

The life of a microtubule

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The Minisymposium “The Life of a Microtubule: Birth, Dynamics and Function” highlighted new findings on how microtubules (MTs) are made, how their length and spatial organization is regulated, and finally how they contribute to cellular functions.

The birth of a microtubule

Making a MT in the cell requires the γ -tubulin ring complex (γ -TuRC), which consists of γ -tubulin and γ -tubulin complex proteins (GCPs) 2–6 in multiple copy numbers. GCP2 and GCP3 directly bind γ -tubulin and form small γ -tubulin complexes (γ -TuSCs). **Andreas Merdes** (Centre de Biologie du Développement, University Toulouse III/CNRS) reported GCPs 4, 5, and 6 to interact laterally with γ -TuSCs, and not at their base as previously thought, thereby positioning these larger GCPs to mediate the assembly of γ -TuSCs into stable and fully functioning γ -TuRCs. **Sabine Petry** (Princeton University) revealed that the well-known MT polymerase XMAP215 unexpectedly functions with γ -TuRC to synergistically nucleate MTs. The N-terminal TOG domains of XMAP215 bind $\alpha\beta$ -tubulin and are sufficient to promote MT polymerization, and the conserved C-terminal domain of XMAP215 is required for efficient MT nucleation and directly binds to γ -tubulin. Cells also need a mechanism to down-regulate MT nucleation at MT organizing centers (MTOCs). **Jeremy Magescas** (Feldman laboratory, Stanford University) defined a two-step mechanism for MTOC inactivation at the centrosome that involves the rapid removal of the inner centrosomal SPD-2 protein followed by slow fragmentation of SPD-5 and γ -TuRC by pulling forces from cortical MTs.

How a microtubule grows and shrinks

Once nucleated, MTs are dynamic polymers that spontaneously switch between growth and shrinking phases in a process called dynamic instability. Regulation of this behavior at the MT plus- and minus-ends determines MT turnover and array architecture. **Chao Yang** (Akhmanova laboratory, Utrecht University) reported that loss of the MT plus-end binding proteins EB1 and EB3 surprisingly affects the organization of MT minus-ends by promoting their detachment from the Golgi apparatus and reducing the length of

CAMSAP2 stretches at the minus-ends. While these defects did not affect cell viability, they perturbed functions such as intracellular trafficking and cell motility. The dynamic instability of MTs is widely considered to be driven by the GTP nucleotide state-dependent conformational changes in tubulin subunits within the MT lattice. Using biochemical experiments with purified proteins coupled to in vivo studies in budding yeast, **Colby Fees** (Moore laboratory, University of Colorado) revealed that the negatively charged carboxy-terminal tail of β -tubulin provides a nucleotide-sensing mechanism that regulates dynamic instability. The length and charge of the carboxy-terminus of β -tubulin is highly variable between species and across isoforms, and this raises the intriguing possibility that this diversity contributes to different functions of the MT cytoskeleton.

Cutting a microtubule down to size

Once a MT has grown, its length and the total number of MTs can be tuned to suit cellular needs. The MT-severing protein, katanin, has emerged as a key regulator of these processes, but the structural basis for how this MT scissor operates and the molecular mechanisms that target and regulate severing activity remain unclear. **Graham Burkart** (Dixit laboratory, Washington University in St. Louis) presented data that showed that the evolutionarily conserved MAP65 family of MT cross-linking proteins potentially protect the side-walls of MTs against severing by inhibiting the binding of katanin. Insight into how katanin performs its severing activity was provided by **Elena Zehr** (Roll-Mecak laboratory, National Institutes of Health). Her elegant cryo-electron microscopy and x-ray crystallography work showed that katanin alternates between an open-spiral and closed-ring state in an ATP-dependent manner that is proposed to represent the power stroke that mediates MT severing. In contrast to katanin, the CLASP family of proteins act as MT rescue factors. While the domain architectures of yeast CLASP and XMAP215 are similar, **Shreoshi Majumdar** (Rice laboratory, University of Texas Southwestern Medical Center) reported that the single TOG2 domain of CLASP was sufficient for rescue activity, unlike XMAP215, which requires two TOG domains for its MT polymerase activity. Her work shed light on structural differences that might account for the inherent functional differences between the CLASP TOG2 and polymerase TOGs.

Microtubules and friends taking care of business

MTs are well known for segregating sister chromatids during mitosis but the biophysical behavior of the MT-kinetochore connections remain mysterious. Using ultrafast force-clamp assays, **Ekaterina Grishchuk** (University of Pennsylvania) discovered that the Ndc80 complex inherently provides differential direction-dependent molecular friction at kinetochores that provides a mechanism for how metaphase chromosome oscillations can occur without kinetochores detaching from MTs. Altered MT dynamics underlies many neurodegenerative diseases. Interestingly, **Jessica Henty-Ridilla** (Goode laboratory, Brandeis University) reported that the actin regulator profilin directly binds to and stimulates MT growth, whereas mutations in human profilin-1 that are associated with amyotrophic lateral sclerosis (ALS) abrogate this activity. High concentrations of actin monomers also attenuated profilin's effect on MT growth, suggesting that actin and MTs compete for profilin binding.

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