FOURTH SPECIAL ISSUE
ON QUANTITATIVE CELL BIOLOGY
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Issue Editors
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Contents

EDITORIAL
Quantitative cell biology: uniting disciplines to understand the cell
Diane S. Lidke 3133

SPECIAL ARTICLE
Receptor-mediated cell mechanosensing
Yunfeng Chen, Lining Ju, Muaz Rushdi, Chenghao Ge, and Cheng Zhu 3134–3155
Mechanosensing depicts the ability of a cell to sense mechanical cues, which under some circumstances is mediated by the surface receptors. In this review, a four-step model is described for receptor-mediated mechanosensing. Platelet GPIb, T-cell receptor, and integrins are used as examples to illustrate the key concepts and players in this process.

BRIEF REPORTS
The desmoplakin–intermediate filament linkage regulates cell mechanics
Joshua A. Broussard, Ruiguo Yang, Changjin Huang, S. Shiva P. Nathamgari, Allison M. Beese, Lisa M. Godsel, Marihan H. Hegazy, Sherry Lee, Fan Zhou, Nathan J. Sniadecki, Kathleen J. Green, and Horacio D. Espinosa 3156–3164
Desmoplakin connects desmosomal core components to intermediate filaments at sites of cell–cell adhesion. Modulating the strength of this linkage using desmoplakin mutants led to alterations in cell–substrate and cell–cell forces and cell stiffness as assessed by micropillar arrays and atomic force microscopy. Perturbation of the actin cytoskeleton leads to abrogation of these effects.

Computer simulations reveal mechanisms that organize nuclear dynein forces to separate centrosomes
Alessandro De Simone and Pierre Gönczy 3165–3170
Computational simulations are used to probe potential mechanisms through which nuclear dynein organizes forces in an anisotropic manner to promote centrosome separation. Two mechanisms are key: one relies on steric interactions between microtubules and centrosomes and the other on the initial position of centrosomes in the cell.
Cortical actin contributes to spatial organization of ER–PM junctions

Ting-Sung Hsieh, Yu-Ju Chen, Chi-Lun Chang, Wan-Ru Lee, and Jen Liou

Endoplasmic reticulum–plasma membrane (ER–PM) junctions serve as the platform for several key cellular activities. Super/high-resolution imaging combined with quantitative analysis reveals morphology and distribution of ER–PM junctions. Evidence suggests the importance of F-actin to these junctional properties and cellular activities mediated by ER–PM junctions.

Nonrandom γ-TuNA-dependent spatial pattern of microtubule nucleation at the Golgi

Anna A. W. M. Sanders, Kevin Chang, Xiaodong Zhu, Roslin J. Thoppil, William R. Holmes, and Irina Kaverina

GDMT (Golgi-derived microtubule) asymmetry is required for polarized cell motility, but its origin is elusive. Combining experimental and computational approaches, we find that GDMTs arise from spatially restricted hotspots that rely on γ-TuNA (γ-TuRC nucleation activator) activity. The nonrandom nucleation pattern underlies GDMT array asymmetry.

ARTICLES

Cell Biology of Disease

Liquid-phase electron microscopy of molecular drug response in breast cancer cells reveals irresponsive cell subpopulations related to lack of HER2 homodimers

Diana B. Peckys, Ulrike Korf, Stefan Wiemann, and Niels de Jonge

Light- and liquid-phase scanning transmission electron microscopy were used to analyze the influence of the drug trastuzumab on HER2 proteins in the plasma membranes of breast cancer cells. The drug was found to induce HER2 uptake for bulk cancer cells. In contrast, HER2 was not internalized in rare subpopulations of resting and cancer stem cells.

Cell Cycle

Analysis of interphase node proteins in fission yeast by quantitative and superresolution fluorescence microscopy

Matthew Akamatsu, Yu Lin, Joerg Bewersdorf, and Thomas D. Pollard

FPALM superresolution microscopy and quantitative confocal microscopy reveal that interphase nodes, the precursors to the fission yeast cytokinetic contractile ring, are discrete unitary structures with defined sizes and ratios of component proteins. Type 1 nodes disassemble during mitosis, but type 2 nodes remain intact throughout the cell cycle.

Cell Interactions

Local cellular neighborhood controls proliferation in cell competition

Anna Bove, Daniel Gradeci, Yasuyuki Fujita, Shiladitya Banerjee, Guillaume Charras, and Alan R. Lowe

Cell competition is a quality-control mechanism through which tissues eliminate unfit cells. Automated microscopy with deep-learning image analysis was used to measure single-cell behavior during competition. Strikingly, the single-cell analysis reveals that tissue-scale population shifts are strongly affected by cellular-scale tissue organization.

Micropipette force probe to quantify single-cell force generation: application to T-cell activation

Anna Sawicka, Avin Babataheri, Stéphanie Dogniaux, Abdul I. Barakat, David Gonzalez-Rodriguez, Claire Hivroz, and Julien Husson

We describe the micropipette force probe, a novel technique that uses a micropipette as a flexible cantilever that aspirates a coated microbead and brings it into contact with a cell. We apply the technique to quantify mechanical and morphological events occurring during T-cell activation.

Cell Motility

A Highlights from MBoC Selection

Centrosome defines the rear of cells during mesenchymal migration

Jian Zhang and Yu-li Wang

Taking advantage of the strong polarity of cells migrating along micropatterned lines, combined with computational modeling and microsurgery, we found that the centrosome must be localized toward the rear of a cell, likely for controlling the distribution of tail formation signals. This discovery clarifies a long-standing controversy in cell biology.
### Cell Physiology

**A Highlights from MBoC Selection**

**Hemodynamic forces can be accurately measured in vivo with optical tweezers**

Sébastien Harlepp, Fabrice Thalmann, Gautier Follain, and Jacky G. Goetz

Force sensing and generation is central to many biological events. There is a growing interest in modern cell biology for methods enabling force measurements in vivo. Here we demonstrate the power of optical tweezing in measuring low-range hemodynamic forces in vivo and, thereby, offer an unprecedented tool for both cell and developmental biology.

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### Cytoskeleton

**Cytoplasmic flows as signatures for the mechanics of mitotic positioning**

Ehsan Nazockdast, Abtin Rahimian, Daniel Needleman, and Michael Shelley

Interactions of astral microtubules (MTs), the pronuclear complex, and the cell cortex with the cytoplasm during pronuclear migration in the first cell division of *Caenorhabditis elegans* have two key consequences: cytoplasm-filled astral MTs behave as a porous medium, and different mechanisms result in different cytoplasmic flows.

**Polarity sorting of axonal microtubules: a computational study**

Erin M. Craig, Howard T. Yeung, Anand N. Rao, and Peter W. Baas

An essential feature of healthy axons is the development of a uniform microtubule (MT) polarity pattern. Computational simulations support a model in which MTs are polarity sorted in the axon by dynein-based gliding, occasionally opposed by plus-directed motors. We predict that cross-linking proteins limit the mobility of longer MTs.

**A node organization in the actomyosin contractile ring generates tension and aids stability**

Sathish Thiyagarajan, Shuyuan Wang, and Ben O’Shaughnessy

Recent experiments showed that key cytokinetic ring proteins organize into membrane-anchored complexes called nodes in the fission yeast cytokinetic ring. A mathematical model based on this organization showed that ring tension arises from myosins pulling anchored actin filaments, and component turnover and anchoring ensure structural stability.

**The molecular architecture of the yeast spindle pole body core determined by Bayesian integrative modeling**


A model of the core of the yeast spindle pole body (SPB) was created by a Bayesian modeling approach that integrated a diverse data set of biophysical, biochemical, and genetic information. The model led to a proposed pathway for the assembly of Spc110, a protein related to pericentrin, and a mechanism for how calmodulin strengthens the SPB during mitosis.

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### Membrane Trafficking

**Adhesion force and attachment lifetime of the KIF16B-PX domain interaction with lipid membranes**

Serapion Pyrpassopoulos, Henry Shuman, and E. Michael Ostap

KIF16B is a motor that binds early endosomes and controls the recycling of receptors. It has a PX domain that binds PI(3)P, which has been proposed to mechanically link motor to cargo. We determined the strength of this bond and its lifetime under load, and found it to be a suitable mechanical linkage for the KIF16B motor under working conditions.

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### Nuclear Functions

**Multi-scale tracking reveals scale-dependent chromatin dynamics after DNA damage**

Judith Miné-Hattab, Vincent Recamier, Ignacio Izeddin, Rodney Rothstein, and Xavier Darzacq

Upon DNA damage, chromatin mobility is modified differently at several time scales, exhibiting increased mobility at large scales but reduced mobility at small scales. Such a pattern of dynamics reveals a global increase in chromatin stiffness upon damage. Scale-dependent nuclear exploration is regulated by Rad51 throughout the genome.
### Highlights from MBoC Selection

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<td><strong>Coordinated increase of nuclear tension and lamin-A with matrix stiffness outcompetes lamin-B receptor that favors soft tissue phenotypes</strong></td>
<td>Amnon Buxboim, Jerome Irianto, Joe Swift, Avathamasa Athirasala, Jae-Won Shin, Florian Rehfeldt, and Dennis E. Discher</td>
<td>3333–3348</td>
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Tissue profiles and MSC transcriptomics separately indicate that LBR varies inversely with lamin-A,C. Such anti-correlations are recapitulated in MSC adipogenesis and osteogenesis as well as with matrix elasticity, knockdowns, overexpression, and myosin-II inhibition, which together suggest the competitive binding of lamin-A,C and LBR for lamin-B.

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Using orientation-independent-DIC microscopy, we revealed that the density of total materials in heterochromatin was only 1.53-fold higher than that of euchromatin, whereas the DNA density was 7.5-fold higher. This surprisingly small difference may be due to the dominance of proteins and RNAs in both chromatin, which may help create a moderate barrier to heterochromatin.

### Differential context-specific impact of individual core promoter elements on transcriptional dynamics

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<td><strong>The roles of individual core promoter elements in transcriptional dynamics of MHC class I gene expression were determined by smFISH in primary B-cells. The elements individually modulated transcriptional bursting, differentially contributing to burst size or burst frequency, to enable combinatorial fine-tuning of the level of transcription.</strong></td>
<td>Oliver Hendy, John Campbell, Jr., Jocelyn D. Weissman, Daniel R. Larson, and Dinah S. Singer</td>
<td>3360–3370</td>
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### Signaling

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Using FRET-based biosensors, we show that sphingosine-1-phosphate promotes endothelial integrity through S1PR\(_1\)-G\(_{\alpha i}\)-Rac1 and S1PR\(_1\)-G\(_{\alpha i}\)-Cdc42 pathways, in addition to activating a barrier disrupting S1PR\(_2\)-G\(_{\alpha 12/13}\)-RhoA pathway. Our data show that the rapid S1P-induced increase in endothelial integrity is mediated primarily by a S1PR\(_1\)-G\(_{\alpha i}\)-Cdc42 pathway.

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<td><strong>The Fc(_{\varepsilon})RI signaling cascade and integrin trafficking converge at patterned ligand surfaces</strong></td>
<td>Devin L. Wakefield, David Holowka, and Barbara Baird</td>
<td>3383–3396</td>
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Surface-patterned ligands reveal spatially targeted signaling events mediated by Fc\(_{\varepsilon}\)RI on mast cells. Distinctively clustered IgE-Fc\(_{\varepsilon}\)RI recruits signaling proteins, including Syk, LAT, and activated PLC\(_{\gamma 1}\). \(\beta 1\)- and \(\beta 3\)-integrins also colocalize at patterned sites, involving actin polymerization and stimulated trafficking from recycling endosomes.

### Differential mast cell outcomes are sensitive to Fc\(_{\varepsilon}\)RI-Syk binding kinetics

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<td><strong>Single-molecule imaging was used to quantify the transient nature of Fc(_{\varepsilon})RI-Syk interactions in a rodent mast cell line. A functional mutation that increases Syk off-rate leads to altered Syk phosphorylation patterns and impaired signaling, highlighting the importance of finely tuned protein interactions in directing cellular outcomes.</strong></td>
<td>Samantha L. Schwartz, Cédric Cleyrat, Mark J. Olah, Peter K. Relich, Genevieve K. Phillips, William S. Hlavacek, Keith A. Lidke, Bridget S. Wilson, and Diane S. Lidke</td>
<td>3397–3414</td>
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### Systems Biology

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<td><strong>Systematic analysis of Ca(^{2+}) homeostasis in <em>Saccharomyces cerevisiae</em> based on chemical-genetic interaction profiles</strong></td>
<td>Farzan Ghanegolmohammadi, Mitsunori Yoshida, Shinsuke Ohnuki, Yuko Sukegawa, Hiroki Okada, Keisuke Obara, Akio Kihara, Kuninori Suzuki, Tetsuya Kojima, Nozomu Yachie, Dai Hirata, and Yoshikazu Ohya</td>
<td>3415–3427</td>
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The global landscape of Ca\(^{2+}\) homeostasis in budding yeast is deciphered. Quantified morphological responses under high concentration of Ca\(^{2+}\) and obtained high-dimensional Ca\(^{2+}\)-genetic interaction profiles show functional gene clusters, which are used to build a global network among the Ca\(^{2+}\) homeostasis units acting in various cellular compartments.
A deep learning and novelty detection framework for rapid phenotyping in high-content screening
Christoph Sommer, Rudolf Hoefler, Matthias Samwer, and Daniel W. Gerlich 3428–3436
CellCognition Explorer provides a generic novelty detection and deep learning framework for high content screening, enabling discovery of rare cell phenotypes without user training.

Cell-cycle transitions: a common role for stoichiometric inhibitors
Michael Hopkins, John J. Tyson, and Béla Novák 3437–3446
The abrupt and irreversible transitions that drive cells through the DNA replication-division cycle are governed by molecular mechanisms that function as bistable “toggle” switches. A common theme of these switches is a network motif consisting of a “beleaguered” enzyme and its “domineering” substrate, locked in a feedback amplification loop.

Testing the time-of-flight model for flagellar length sensing
Hiroaki Ishikawa and Wallace F. Marshall 3447–3456
A combination of quantitative imaging, modeling, and genetics has been used to test a proposed mechanism for measuring the size of an organelle. One way to measure distance is to send a clock out on a train and measure the elapsed time when the train returns. We tested a molecular version of this model as a possible regulator of intraflagellar transport by altering the return speed of the transport machinery and probing the effect on a known length-dependent process.

Theory
Modeling neutrophil migration in dynamic chemoattractant gradients: assessing the role of exosomes during signal relay
Alex C. Szatmary, Ralph Nossal, Carole A. Parent, and Ritankar Majumdar 3457–3470
Cells chemotaxing in decaying gradients of primary chemoattractants maintain their chemotactic response by releasing secondary chemoattractants. Steep, local gradients of secondary chemoattractants can be reached with molecules of higher hydrophobicity, whereas temporal stability can be achieved by packaging in extracellular vesicles.