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Scaling the cellular frontier: Mechanobiology, tissue dynamics and function

JoAnn Trejo and Giorgio Scita

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> "Life is both chemical and physical. To paraphrase Stuart Kaufmann: "*Living systems exist in the solid regime* near the edge of (liquid) chaos, *and natural selection achieves and sustains such a poised state*".

Cells adapt and change behavior in response to a variety of mechano-chemical cues. The recent explosion of mechanobiology research has revealed fundamental physical principles that govern various aspects of cell and tissue biology across different spatial and temporal scales. How cues and cellular responses culminate in mechanical challenges and are translated into biochemical messages and reactions, and the molecular mechanisms that enable cells and tissues to sense and transduce biophysical cues are becoming a major focus of attention.

Cell mechanotransduction or mechanochemical feedback loops are now recognized as pivotal in shaping cell and tissue behavior both in physiology and pathology and control a vast range of signaling pathways and processes (from cell fate to migration and invasion, metabolism, vasculature integrity, immune responses, and cancer progression). Moreover, it has become increasingly clear that principal physical processes, such as liquid-liquid phase transitions or the state of molecular crowding, control the assembly of macromolecular signaling entities and virtually all biochemical and metabolic cellular reactions across different scales, from molecules to cells and tissues. In this issue, a collection of articles provides an overview of recent studies illustrating the extent of interconnected physical, biochemical, and metabolic interactions and their impact on mechanosensation and signal transduction.

Notably, mechanical sensing and transduction influence several different spatial scales from molecules to subcellular organelles and cellular processes to tissue organization and morphogenesis. How to causally link and connect these events occurring at different scales remains a major conceptual and technical challenge.

At the molecular scale, general physical principles of molecular organization impinge on the qualitative and quantitative outcomes of signal transduction, as demonstrated for liquid-liquid phase separation of

molecular complexes and molecular crowding. **X. Cheng and L.B. Case** discuss the role of phase separation in mechanosensing in Hippo pathway signaling and at focal adhesions. The importance of molecular crowding is presented by **M. Delarue** and colleagues, they explore how cells can sense and adapt to changes in molecular crowding through modulation of biochemical reactions in the absence of a specific sensor and further link molecular crowding to phase separation of macromolecular complexes. A fundamental question, related to the time scale of mechano-sensing and responses is the reversibility of mechano-transduction process discussed by **A. Beedle and P. Roca-Cusachs**. They highlight that while the activation of mechano-transduction is well studied, the process's reversibility is not. Specifically, how cells disassemble and reverse force-activated signaling pathways after mechanical stimulation ceases, is rarely explored. They further discuss experimental techniques and key findings related to the understudied reversibility of mechanical signaling.

Several articles focus on the general principles of how mechanics impinge on cellular signaling discussing the well-studied Notch receptor (by **F.S. Rodriguez, S. Sanlidag, and C. Sahlgre**), extracellular signal-regulated kinase $^{1}/_{2}$ (ERK1/2) cascade (by **T. Hirashima, N. Hino, K. Aoki, and M. Matsuda**), G protein-coupled receptors (GPCRs), and stretch-activated channels signaling pathways (by **R. Xiao, J. Liu, and X.Z. Shawn Xu**). Stretch-activated channel-induced signaling is discussed in the context of sheer stress in endothelial cells. The impact of mechanical input on epithelial–mesenchymal transition (EMT), a process where epithelial cells transition to mesenchymal states, an event crucial for migration and invasion, is discussed by **C.A. Horta, K. Doan, and J. Yang**. They describe recent studies showing that increased extracellular matrix (ECM) stiffness regulates cellular signaling and promotes breast carcinoma EMT, which suggests a significant role of mechanical forces in tumor progression, invasion, and metastasis.

The next spatial scale of mechanics under intense study is that of subcellular organelles. **G. Bastianello and M. Foiani** examine the role mechanics of the nucleus, an arguably stiffer cellular compartment that is emerging as a signaling and sensory hub whose intrinsic mechanical properties must be precisely preserved. They delve into the intricacy of how cells respond to physical cellular and nuclear perturbations by deploying a multitude of molecular pathways to maintain nuclear shape stability and to prevent nuclear morphological abnormalities. They further discuss how these mechanisms influence and mediate pathophysiological processes and consequences related to clinical disease. **A. Ghisleni and N. Gauthier**, discuss the homeostatic tensional state of the plasma membrane which is portrayed as a bilayer continuum acting as a two-dimensional fluid, comprised of an infinite combination of proteins, lipids, and glycans that interact with both the extracellular and intracellular environments. This results in a tridimensional composite material with nontrivial dynamics and physics and a variable ability to sense and propagate stresses, particularly during the spreading and migration of cells.

The work by **K.M. Young and C. A. Reinhart-King** discusses recent advances by which several canonical mechano-responsive pathways like YAP/TAZ, FAK/Src, RhoA/ROCK, and Piezo1 enable cells to sense and transduce mechanical signals through focal adhesions to the nucleus. New insights that highlight the impact of matrix rigidity on cell mitochondrial function and metabolism are also provided, offering an exciting direction into the emerging field of mechano-metabolism. The field of mechano-metabolism is a burgeoning, rapidly expanding yet still uncharted research area, where numerous unexpected connections between the cell and tissues' physical features and their metabolic states are intermingled and likely to provide a new comprehensive framework to interpret diverse cellular processes. These range from tissue morphogenesis and organ development, illustrated by **B. Lemma and C.M. Nelson**, to derailed mechano-metabolism in malignant cells (by **R. Bertolio, F. Napoletano, and G. Del Sal**). Whereas **L. W. Dawson, N.M. Cronin, and K.A. DeMali** focus on epithelial and endothelial cells that are continuously subjected to mechanical stresses, reinforcing their structures at an energetic cost, raising the issues of how these cells meet the energy demands in response to mechanical cues. In this context, the authors discuss the energetic requirements of epithelial and endothelial cells, highlighting the mechanisms employed to enhance glycolysis, oxidative phosphorylation, and fatty acid metabolism.

Elaborating further on the vascular endothelium and mechanical forces, **A. Dominguez and M.L. Iruela-Arispe** discuss the intricate relationship between endothelial cell responses and hemodynamic forces in blood vessels. They explore how these endothelial cells sense and react to mechanical challenges, showcasing recent breakthroughs in molecular mechanisms, from protein compartmentalization to glycocalyx contributions and the specific role of ion channels. They further highlight the role of the ALK5 receptor in sensing turbulent flow. Whereas **A. McQueen and C. M. Warboys** address endothelium barrier integrity response to changes in flow. They explore how both disturbed and undisturbed flow control paracellular and transcellular permeability. Additionally, they highlight cellular targets that may serve as new potential therapies for prevention of cardiovascular disease.

Finally, **D. Pinheiro and J. Mitchell** offer an elegant and comprehensive analysis of how collective epithelial entities and tissues exhibit properties typically associated

with ensembles of inert, soft material. These tissues can transition from rigid, static, or jammed masses to flowing liquid entities during morphogenesis, regeneration, or wound repair. The authors discuss the inner physical and molecular principles governing changes in cell density, self-locomotion, or cell shape, which are critical determinants of the dynamic state of tissue. Additionally, they provide evidence identifying the initial biological signals determining the collective state of living tissues, with a focus on how these mechanisms are exploited for functionality across biological contexts, including solid tumor progression.

Notably, epithelial-derived carcinomas have been shown to acquire fluid properties and sometimes behave as flocking-fluid entities, similar to an ensemble of starling flocks. This behavior enables malignancies to overcome the jammed, crowded cellular landscape of overgrown tumoral masses and invade surrounding tissue, marking the crucial first step in metastatic progression [1—4]. However, this solid-to-fluid transition comes at a cost, as it is associated with tremendous mechanical stress that impacts nuclear integrity, leading to the release of DNA into the cytosol and the potent activation of potentially antitumorigenic immune responses, as recently demonstrated [1].

The collection of articles provides a comprehensive overview of the complexity of mechanical forces and their impact on biological function on different cellular scales including organelles, individual cells, and tissues.

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