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Milestone 4

Snakes and ladders

How do microtubules reorganize from a radial array during interphase into a spindle during mitosis? Molecular cell biologists were burning to tackle this question after microscopists first described these structures, but the chemical nature of these cytoskeletal filaments remained elusive for decades.

A breakthrough came in 1968, when Taylor and colleagues identified tubulin as the protein subunit of microtubules. For this, they took advantage of the affinity of colchicine - a well-known inhibitor of mitosis - for a protein associated with the mitotic spindle and microtubules. This discovery finally provided the necessary basis for studying microtubule organization at the molecular level.

But exactly how tubulin polymerizes into microtubules was still not well understood 16 years later, in 1984. Enter the concept of dynamic instability, proposed by Tim Mitchison and Marc Kirschner.

The authors set up a series of *in vitro* microtubule-polymerization assays that allowed them to measure the length and number of individual microtubules rather than bulk populations. To their great surprise, they found that microtubules coexist in growing and shrinking populations that interconvert infrequently - a state that the authors coined 'dynamic instability'. To explain their findings, the authors proposed that most microtubules grow slowly at steady state, whereas a minority shrink rapidly, allowing the net polymer mass to remain constant. Transitions between growth and shrinkage are infrequent, but they can occur over a wide range of tubulin concentrations, consistent with the authors' observation that individual microtubules grew transiently, even at tubulin concentrations below the steady-state concentration.

So, how could microtubule polymerization and depolymerization be controlled? The authors hypothesized that GTP caps, which could exist if the rate of GTP hydrolysis lagged slightly behind that of tubulin polymerization, might control microtubule dynamics. Ends without a GTP cap would have high tubulin 'off' rates and shrink, whereas ends with a GTP cap would grow. The length of the cap could depend on various factors including, for instance, the concentration of free tubulin, providing a simple means to rapidly reorganize microtubules in response to changing cellular conditions.

But how do these *in vitro* studies relate to the *in vivo* situation in which the minus ends of microtubules are anchored at centrosomes? In a second paper in the same issue of *Nature*, Mitchison and Kirschner showed that dynamic instability also governs the growth of microtubules from centrosomes. The only difference is that centrosomes can nucleate microtubules at tubulin concentrations that are well below the steady-state concentration. But to even start to understand how centrosomes nucleate microtubules, scientists had to wait until 1989 when Oakley and colleagues discovered γ-tubulin and its microtubule-nucleating properties.

Raluca Gagescu, Associate Editor, *Nature Reviews Molecular Cell Biology*

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Tubulin and microtubules