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Cell structure and dynamics

Editorial overview

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Cells are composed of highly organized assemblies of macromolecules, which undergo continuous dynamic rearrangements. Our contributors in this issue of *Current Opinion in Cell Biology* review some of the most exciting recent advances in our understanding of how various such dynamic assemblies function at the molecular level. As (to use the much-quoted phrase of Theodosius Dobzhansky) ‘nothing in biology makes sense except in the light of evolution’, our contributors also weigh how the remarkably complex and finely tuned cellular nanomachines we see today could have evolved from simpler progenitors.

Starting with an evolutionary theme, Mark Field and Joel Dacks describe exciting recent discoveries on two very ancient protein families with roles in membrane trafficking: the coatamer family of vesicle coating complexes are shown to have significant structural relationships among themselves and, tellingly, to the nuclear pore complex; while the ESCRT system has been found to have a lineage that extends back into the Archea. Analyses of these factors indicate that a complex endomembrane system predates the initial radiation of eukaryotic lineages, and suggest new insights into the origins of eukaryotes.

Continuing the evolutionary theme, the review by Wallace Marshall summarizes the evidence supporting an unexpectedly simple model for the evolution of one of the most beautiful and seemingly complex of cellular nanomachines: the centriole. With an insightful discussion of informational and algorithmic complexity, he argues persuasively that the problem is not as insurmountable as some had thought, and does not require the elaborate assumptions made by some previous theories.

A mainstay of this review series has been the relentless and exciting progress made on the cytoskeleton. As several topics including septins, intermediate filaments, and the bacterial cytoskeleton were covered in excellent reviews in last year’s issue, this year we focused instead on recent progress on actin and microtubule function in cells.

The review by Brian Galletta and John Cooper summarizes the role of actin in endocytosis. Although elucidated relatively recently, they describe evidence that the partnership between actin and endocytosis is evolutionarily ancient, and they highlight thorny mechanistic questions that remain to be resolved in order to understand exactly how actin filaments participate in the process of endocytosis.

After decades in which the mechanisms of actin filament nucleation within cells remained mysterious, the past few years have seen an explosion in the number of identified actin nucleators. Melissa Chesarone and Bruce Goode

provide a masterful overview of actin nucleation and elongation factors, emphasizing the surprising diversity in their mechanism of action. They also highlight emerging connections between these factors, which appear to collaborate with each other to remodel the actin cytoskeleton, endowing it with a remarkable plasticity.

The review by Viola Vogel and Michael Sheetz covers the fascinating question of how animal cells react to mechanical stimuli. In addition to summarizing studies on how force-induced protein unfolding triggers biochemical signaling, they emphasize the fact that mechanical processes like extension and retraction of cell protrusions are frequently cyclical, in a manner that depends on the stiffness of their surroundings. The companion review by Yunfei Cai and Michael Sheetz focuses on the question of how animal cells within tissues can withstand and transmit forces despite lacking a rigid cell wall. In contrast to tensegrity models of cell architecture, they argue that the mechanical coherence of animal cells stems from a force balance between the contractile actomyosin cortex and the load-bearing adhesions between cells and their neighbors or the extracellular matrix. To adapt to external forces while maintaining cell integrity, there must be a very dynamic remodeling of the cortical cytoskeleton in response to force.

A distinct, microtubule-based force-sensing system is the mitotic spindle, which must capture each pair of sister chromatids in a bi-oriented manner such that one sister will be inherited by each daughter cell following mitosis. Elegant classical studies manipulating chromosomes in living cells indicated that physical tension between the sisters provides information critical for error correction during spindle biogenesis, and more recent work stemming from yeast genetics identified the ‘chromosomal passenger complex’, and the Aurora B kinase it contains, as key elements in tension-based error correction. Alexander Kelly and Hiro Funabiki dissect and compare several current models for how Aurora B transduces mechanical force into regulation of the attachment of sister chromatids to the spindle.

The question of how cytoskeletal motor proteins convert chemical energy into mechanical motion has been under intense study for decades. Processive two-headed motors must also possess the ability to communicate between the two heads so that the ‘back’ head steps ‘forward’ rather than vice versa. As with the examples discussed above, this too exploits mechanical strain as a source of information. Arne Gennerich and Ron Vale lucidly discuss several models for the mechanisms of head–head communication in the case of kinesin and dynein, and summarize the evidence in favor of each. Much of the data come from elegant single-molecule studies, shedding new light on how these motors ‘walk the walk’.

Motor proteins are not the only method whereby cargoes can move up and down microtubules. Another, perhaps less studied, method is ‘microtubule lattice diffusion’, in which cargoes are jostled back and forth along the length of the microtubule. As Jeremy Cooper and Linda Wordeman point out, this is a way in which the cell can target cargoes ‘on the cheap’, scanning rapidly over short distances between both ends of a microtubule without the need for measured-paced ATP-driven motor complexes.

Matthew Onsum and Christopher Rao summarize the rapidly growing interface between mathematical modeling and experimental approaches to the issue of cell polarity. For many years theorists and experimentalists addressed this issue separately, until our growing knowledge of the molecules and processes that govern polarization in different cells increased to the point that productive interaction became possible. Deepening of the interactions between modelers and experimenters is accelerating rapidly, and this review provides a great introduction to the current state of affairs, hinting at where the field hopes to go once it achieves a full integration.

A variety of morphological changes are triggered by cell cycle regulators, and the review by James Moseley and Paul Nurse summarizes recent advances from budding and fission yeasts on the molecular connections between Cdk1, the core kinase of the cell cycle engine, and various targets that regulate cell polarity. They also highlight the bidirectional nature of this communication, showing how morphological features such as cell shape and size can feed back on Cdk1 to impact cell cycle progression.

The next two reviews focus on methodological advances that are allowing us to appreciate cell structure and dynamics in ever-increasing detail. Arguably one of the most powerful methods for gaining information on the structure and disposition of macromolecular assemblies is electron microscopy. Recent advances in sample preparation, imaging, and image processing are now allowing the visualization of the cellular organization of macromolecules in unprecedented detail. Andreas Hoenger and Richard McIntosh discuss these advances, and illustrate them with remarkable examples from bacteria, animals, and plants showing how new electron tomographic techniques can resolve and map individual cellular macromolecules and macromolecular assemblies *in situ*.

No single method, either experimental or computational, is able to gather high-resolution structural and kinetic data on the macromolecular assemblies that maintain and replicate a cell at all the relevant spatial and temporal scales. However, Andrej Sali and colleagues discuss a cornucopia of powerful emerging new approaches that allow the synergistic integration of diverse sources of structural and kinetic data into unified representations

of dynamic macromolecular assemblies in action. Moreover, they discuss the *kinds* of information that experimentalists will need to garner for such assemblies to be visualized in this way.

Spliceosomes and ribosomes are ancient, conserved ribonucleoprotein machines that respectively catalyze splicing of introns from pre-mRNAs, and then translation of those mRNAs to produce proteins. On the face of it, the dynamic assembly of these two machines appears mind-bogglingly complicated, involving the coordinated action of literally hundreds of assembly factors. How do all of these factors work at the molecular level? How can they have coordinately evolved into the intricate assembly process we see in modern cells? As Jonathan Staley and John Woolford discuss, answers to both of these questions are beginning to emerge, and it turns out that similar principles underlie the assembly of both ribosomes and spliceosomes. Both require assembly cofactors that often act sequentially in subcomplexes to ensure an ordered and modular assembly process, in a manner analogous to an industrial assembly line. Intriguingly, it seems that some of the mechanisms used by the spliceosome may have originated in the ribosome, giving insights into the evolutionary origin of both assembly processes.

The biogenesis of cellular organelles represents another huge leap in complexity, generally involving either division of pre-existing organelles or *de novo* assembly from precursors generated by other organelles. Jennifer Smith and John Aitchison discuss the strange case of the peroxisome, whose mode of biogenesis has been contro-

versial. Peroxisomes are vesicle-like packets containing specialized enzymes that rid cells of toxins and utilize fats as an energy source. They can be called into being or dismissed depending upon the metabolic needs of the cell, which may therefore have few or many peroxisomes at different times. Significant recent progress has been made in understanding peroxisomal biogenesis, and it turns out both fission and *de novo* assembly occur, depending on the cellular circumstances. The ER provides membranous materials for both processes, while the contents of the peroxisomes are imported by a long-mysterious mechanism that is only now being revealed.

The nucleus is arguably the largest and most complicated organelle. The role of the spatial organization of chromatin within the nucleus has been debated for years. General principles (e.g. peripheral location confers repression) were thought established, but numerous contradictions have emerged. Recent work has begun to shed light on what genes are controlled by spatial organization, and mechanistically how this is achieved. Jason Brickner discusses these developments, including his own work, which has revealed that certain genes are specifically targeted to the nuclear periphery upon activation, and remain there with a 'memory' of that activation even when turned off again — allowing them to be re-activated much more rapidly should the need arise. Remarkably, such genes seem to have a 'DNA zip code' that targets them to the nuclear periphery, where this adaptive memory requires certain chromatin remodeling factors and histone variants. These discoveries are placed in the broader context of new findings about the importance of nuclear gene positioning to gene regulation.