Microtubules and motors

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New tools and approaches are providing exciting new insights into the structure and function of motors and microtubules and their contributions to cell migration, mitosis, and neuronal function.

Janel Titus, from the Wadsworth laboratory (University of Massachusetts, Amherst), discussed the regulation of the plus end–directed mitotic motor Eg5 by the spindle assembly factor, TPX2. Spindle formation in cells expressing truncated TPX2, which lacks the Eg5-binding region, was defective. Acute inhibition of the TPX2-Eg5 interaction in metaphase cells resulted in spindle lengthening, suggesting TPX2 functions to modulate or restrict Eg5 motor activity. To test this possibility, in vitro biophysical experiments with purified proteins were used to show that TPX2 reduces Eg5-dependent microtubule gliding and sliding and is important for targeting Eg5 to the microtubule.

Microtubules are dynamic polymers that convert stochastically between growing and shrinking phases. **Joe Howard**, from the Max Planck Institute of Molecular Cell Biology and Genetics, reported the unexpected discovery that catastrophe, the conversion of a growing microtubule to a shrinking one, is a multistep process in which the rate of catastrophe increases with time. The budding yeast kinesin-8, Kip3, increases catastrophe frequency by increasing the rate of each step, whereas the mammalian kinesin-13 MCAK increases catastrophe frequency by decreasing the number of steps to catastrophe. By differentially regulating different aspects of the catastrophe mechanism, the kinesins are able to differentially control both microtubule length and its variance.

In polarized, directionally migrating cells, microtubules show persistent growth at the leading edge, but the mechanism responsible for local control of microtubule dynamics is not established. **Kenneth Myers**, from Clare Waterman's laboratory (National Institutes of Health), used automated microtubule tracking to test the contribution of the microtubule depolymerase mitotic centromere-associated kinesin (MCAK) to this process. Knockdown of MCAK homogenized microtubule dynamic instability by promoting long-lived microtubule growth throughout the entire cell, resulting in the loss of directed cell migration. The effects of MCAK on microtubule dynamics were discovered to be dependent on the activity of Aurora A kinase, suggesting that active Aurora A regulates the depolymerase activity of MCAK in migrating cells. Expression of a constitutively active form of the small GTPase Rac1 promoted long-lived microtubule growth in an MCAK- and Aurora A–dependent manner, establishing a signaling pathway in which local inhibition of MCAK depolymerase activity downstream of Rac1 and Aurora A drives polarized microtubule growth and thereby promotes directed cell migration.

Melissa Rolls (Pennsylvania State University), winner of the ASCB 2011 Women in Cell Biology Junior Award, described her work on the microtubule cytoskeleton of neurons and how axon injury triggers a microtubule-based pathway that protects dendrites. Working with *Drosophila* neurons, the Rolls group observed an increase in growing microtubules after injury. The increased microtubule dynamics were dependent on new nucleation, but were not required for axon regeneration. Rather, microtubule dynamics protected dendrites from degeneration following injury. The results indicate that a dynamic microtubule array protects dendrites while the cell is attempting to repair itself.

Cytoplasmic dynein transports diverse cargoes in cells and can tether cargoes at specific destinations. **Anthony Roberts,** from the Reck-Peterson laboratory (Harvard Medical School), addressed the mechanism of dynein regulation, using purified yeast proteins and single-molecule microscopy. The data show that Lis1/Pac1 reduces dynein velocity and increases encounter time with the microtubule, inducing a novel anchored state of the enzyme without catalytic arrest. Structural work shows that Lis1 binds at the interface between dynein's ATPase domain and the microtubule-binding stalk. Taken together, the results suggest that Lis1 could alter communication between different motor domains, thus regulating motor function in cells.

Antonina Roll-Mecak (National Institutes of Health) presented the first structural studies of tubulin tyrosine ligase (TTL), the enzyme responsible for the addition of tyrosine to the C-terminus of α-tubulin. Although tyrosination–detyrosination of tubulin has long been known to affect microtubule dynamics, the molecular mechanism of TTL is not established. The new results show that TTL engages the C-terminal tail of tubulin via low-affinity, high-specificity interactions. Additionally, the enzyme forms a tight complex with tubulin, which blocks the longitudinal tubulin interface and prevents tubulin addition onto the microtubule end. These insights suggest that the TTL interaction with tubulin could affect the polymerization-competent pool of tubulin in cells.

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