Bioengineering and mechanobiology: pushing (and pulling) the limits of cellular mechanics

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The Minisymposium on Bioengineering and Mechanobiology focused on engineering approaches to investigate the mechanical signaling of cells and tissues and was cochaired by Adam J. Engler (University of California, San Diego) and Celeste M. Nelson (Princeton University). The program moved thematically from the mechanics of the nucleus to those of the cell cortex and finally to the mechanical behaviors of tissues.

Jan Lammerding (Cornell University) described work probing the role of the nuclear envelope proteins, lamin A and C, in the structure and mechanical properties of the nuclei of individual cells and whole tissues. Fibroblasts isolated from patients harboring mutations in the *LMNA* gene that cause muscular dystrophies had softer nuclei than controls. Expressing these mutated forms of the *LMNA* gene in otherwise lamin A/C–deficient mouse embryonic fibroblasts also yielded softer nuclei and defects in coupling of the nucleus to the cytoskeleton. Importantly, applying strain to the body wall musculature of genetically modified *Drosophila melanogaster* showed that lamin mutations altered nuclear mechanics within intact muscle tissues.

Ben Fabry (University of Erlangen–Nuremberg) demonstrated that the binding between the focal adhesion proteins p130Cas and vinculin is important for mechanotransduction. Mechanical stress is coupled to p130Cas through vinculin and initiates the activation of downstream signaling through pathways such as the extracellular signal–regulated kinase (ERK1/2) pathway. Phosphorylation of p130Cas on residue Y12 or mutation of this residue to a phosphomimicking glutamate prevents vinculin binding, reduces the localization of p130Cas to focal adhesion sites, and suppresses ERK1/2 signaling in response to mechanical stretch.

Yee Seir Kee (Robinson and Iglesias Laboratories, Johns Hopkins University School of Medicine) used micropipette aspiration and compression approaches to investigate how assembly of the cleavage furrow responds to mechanical stress in *Dictyostelium*. During cytokinesis, cell shape is controlled by a mechanosensory system that includes the myosin II motor protein and the actin cross-linker, cortexillin I. Accumulation of myosin II at the cleavage furrow is governed by a regulatory network composed of IQGAP1, IQGAP2, kinesin-6, and INCENP. Feedback loops present within this network are responsible for regulating the levels of myosin II at the cleavage furrow.

Celeste Nelson (Princeton University) presented results suggesting that cells respond to the mechanical properties of their surrounding microenvironment, in part by regulating the subcellular localization of small GTPases and the assembly and activation of NADPH oxidase. Mammary epithelial cells underwent epithelial–mesenchymal transition (EMT) on stiff, but not soft, substrata. Cells on stiff substrata apportioned Rac1b, a splice variant of Rac1, to the plasma membrane, at which it formed an activated complex with NADPH oxidase and permitted the generation of reactive oxygen species. The complex did not form on soft substrata, and blocking membrane localization of Rac1b prevented EMT on stiffer microenvironments.

Dylan Tyler Burnette (Lippincott–Schwartz Laboratory, National Institutes of Health) was the recipient of the Merton Bernfield Memorial Award, which is given every year to one graduate student or postdoctoral fellow in recognition of his or her meritorious achievements in cell biology research. Burnette discussed his efforts in expanding the imaging toolbox to the nanometer scale using conventional fluorophores, in an approach dubbed bleaching/blinking-assisted localization microscopy (BaLM; Burnette *et al.*, 2011). Point localization–based superresolution images with a resolution on the scale of tens of nanometers can be produced from commonly used fluorescent molecules by taking advantage of their intrinsic bleaching and blinking. Four-color images can be generated via BaLM with standard electron-multiplying charge-coupled device cameras by using multiple fluorophores in a single cell and can resolve individual motor proteins along intact cytoskeletal networks.

Adam Engler (University of California, San Diego) reported on the differences in differentiation response between adipose-derived and bone marrow–derived stem cells. Both types of stem cells are sensitive to the stiffness of their surrounding microenvironment and differentiate down a muscle lineage when cultured on extracellular matrix of a specific compliance mimicking that of muscle in vivo. The adipose-derived stem cells (ASCs), however, express markers of muscle differentiation at 10-fold higher levels than do the bone marrow–derived stem cells. Furthermore, a fraction of ASCs cultured under these conditions form multinucleated myotubes, which could be maintained when replated on nonpermissive substrata.

REFERENCE

Burnette DT, Sengupta P, Dai Y, Lippincott-Schwartz J, Kachar B (2011). Bleaching/blinking assisted localization microscopy for superresolution imaging using standard fluorescent molecules. Proc Natl Acad Sci USA 108, 21081–21086.

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