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Review

Interplay between microtubule dynamics and intracellular organization

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ABSTRACT

Microtubules are hollow tubes essential for many cellular functions such as cell polarization and migration, intracellular trafficking and cell division. They are polarized polymers composed of α and β tubulin that are, in most cells, nucleated at the centrosome at the center of the cell. Microtubule plus-ends are oriented towards the periphery of the cell and explore the cytoplasm in a very dynamic manner. Microtubule alternate between phases of growth and shrinkage in a manner described as dynamic instability. Their dynamics is highly regulated by multiple factors: tubulin post-translational modifications such as detyrosination or acetylation, and microtubule-associated proteins, among them the plus-tip tracking proteins. This regulation is necessary for microtubule functions in the cell. In this review, we will focus on the role of microtubules in intracellular organization. After an overview of the mechanisms responsible for the regulation of microtubule dynamics, the major roles of microtubules dynamics in organelle positioning and organization in interphase cells will be discussed. Conversely, the role of certain organelles, like the nucleus and the Golgi apparatus as microtubule organizing centers will be reviewed. We will then consider the role of microtubules in the establishment and maintenance of cell polarity using few examples of cell polarization: epithelial cells, neurons and migrating cells. In these cells, the microtubule network is reorganized and undergoes specific and local regulation events; microtubules also participate in the intracellular reorganization of different organelles to ensure proper cell differentiation.

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Abbreviations: APC, Adenomatous Polyposis Coli; CLASP, CLIP-Associated Protein; CLIP, cytoplasmic linker protein; EB, End-Binding (protein); ER, endoplasmic reticulum; GTP, guanoside-triphosphate; GSK3β, Glycogen Synthase Kinase 3β; γ-TuRC, γ-Tubulin Ring Complex; MAP, microtubule-associated protein; MCAK, Mitotic-Centromere Associated Kinase; MTOC, Microtubule Organizing Center; STIM1, Stromal-Interaction Molecule 1; +TIP, plus-end tracking protein.

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1. Introduction

Microtubules are essential components of the cytoskeleton that play a major role in many cellular functions such as cell migration and polarization, intracellular trafficking and cell division. Microtubules are hollow tubular structures constituted of heterodimers of α and β tubulin. In most vertebrate cells, they are nucleated at the centrosome that works as a MTOC (Microtubule Organizing Center) in the perinuclear region. It is constituted of two centrioles, each composed of nine triplets of microtubules, surrounded by peri-centriolar material that contains proteins implicated in microtubule nucleation and organization. Among them, the γ-tubulin associates with other proteins to form a ring complex, the γ-TuRC (Tubulin Ring Complex), onto which dimers of α and β tubulin are added to build a microtubule. Microtubules are thus polarized with a minus-end capped and anchored at the MTOC and a plus-end generally localized at the periphery of the cell.

Microtubule minus-ends can elongate *in vitro* but at lower speed than the plus-ends, and they are mostly stable or depolymerizing in cells. They are capped by the γ-TuRC (see Raynaud-Messina and Merdes, 2007). The plus-ends explore the cytoplasm in a very dynamic manner. Microtubules undergo phases of growth, pause and shrinkage, separated by rescue (transition from shrinkage to growth phase) or catastrophe (transition from growth phase to shrinkage) events. This dynamic behavior was termed "dynamic instability" by Mitchison and Kirschner (1984) (for a review see Desai and Mitchison, 1997). During microtubule polymerization, heterodimers of guanoside-triphosphate (GTP)-bound tubulin are added at the plus-end of microtubules. A slight delay between polymerization and hydrolysis of the GTP by β-tubulin creates a GTP-tubulin cap. The loss of this cap induces a rapid depolymerization of the microtubule. In this model, stochastic rescue events allow the microtubule to enter a new phase of polymerization. Another model suggests that rescue events might not be stochastic. Dimitrov et al. (2008) showed *in vivo*, using a conformation-sensitive antibody, that GTP-tubulin was found not only at the plus-ends of microtubules, but GTP-tubulin remnants were also identified in older parts of the polymer. Upon depolymerization of the microtubule, they would be exposed and behave as a GTP-cap to promote rescue events. Lattice defects or specific structures within the microtubule lattice could also play a role in regulation of microtubule dynamics.

2. Regulation of microtubule dynamics

Intrinsic processes such as the presence of the GTP-cap and GTP-islands thus regulate microtubule dynamics. Extrinsic regulation of microtubule is mostly due to the numerous MAPs (microtubule-associated proteins) that bind to microtubules, and especially to the family of proteins that bind to the plus-ends of microtubules. We will summarize in the first part the role of MAPs and plus-ends binding proteins and will discuss in the second part the role of microtubule post-translational modifications on the regulation of microtubule dynamics (see Fig. 1).

2.1. Microtubule-associated proteins

MAPs have been shown to play a crucial role in the regulation of microtubule dynamics. The most studied stabilizing MAPs are Tau, MAP2 and MAP4, the first two being strongly expressed in neurons. Other MAPs have a destabilizing effect on microtubules, either by severing microtubules or by inducing depolymerization. Three proteins, katanin, spastin and fidgetin regulate the number and length of microtubules through their severing activity (Zhang et al., 2007). In particular, they increase the number of

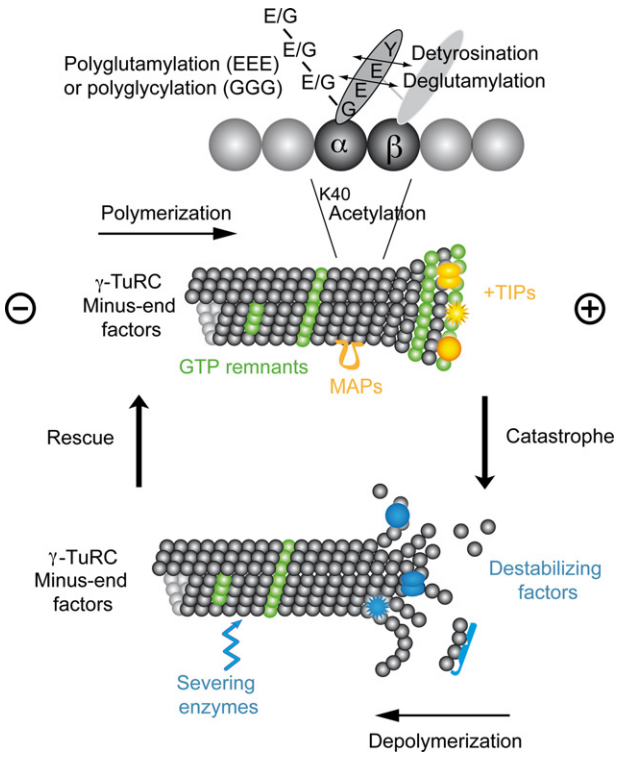

Fig. 1. Regulation of microtubule dynamics. Microtubules are highly dynamic structures that alternate between phases of growth, pause and shrinkage, separated by catastrophe and rescue events. The presence of GTP-bound β-tubulin subunits (in red) at the microtubule plus-end (GTP-cap) or along the microtubule (GTP-remnant) promotes stabilization. Microtubule dynamics is also regulated by external factors: stabilizing factors including +TIPs, MAPs and minus-end capping proteins, destabilizing factors and severing proteins. Microtubules can undergo multiple post-translational modifications that often correlate with stability. Most of them occur on the C-terminal tail of α and β-tubulin except detyrosination that only concerns the α-subunit, and the acetylation of Lysine40 which is located in the lumen of the microtubule. E, glutamate; G, glycine; K, lysine, Y, tyrosine; +TIP, plus-tip tracking protein; MAP, microtubule-associated protein; γ-TuRC, γ-tubulin ring complex.

microtubules, which is necessary for the formation of the mitotic spindle and in some polarized cells. Some MAPs induce depolymerization: stathmin binds to free tubulin dimers (Belmont et al., 1996) and favors GTP hydrolysis (Howell et al., 1999); proteins from the kinesin-13 family induce a conformational change of the tubulin dimers that triggers catastrophe events (reviewed in Ems-McClung and Walczak, 2010). Interestingly, some proteins may be involved both in microtubule nucleation and in the regulation of microtubule dynamics. Recent studies indeed showed that a fraction of the γ-TuRC localized along microtubules regulate microtubule dynamics by inducing pauses (Bouissou et al., 2009). More recently, Goodwin and Vale identified in Drosophila cells a minus-end-specific-protein "cap": Patronin protects the minus-ends of microtubule from depolymerization (Goodwin and Vale, 2010). In mammals, one of its homologue, Nezha binds to microtubule minus-ends *in vitro* and anchors microtubule minus-ends to adherens junctions in epithelial cells (Meng et al., 2008).

A important family of MAPs, the plus-end tracking proteins (+TIPs), dynamically track the growing plus-ends of microtubules (for reviews, see Akhmanova and Steinmetz, 2010; Schuyler and Pellman, 2001). Because of their localization, they play a major role in the regulation of microtubule dynamics. They also participate in the interactions of microtubules with the chromosomes during mitosis and with the cellular cortex both in interphase and mitosis. CLIP170 (cytoplasmic linker protein) was the first MAP to be identified as a +TIP (Perez et al., 1999). It was later shown