CellPress

Special Issue: Quantitative Cell Biology

Review

Regulation of Microtubule Growth and Catastrophe: Unifying Theory and Experiment

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Recent studies have found that microtubule-associated proteins (MAPs) can regulate the dynamical properties of microtubules in unexpected ways. For most MAPs, there is an inverse relationship between their effects on the speed of growth and the frequency of catastrophe, the conversion of a growing microtubule to a shrinking one. Such a negative correlation is predicted by the standard GTP-cap model, which posits that catastrophe is due to loss of a stabilizing cap of GTP-tubulin at the end of a growing microtubule. However, many other MAPs, notably Kinesin-4 and combinations of EB1 with XMAP215, contradict this general rule. In this review, we show that a more nuanced, but still simple, GTP-cap model, can account for the diverse regulatory activities of MAPs.

Trends

The standard GTP-cap model of microtubule dynamics predicts that faster growing microtubules have a larger stabilizing cap, which results in a lower catastrophe frequency. Recent studies show that for many microtubule-associated proteins (MAPs) this inverse relationship between growth and catastrophe breaks down.

MAPs whose effects on microtubule dynamics do not accord with the standard GTP-cap model include XMAP215, kinesin-8, EB1, and kinesin-4.

GTP-cap models in which hydrolysis cannot occur in the GTP-tubulin subunits at the end of the protofilaments (i.e., hydrolysis is coupled to polymerization) but does occur stochastically in the lattice (i.e., random hydrolysis) account for the observed effects of MAPs on microtubule dynamics.

Microtubules Are Dynamic Polymers

Microtubules are cytoskeletal polymers that play essential roles in cytoplasmic transport, as the tracks along which motor proteins move intracellular cargoes, in cell division, by forming the mitotic spindle, and in cell motility, by constituting the structural core of cilia and flagella (Figure 1A). Pathologies in microtubule structure and regulation are associated with mitotic and neurodegenerative disorders [1–3].

Microtubules are cylindrical polymers composed of α–β-heterodimers, which are typically arranged into 13 protofilaments and which nucleate from microtubule-organizing centers [4]. The polarity of the tubulin heterodimers induces a polarity to the microtubule. The end that exposes the α-tubulin is referred to as the minus end because it grows more slowly. In cells, the minus end is typically associated with the microtubule-organizing center or Golgi apparatus and is less dynamic than the plus end, although recent work suggests that, like the plus end, the minus end is also tightly regulated [5–8]. The faster growing plus end exposes the β-tubulin, which binds the exchangeable nucleotide, GTP or GDP (Figure 1B). In cells, the plus end typically grows out from the nucleation center towards the chromosomes in mitosis or towards the cell cortex in interphase cells [9]. If a microtubule end finds a target, such as the kinetochore of chromosomes [10,11] or plus-end binding proteins on the Golgi and endoplasmic reticulum (ER) [12–14] or plasma membrane [15–18], it will be temporarily immobilized to generate pushing or pulling forces [19]. If it fails to find a target, the microtubule will rapidly depolymerize [20]. This switch from a period of comparatively slow growth to one of rapid shrinkage is called catastrophe and is a key feature of dynamic instability, which was discovered by Mitchison and Kirschner [21].

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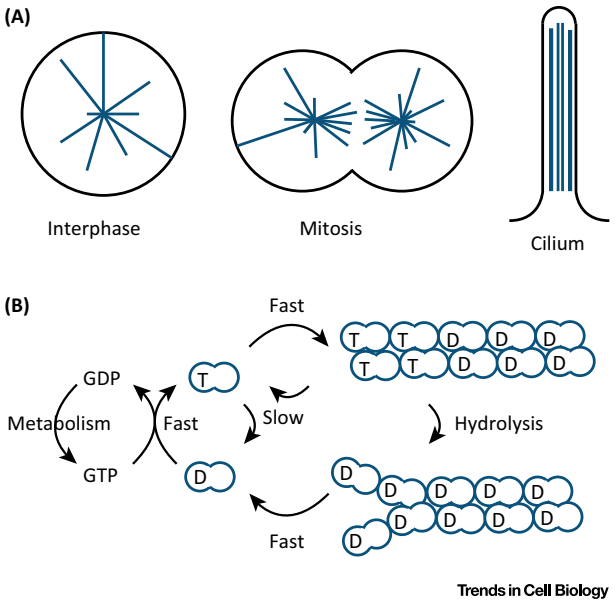

Figure 1. Microtubules in Cells and Their GTP Hydrolysis Cycle. (A) Microtubules (in blue) are dynamic polymers that form a radial cytoskeleton (left), a bipolar mitotic spindle (center), and the linear axoneme of cilia (right). (B) Tubulin is a GTPase. The predominant tubulin species in solution has GTP bound to the β-subunit. Hydrolysis of GTP by the dimer in solution is slow. Hydrolysis is accelerated by incorporation of the GTP dimer into the microtubule lattice. To enter the lattice, the GTP dimer first associates transiently with the end before becoming strongly bound; the dissociation of the strongly bound GTP dimer is slow and its hydrolysis occurs with a delay, resulting in a cap of GTP-tubulin at the end. The cap stabilizes the microtubule against depolymerization. If the cap is lost and GDP-tubulin is exposed at the end, depolymerization is rapid, thereby completing the hydrolysis cycle. Microtubule-associated proteins (MAPs) upregulate and downregulate all steps in this pathway, thereby allowing cells exquisite control of their microtubule cytoskeleton.

How does microtubule catastrophe arise? The widely accepted, textbook explanation is that catastrophe occurs once a stabilizing cap of GTP-tubulin disappears from the plus end of the microtubule [22], a process that occurs stochastically [21,23–25]. Because GTP-tubulin is the predominant species in solution, the end subunits initially have GTP bound to them (Figure 1B); some time later, when the subunit is in the lattice, the GTP is hydrolyzed [26]. The length of the GTP-capped region depends on the molecular rate constants: the binding and unbinding of GTP-tubulin and the hydrolysis rate. The length is expected to fluctuate due to the stochasticity associated with the molecular processes [27–30]. According to this model, which we call the standard GTP-cap model, increasing cap size by increasing the growth speed [31] or decreasing cap size by increasing the rate of depolymerization of the cap [29] will, respectively, decrease or increase the catastrophe frequency. Note that the standard GTP-cap model is a conceptual, as opposed to mathematical, model and thus makes qualitative rather than quantitative predictions.

Over the past few years, it has been found that in the presence of many microtubule-associated proteins (MAPs), this inverse correlation between growth and catastrophe frequency breaks down (see next section). Therefore, the standard GTP-cap model needs to be reevaluated. Concurrent with this new work on MAPs, theoretical work has led to analytic and computational solutions to a large number of different GTP-cap models. Now is a good time to ask whether these new models can account for the unexpected regulatory properties of MAPs.

Regulation of Dynamics by MAPs

MAPs regulate microtubule dynamics in many ways [32–34]: for example, by altering the speed of microtubule growth and shrinkage, or by altering the frequency of catastrophe or rescue (the