent on the frequency. These results might be useful in explaining a biphasic behavior of cell reorientation. In the third study, Li *et al*. developed an anomalous space subdiffusion model to simulate spatial characteristics of Ca^{2+} sparks recorded experimentally during an excitation-contraction coupling process in cardiac myocytes. Results from the simulation fitted well to experimental data, suggesting that anomalous space subdiffusion was the dominant mode of Ca^{2+} transport in the spark event.

In conclusion, the experimental and theoretical investigations discussed above were aimed to elucidate various mechanisms in cellular mechanobiology and molecular mechanochemistry. The theoretical models were also used to integrate biological information collected at cellular, subcellular, and molecular levels. The mechanistic insights into cellular and molecular biomechanics, obtained in these studies, may lead to development of novel strategies in translational medicine and clinical engineering.

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