REVIEW ARTICLE
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Shaping Microtubules Into Diverse Patterns: Molecular Connections for Setting Up Both Ends

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Microtubules serve as rails for intracellular trafficking and their appropriate organization is critical for the generation of cell polarity, which is a foundation of cell differentiation, tissue morphogenesis, ontogenesis and the maintenance of homeostasis. The microtubule array is not just a static railway network; it undergoes repeated collapse and reassembly in diverse patterns during cell morphogenesis. In the last decade much progress has been made toward understanding the molecular mechanisms governing complex microtubule patterning. This review first revisits the basic principle of microtubule dynamics, and then provides an overview of how microtubules are arranged in highly shaped and functional patterns in cells changing their morphology by factors controlling the fate of microtubule ends. © 2011 Wiley Periodicals, Inc.

Key Words: microtubule, microtubule-end-binding proteins, +TIPs, cell polarity, morphogenesis

Introduction

Cell morphology is established and maintained through the dynamic assembly and regulatory processes of molecular components, which provide a variety of spatial structures to express a given cellular function. Cells sense their surrounding environment via mechanical and chemical stimuli, such as light or forces, cell–cell and cell–extracellular matrix (ECM) interactions or gradients of signaling molecules, and they respond by developing an axis of polarity. The key element controlling cell shape is the cytoskeleton. The cytoskeleton consists of distinct filamentous systems: actin filaments, intermediate filaments, microtubules, and an emerging noncanonical cytoskeleton composed of septins. These are all polymers, having the ability to reversibly assemble and disassemble. Intermediate filaments and septins confer cortical rigidity and actin filaments generate the driving force for cell migration and form cell shape, while microtubules serve as tracks for the directional transport of molecular components or drag ropes for the movement of organelles. Although these cytoskeletal systems have distinct roles, they interact with each other. The importance of interactions between microtubules and actin in establishing and maintaining cellular asymmetry has been described [Rodriguez et al., 2003]. In addition, accumulating evidence is revealing a novel linkage between microtubules and septin, which is discussed below.

Microtubules have an intrinsic structural polarity, which is fundamental to the directional transport mediated by motor proteins [Vallee and Sheetz, 1996; Hirokawa, 1998]. The appropriate delivery of physiologically active substances is crucial for their asymmetric distribution; therefore, the control of directionality and organization of microtubules in cells is essential to cell morphogenesis and function, and thus microtubule dynamics are a major target of signaling pathways. Following the pioneering in vitro studies that demonstrated the biochemical and structural properties of microtubules, recent progress, achieved by employing molecular cell biological approaches, have shed light on the molecular mechanisms underlying microtubule organization.

Dynamic Instability

Our initial understanding of microtubule regulation came from in vitro analyses of purified microtubules. Microtubules are self-organized by the polymerization of α-/β-tubulin heterodimers that are arranged parallel to a cylindrical axis, with α-tubulin and β-tubulin having exposed minus and plus ends, respectively (Figs. 1A-a and 1A-b). Each tubulin subunit contains one binding site for guanine nucleotides, but only β-tubulin contains an exchangeably bound nucleotide [Weisenberg et al., 1968; Berry and Shelansk, 1972]. After microtubule assembly the β-tubulin-bound guanine triphosphate (GTP) is

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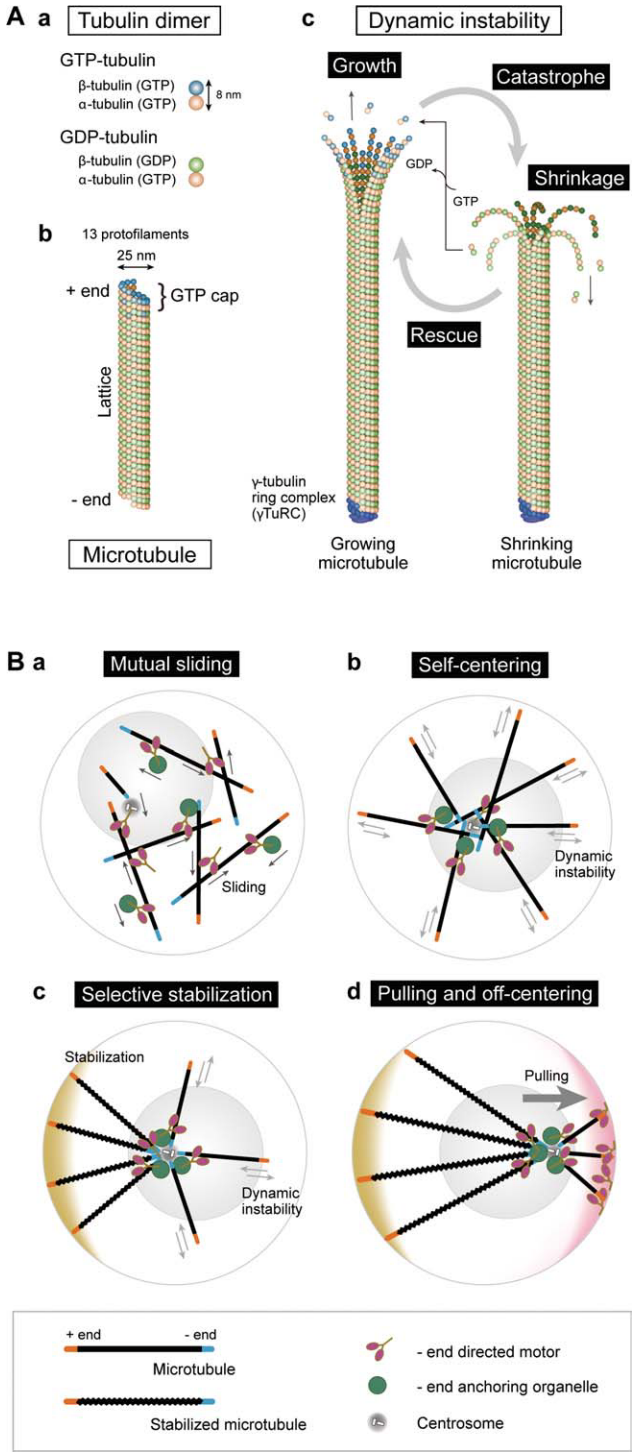
hydrolyzed to guanosine diphosphate (GDP) (Fig. 1A-c) [Jacobs et al., 1974; Weisenberg and Deery, 1976]. The hydrolysis of the nucleotide is not necessary for microtubule formation; however, the portion of microtubule carrying GTP, termed the "GTP cap" (Fig. 1A-b), is stable and displays a steady state assembly [reviewed by Howard and Hyman, 2009]. In contrast, the GDP-bound tubulins are prone to dissociate from the microtubule by increasing the curvature of protofilaments in the microtubule and putting strain on the lattice [Elie-Caille et al., 2007].

In a population of microtubules in a steady state of assembly/disassembly, an individual microtubule interconverts stochastically between periods of slow growth and rapid shortening at the plus end, a behavior known as "dynamic instability" (Fig. 1A-c) [Mitchison and Kirschner, 1984; Hotani and Horio, 1988]. Minus ends are generally not dynamic and depolymerize continuously if the ends are not capped and stabilized. In cells, dynamic instability has a functional role in controlling the disposition of the microtubule arrays upon external stimuli: the fast disassembly provides a means for the rapid re-organization of microtubules in response to changing cellular requirements.



Default: Self-Centering Activity of the Cytoplasm

If one looks at the pattern of microtubules in a single cultured cell that is not in contact with surrounding cells, one will generally see microtubules distributed with their minus ends clustered together around the cell center and their plus ends extending out into the cytoplasm. At the cell center, a canonical microtubule nucleator centrosome or microtubule organizing center, as well as microtubule minus end-associating organelles, such as the Golgi apparatus, centriolar satellites and nucleus, will be located near the cluster of minus ends. This radial plus end-out orientation of microtubules is established through the combination of microtubule-dependent transport of minus end-nchoring materials by a minus end directed molecular

Fig. 1. Microtubule structure and conceptual diagrams for the microtubule patterning process. (**A**) Microtubules are composed of stable α/β-tubulin heterodimers (a) that are aligned in a polar head-to-tail fashion to form protofilaments (b). GTP bound to α-tubulin is non-exchangeable and is never hydrolyzed. The cylindrical and helical microtubule wall typically comprises 13 parallel protofilaments with a diameter of 25 nm (b). Assembly and disassembly of microtubules is driven by the binding, hydrolysis and exchange of a guanine nucleotide on the β-tubulin (c). GTP hydrolysis occurs shortly after incorporation. It has been postulated that GTP hydrolysis changes the conformation of a protofilament to a profoundly curved structure, which makes the tubulin dimer easier to dissociate from the filament. A 'cap' of tubulin-GTP subunits (GTP cap) stabilizes the filament. The GDP of the disassembly products is exchanged with GTP. This stochastic assembly-disassembly cycle is termed "dynamic instability". (**B**) In the non-polarized cytoplasm, motor protein-based mutual sliding of microtubules and movement of motor-associated organelles results in the self-centering of the subcellular components (a and b). Microtubules undergoing dynamic instability reach and capture the specialized sites at the cell cortex and are followed by stabilization of their entire length (c). A cortically bound form of the minus-end-directed microtubule motor protein pulls the microtubule network and associated organelles to one side (d).

motor, typified by dynein, and growth of the plus ends [Rodionov and Borisy, 1997] (Figs. 1B-a and 1B-b). Even in an isolated centrosome free cytoplast, dynamic microtubules interacting with membranous organelles and motor proteins arrange themselves into a radial array [McNiven et al., 1984]. Microtubules and purified oligomeric motors only are sufficient to organize microtubules into asters in vitro [Urrutia et al., 1991; Nédélec et al., 1997]. This ability of the microtubule-based system to find the center establishes a general coordinate system, which is then used to position organelles within the cell.

Generation of Asymmetry in the Microtubule Pattern

A cell is polarized when it has developed a main axis of organization following a trigger by external signals in variety cell types. During this process, in numerous cell types, microtubules are dramatically reorganized [reviewed by Bartolini and Gundersen, 2006]. This reorganization can be regulated by two classes of tubulin/microtubule modulators: (1) diffusible factors that regulate the amount of functional tubulin or affecting the overall microtubule dynamics/stability and (2) localized factors that position microtubule plus and minus ends at specific sites within cells.

The diffusive factors include chaperons that regulate tubulin protein production [reviewed by Lundin et al., 2010], the conventional microtubule-associated proteins (MAPs; including MAP2, MAP4 and tau) that stabilize the entire length of the microtubule lattice [reviewed by Amos and Schlieper, 2005], the microtubule destabilizing factor stathmin/OP18 [reviewed by Cassimeris, 2002] and the microtubule severing enzymes (Spastin, Fidgetin, and Katanin) [reviewed by Roll-Mecak and McNally, 2010]. Interestingly, a subset of kinesin motor proteins, including kinesin-8, -13, and -14, not only walks on microtubule lattices, destabilizes microtubules by removing tubulin dimers from the ends, resulting in microtubule depolymerization [Wordeman, 2005; Kinoshita et al., 2006; Howard and Hyman, 2007]. In contrast, a TOG domain family protein, XMAP215, is a potent growth-promoting factor that moves with the growing microtubule plus ends where it catalyzes the addition of tubulin subunits [Brouhard et al., 2008]. These classes of molecules can regulate tubulin/microtubules throughout the cytoplasm, but occasionally they/their activities can also be localized spatially by upstream signals; for example, stathmin/OP18 is locally inactivated in motile membrane protrusions during interphase and around chromosomes during mitosis [Niethammer et al., 2004], and XMAP215 and kinesin-13s are localized to the mitotic spindle pole to stabilize and destabilize centrosomal microtubules, respectively [Lee et al., 2001; reviewed by Ems-McClung and Walczak, 2010]. Another class of diffusible factors that can regulate microtubule function is enzymes that modify tubulin in microtubules post-translationally. Examples of these modifications include acetylation, polyglycylation and polyglutamylation, tyrosination/detyrosination, and palmitoylation. These tubulin post-translational modifications specialize the function of subsets of microtubules by changing the affinity of motor proteins and MAPs to the microtubules [reviewed by Janke and Kneussel, 2010; Wloga and Gaertig, 2010].

The second class of modulators, localized factors, is of crucial importance for the generation of polarity, and is the main focus of this review (Table I). The basic concept explaining the generation of microtubule asymmetry, termed the "selective stabilization model" or "search-and-capture model," involves local stabilization of a subset of microtubules [Kirschner and Mitchison, 1986] (Fig. 1B-c). In this model, dynamic instability allows microtubules to search stochastically the three-dimensional space within cells to find and capture specific target sites on the cell periphery that have been activated by environmental signals. The plus ends attaching to the cell cortex are stabilized at their ends by local factors, resulting in increased lifespan of the entire microtubule (Fig. 1B-c). These long-lived microtubules are a primary target for the post-translational modification [reviewed by Gundersen and Cook, 1999]. Recent studies have, however, revealed that the control of microtubule length and behavior after end-attachment is more complex; the fate of microtubule ends is differentially regulated by various microtubule end-binding proteins, including plus-end-tracking proteins (+TIPs) and the motor proteins, dynein and kinesin (Fig. 2, Table I).

Following the assembly of microtubule arrays, the entire network needs to have the ability to be pulled to one side of the cell by the tractive force. Motor proteins, which produce force directed towards either end of the microtubule (Figs. 1B-d and 2A-b), achieve this function. A cortically bound form of dynein, a minus end directed microtubule motor protein that is conserved from yeast to mammals, is indeed involved in nuclear migration, mitotic spindle orientation and cytoskeletal reorientation during wound healing [reviewed by Dujardin and Vallee, 2002; Yamamoto and Hiraoka, 2003]. Recent computer simulation approaches confirmed that the pulling force generated at the interface between the microtubule plus ends and the cell cortex is the primary driver for the movement of the nucleus and centrosome in *C. elegans* early embryos [Kimura and Onami, 2005; Kimura and Onami, 2007]. In contrast, microtubule-depolymerizing kinesins remove tubulin dimers from the ends (Fig. 2A-e), which results in the release of microtubule attachment to the cellular structure or in the generation of motive force to pull the microtubule associating material if it can remain attached to the shrinking microtubule ends.

Table I. Representative Factors Acting at Microtubule Ends to Organize the Microtubule Network

Human (homo sapiens:hs) or fly (Drosophila meranogaster:dm)				
End-binding proteins		**MT end**	**Action on MT end**	**Site of MT anchor / Receptor molecule(s)**
+TIPs	EB1 family (EB1, 2, 3)	+	Anchor	Neuronal growth cone / Drebrin
		+	Anchor	Neuronal dendritic spine / p140Cap, cortactin
		-	Anchor	Centrosome / CAP350 and FOP
	EB1/MT-binding proteins: ACF7	+	Anchor	Cell cortex, leading edge / Actin
	APC tumor suppressor protein	+	Guide	Cell cortex, leading edge, plasma membrane / DLG1
		+	Guide	Cell cortex, leading edge / IQGAP1, actin
		+	Guide	Cell cortex, leading edge / mDia
		+	Anchor?	Plasma membrane / AMER1, 2 (APC membrane recruitment 1, 2)
		+	Anchor?	Mitotic cell cortex of *Drosophila* male germline stem cells / DE-cadherin, Armadillo, actin
		+	Anchor	Mitotic kinetocore / nd
		-	Anchor	Mitotic SPB / nd
	CLASPs	+	Anchor	Cell cortex, cell periphery in HeLa, basal cortex in epithelia / LL5α and LL5β
		+	Anchor	Cell cortex, leading edge / IQGAP1
		-	Anchor	Golgi structure / GCC185
	CLASPs, with astrin & Kif2b	+, -	Anchor	Mitotic kinetochore, SPB / CENP-E (at +), nd (at -)
	CLIP-170	+	Anchor or guide?	Cell cortex, leading edge / IQGAP1
	Dynein-dynactin complex	+	Guide & pull?	Cell cortex, leading edge / GKAP-Dlg1
		+	Anchor	Adherens junctions / β-catenin
		+	Anchor & pull?	Leading edge, cell-cell adhesion sites / Par3, through dynein light intermediate chain 2 (LIC2)
		+	Pull	Mitotic cell cortex / NuMA, LGN, Gα(hs); Mud, Pins, Gα(dm)
		-	Anchor	Centrosome / Nudel, Par6
		-	Anchor	Nuclear pore / Bicaudal D2
	Dynein-dynactin-CLIP-170 complex	+	Pull	Mitotic kinetochore / Rod–ZW10–Zwilch (RZZ) complex, NudeE/Nudel-Lis1 complex, Spindly
	MCAK/Kif2C (kinesin-13), with APC	+	Shrinkage	Mitotic kinetochore / nd
Kif2A (kinesin-13)		+	Shrinkage	Mitotic SPB / DDA3
Kif2B (kinesin-13)		+, -	Shrinkage	Mitotic kinetocore and SPB / nd
KLP10A , KLP59C (kinesin-13) (dm)		+, -	Shrinkage	Mitotic kinetocore and SPB / nd
Kif18A (kinesin-8)		+	Shrinkage	Mitotic kinetocore / nd
CENP-E (kinesin-7)		+	Elongation	Mitotic kinetocore / BubRI
XMAP215 (Dis1/TOG/XMAP215 family)		- (also + in the cytoplasm	Anchor (at -)	Mitotic SPB, Centrosome, cytoplasm / transforming acidic coiled coil (TACC)
γ-TuRC		-	Anchor	Centrsosome / GCP-WD, ASP, CG-NAP (AKAP450), NLP, centrosomin, NEDD1, kendrin/pericentrin
		-	Anchor	*cis*-Golgi apparatus / AKAP450, GM130
ninein		-	Anchor	Centrosome (mother centriole appendage), close proximity to adherens junctions in the inner pillar of organ of Corti / nd
ninein, Ndel1, Lis1, CLIP-170		-	Anchor	Desmosomes in epidermis / Desmoplakin
ninein, pericentrin, γ-TuRC		-	Anchor	Myotube nuclear envelope / nd
Nezha		-	Anchor	Cell adhesion / E-cadherin, p120 catenin, PLEKHA7
Budding yeast (*Saccharomyces cerevisiae*)				
End-binding proteins		**MT end**	**Action on MT**	**Site of MT anchor / Receptor molecule(s)**
+TIPs	Bim1P (EB1 family)	+	Delivery & anchor	Bud tip / Kar9-Myo2, walking along actin cables
	Kip3p (kinesin-8), with Bim1p	+	Anchor & shrinkage	Bud tip / Kar9
	Kar3p (kinesin-14) & Bik1p (CLIP-170)	+	Anchor & pull	Shmoo tip / mating-specific Gα protein, Gpa1
	Stu1 (CLASP), with DASH complex	+	Anchor	Mitotic kinetochore / Ndc80 complex
	Dynein, with Bik1p (CLIP-170), Kip2p (kinesin-7)	+	Slide & pull	Bud cortex / Num1p through dynein intermediate chain Pac11p
DASH complex		+	Anchor and pull	Mitotic kinetochore / Ncd80, Mis12 complexes
Stu2p (Dis1/TOG/XMAP215 family)		- (also + in the cytoplasm)	Anchor	Centrosome and mitotic SPBs / Spc72, with yeast γ-tubulin complex
γ-TuSC		-	Anchor	SPB / Spc110
Fission yeast (*Schizosaccharomyces pombe*)				
End-binding proteins		**MT end**	**Action on MT**	**Site of MT anchor / Receptor molecule(s)**
+TIPs	Mal3p (EB1 family)	+	Anchor	Cell end / moe1p
	EB1/MT-binding proteins: Tea1p, Tea2p (kinesin-7), Tea3p, Tea4p, Tip1p (CLIP-170)	+	Anchor	Cell end / Mod5p, tea3p, bud6p, for3p
	Tip1p (CLIP-170)-Tea2p (kinesin-7) complex	+	Anchor	Mitotic kinetochore / nd
	Peg1 (CLASP) & dynein	+	Anchor	Cell end / nd
	Dynein	+	Pull	Meiotic cell cortex / Num1/Mcp5
DASH complex & Klp5/6 (kinesin-8)		+	Anchor & pull	Mitotic kinetochore / Ndc80, Mis12 complexes
Dis1 (Dis1/TOG/XMAP215 family)		+	Anchor	Mitotic kinetochore / Ndc80 complex
Alp14 (Dis1/TOG/XMAP215 family) & Klp5/6 (kinesin-8)		+	Anchor & pull	Mitotic kinetochore / nd
Alp14 (Dis1/TOG/XMAP215 family)		-	Anchor	Mitotic SPB / Alp7 (TACC homologue)
γ-TuRC		-	Anchor	Mitotic SPB / Pcp1, Myo1, Msd1

List of representative microtubule end-binding proteins involved in microtubule patterning. In vertebrates most proteins listed are conserved; therefore, only human protein nomenclature is shown (hs), except for several *Drosophila* proteins (dm). Budding yeast and fission yeast proteins are listed separately. Microtubule: MT, microtubule plus-end-tracking proteins: +TIPs, spindle pole body: SPB, γ-tubulin ring complex: γ-TuRC, γ-tubulin small complex: γ-TuSC, not determined: nd.

Molecules Involved in Microtubule End Positioning

The representative factors acting on microtubule ends are listed in Table I. The γ-tubulin ring complex (γ-TuRC) is well known as a minus end-capping complex that protects the microtubule minus ends from depolymerization and anchors them to the centrosome (Fig. 2B-c). Ninein is a minus end-anchoring protein, which is distinct from the

Table I. Continued

Upstream signal or event	References
Neuritogenesis	Geraldo et al. 2008
Dendritic spine formation	Jaworski et al. 2009
Radial MT organization	Yan et al. 2006
Directional migration	Kodama et al. 2003
Cdc42 and Par6–PKCζ	Etienne-Manneville et al. 2005; Mimori-Kiyosue et al. 2007
Rac1, Cdc42	Watanabe et al. 2004
LPA, Rho	Wen et al. 2004
nd	Grohmann et al. 2007
Mitotic spindle orientation	Reviewed by Yamashita 2009
Mitotic spindle organization & checkpoint	Fodde et al. 2001; Kaplan et al. 2001
Mitotic spindle organization & regulation	Louie et al. 2004
PI3 kinase, ECM-integrin association	Hotta et al. 2010; Lansbergen et al. 2006; Mimori-Kiyosue et al. 2005
GSK3β	Watanabe et al. 2009
Nucleation of noncentrosomal MTs	Efimov et al. 2007
Mitotic spindle organization & regulation	Maffini et al. 2009; Manning et al. 2010
CDC42, Rac	Fukata et al. 2002
Directional migration	Manneville et al. 2010
Cell-cell adhesion	Ligon et al. 2001
Directional migration, cell-cell adhesion	Schmoranzer et al. 2009
Mitotic spindle orientation	Reviewed by Radulescu and Cleveland 2010; Siller and Doe 2009; Wilkie and Kinch 2005
MT anchoring at the centrosome	Guo et al 2006; Kodani et al. 2010
Centrosome centering	Splinter et al. 2010
Mitotic spindle formation and chromosome segregation	Reviewed by Kardon and Vale 2009
Aurora A, B kinases	Banks and Heald 2004
Aurora B, Polo-like kinase Plk1	Jang et al. 2008; Knowlton et al. 2009
Aurora A, B kinases	Reviewed by Ems-McClung and Walczak 2010
Moving chromatids by means of poleward flux	Rogers et al. 2004
Mitotic chromosome alignment	Stumpff et al. 2008
Chromosome congression	Sardar et al. 2010
MT nucleation and spindle formation	Brouhard et al. 2008; Lee et al. 2001
MT nucleation	Reviewed by Luders and Stearns 2007
MT nucleation	Rivero et al. 2009
Minus end anchoring in differentiated cells	Mogensen et al. 2000; Moss et al. 2007
Cortical MT organization in epidermis	Lechler and Fuchs 2007; Sumigray et al. 2011
Muscle cell differenciatoin	Bugnard et al. 2005
Cell-cell adhesion	Meng et al. 2008

Upstream signal or event	References
Budding, cdc42	Hwang et al. 2003; Korinek et al. 2000; Lee et al. 2000
Mitotic spindle positioning	Gupta et al. 2006
Mating-specific pheromone	Molk et al. 2006; Sproul et al. 2005; Zaichick et al. 2009
Establishment and maintenance of mitotic spindle	Ortiz et al. 2009
Nuclear migration	Reviewed by Miller et al. 2006; Yamamoto and Hiraoka 2003
Mitotic chromosome movement	Reviewed by Buttrick and Millar 2011
Anchorage of astral MTs at SPB and MT nucleation	Usui et al. 2003; Wolyniak et al. 2006
MT nucleation	Kilmartin, 1996; Kollman, 2010; reviewed by Helfant 2002

Upstream signal or event	References
End growth and mitosis	Chen et al. 2000; Chen et al. 1999
End growth, cdc42	Reviewed by Chang and Martin 2009; Hayles and Nurse 2001
Chromosome poleward movement	Goldstone et al. 2010
End growth and mitosis	Grallert et al. 2006
Nuclear migration	Saito et al. 2006; Yamashita and Yamamoto 2006
Mitotic chromosome movement	Sanchez-Perez et al. 2005, reviewed by Buttrick and Millar 2011
Kinetochore-spindle attachment	Hsu and Toda 2011
Kinetochore-spindle attachment	Garcia et al. 2002
Bipolar spindle formation	Sato et al. 2004
Anchoring of spindle MT to SPB	Flory et al. 2002; Samejima et al. 2008; Toya et al. 2007

γ-TuRC, and is localized at centrosomal and non-centrosomal sites [Mogensen et al., 2000]. Of special note is the recent discovery of a new minus end-stabilizing/anchoring molecule, Nezha (also termed Patronin in *Drosophila* together with other Patroin family members) [Goodwin and Vale, 2010; Meng et al., 2008] (Fig. 2B-a).

At the plus end a large number of "microtubule plus end-tracking proteins (+TIPs)" have been identified over the past decade (Fig. 3) [reviewed by Akhmanova and Steinmetz, 2008; Mimori-Kiyosue and Tsukita, 2003; Schuyler and Pellman, 2001]. +TIPs are a diverse group of specialized MAPs that are evolutionarily conserved and that

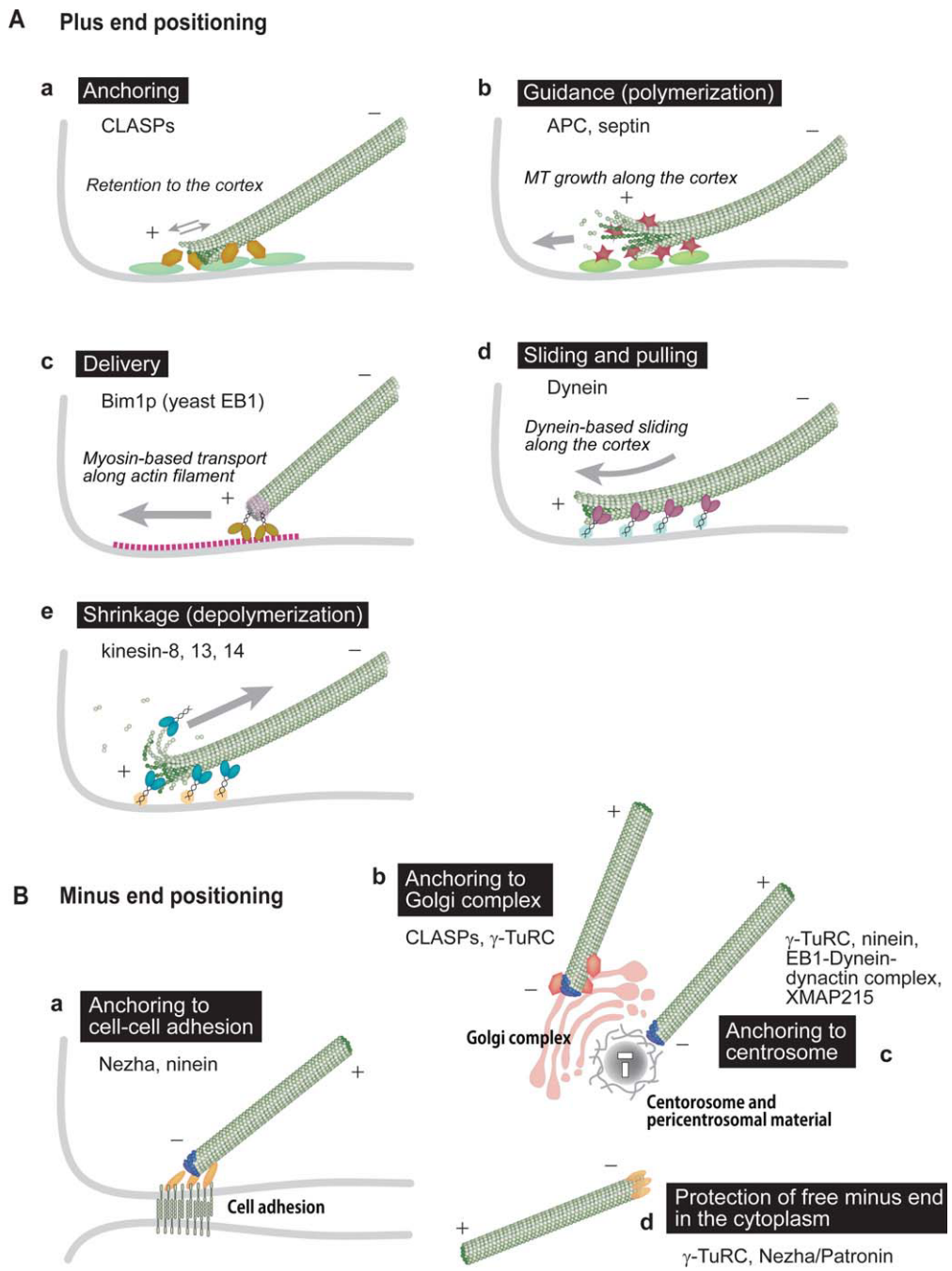


Fig. 2. The fate and position of microtubule ends are differently regulated by end-binding proteins. Examples of the mode of action of end-binding proteins at the plus end (**A**) and the minus end (**B**). Microtubule: MT, γ-tubulin ring complex: γ-TuRC.

accumulate at the ends of growing microtubules (Table I). Many +TIPs are targeted to the growing plus ends through interaction with EB1 (end-binding 1) family proteins. EB1 family proteins are autonomous plus end-binding proteins recognizing the end-specific tubulin structure independently of any binding partners [Bieling et al., 2007], probably by recognizing the GTP cap [Zanic et al., 2009], and may form a cross-bridge between adjacent protofilaments to stabilize the lattice [des Georges et al., 2008] (Fig. 3A, Table I). Thus, EB1 family proteins are core components of +TIP complexes (Fig. 3). In addition, XMAP215 has also been reported to autonomously bind to the plus ends [Brouhard et al., 2008]. Both EB1 family proteins and XMAP215 can act independently as microtubule growth promoters, but in some instances they are linked by SLAIN motif family proteins, which strongly stimulate processive microtubule growth in interphase cells [van der Vaart et al., 2011]. The dynein-dynactin complex can also access microtubule ends in both EB1-dependent and independent manners [Miller et al., 2006; Watson and Stephens, 2006]. It is noteworthy that

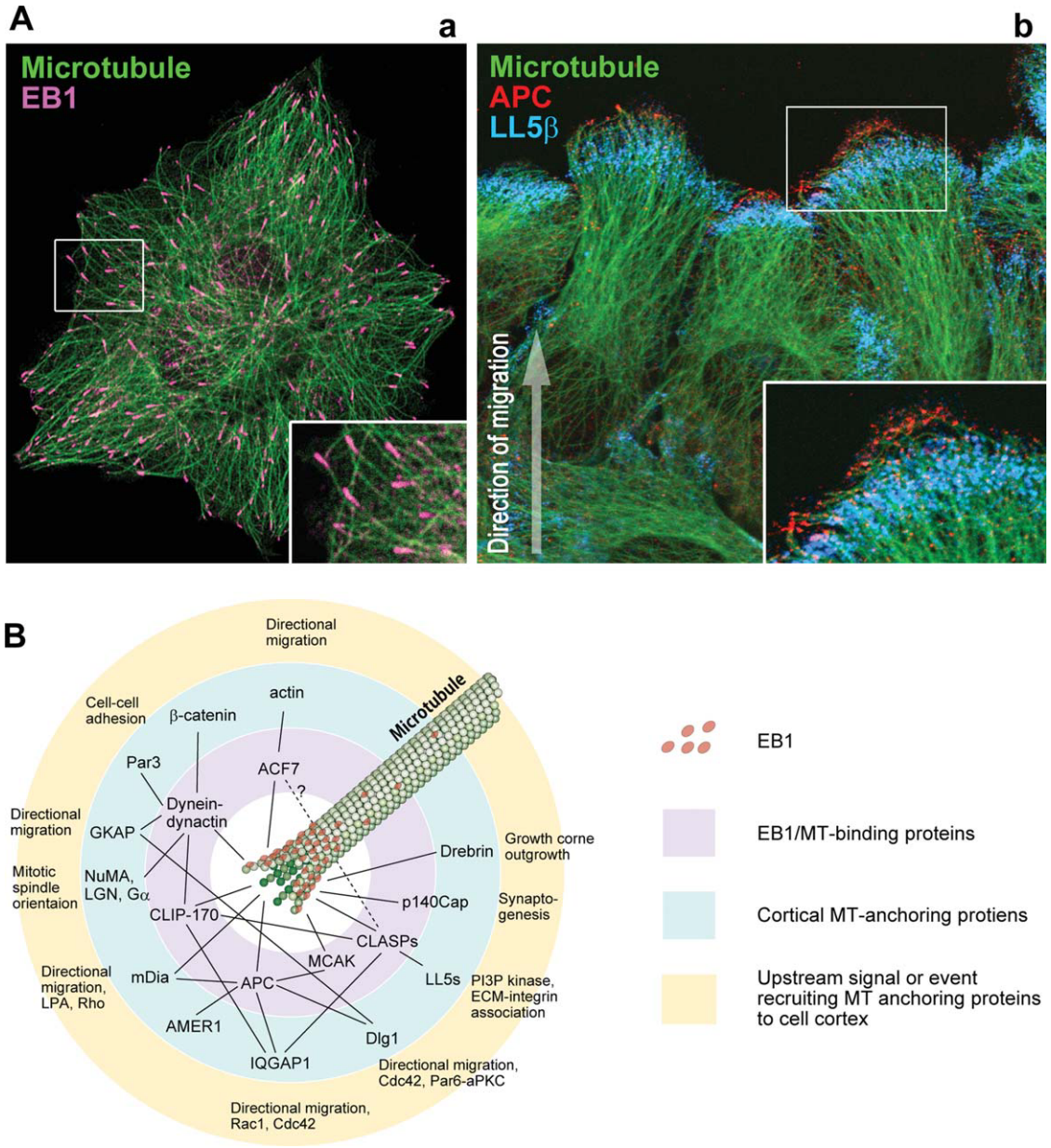


Fig. 3. Subcellular distribution of +TIPs and molecular linkage among +TIPs. (**A**) Distribution of microtubules visualized with GFP-tubulin (green) and EB1 (magenda) in HeLa cells seeded on a collagen coated cover slip (a), and microtubule (green), APC tumor suppressor protein (red) and CLASP-anchoring protein LL5β (cyan) in mouse NIH/3T3 fibroblasts undergoing directional migration in response to monolayer scratching (b). EB1 localizes to every growing microtubule end throughout the cytoplasm. Note that APC is accumulated in the pioneering microtubule ends in the lamellipodia extending toward the scratched area, while LL5 is concentrated at the base of the lamellipodia where many microtubule ends are terminated. (**B**) The molecular linkage between +TIPs at the microtubule plus-end and the upstream signal or events are shown diagrammatically. Most +TIPs bind to EB1 at the ends, and at the same time associate with the cellular structure, such as the cell cortex or mitotic kinetochores, and thereby attach the microtubule ends to these structures.

some plus end-binding proteins can also be localized at the minus end, and have roles as microtubule-anchoring and/or as microtubule-nucleating factors (Fig. 2B-b, Table I). In most cases, the factors described above exert microtubule stabilizing or growth promoting effects, and form large multi-molecular complexes that associate with cellular structures to attach microtubule ends to these structures (Fig. 3).

In contrast, microtubule-depolymerizing kinesins, including kinesin-8, -13 and -14, removes tubulin dimers from the ends and induces microtubule shortening (Fig. 2A-e). A budding yeast kinesin-8 Kip3p walks processively towards the plus end, and at the end it remains there and disassemble microtubules exclusively at the plus end, whereas the kinesin-13 family member, mitotic

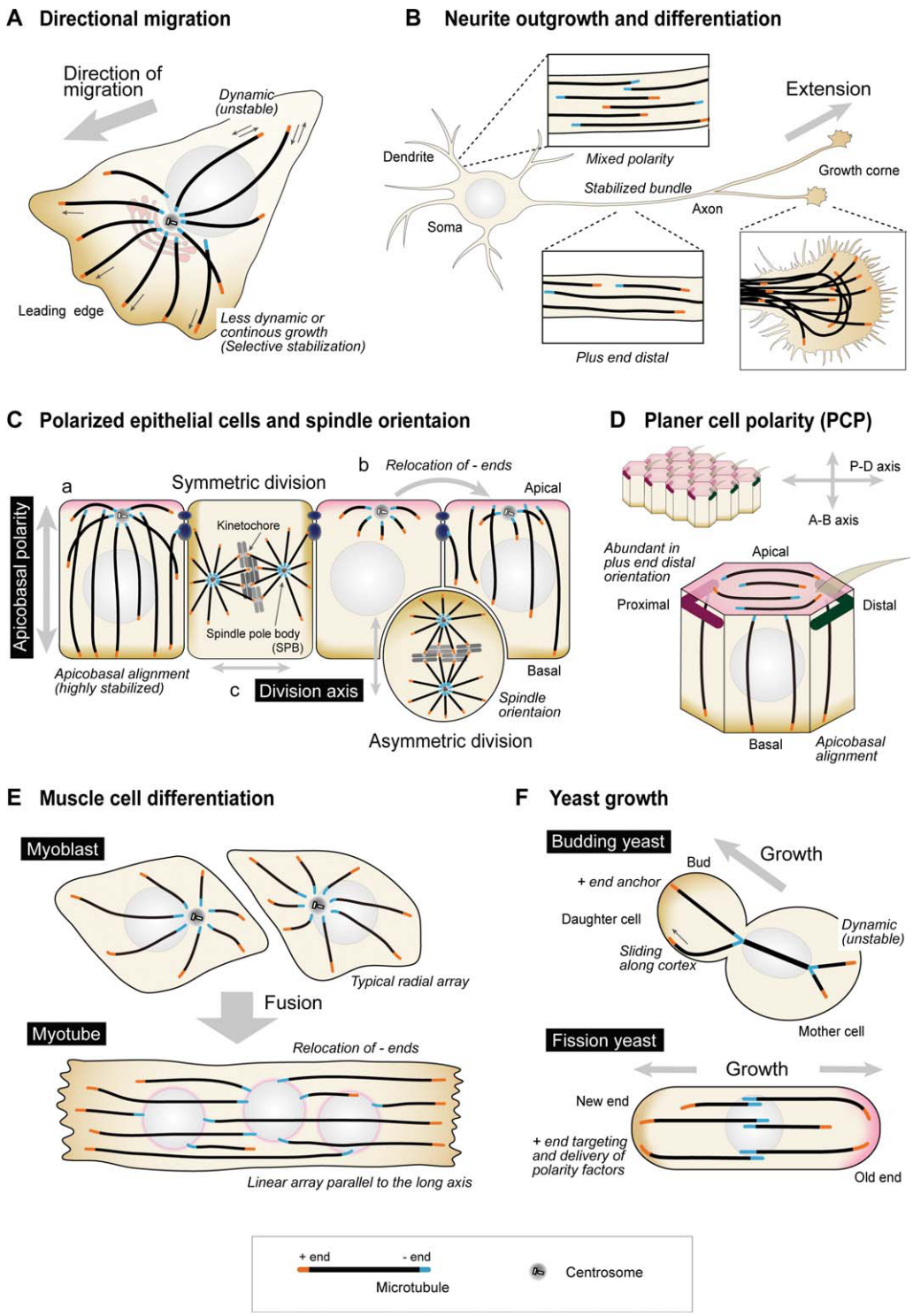


Fig. 4. Schema of polarized cell architecture and microtubule patterns. Typical microtubule network patterns and the position of plus (orange) and minus (blue) ends in polarized cells are illustrated. Microtubule: MT.

centromere-associated kinesin (MCAK), acts at both ends [Varga et al., 2006]. Kinesin-mediated microtubule shrinkage at the plus end may generate the driving force to move organelles: budding yeast Kar3p, a minus end-directed kinesin-14 motor, localizes to plus ends tethered to the shmoo tip and microtubule depolymerization pulls the nucleus to the cell tip [Molk et al., 2006].

In certain cases, factors having different effects on microtubule ends, e.g. stabilizing and destabilizing effects, form a complex to determine appropriate microtubule length. A specific example is the complex of kinesin-13 Kif2b with CLIP-associating protein 1 (CLASP1) at mitotic kinetochores where it exhibits microtubule-depolymerizing activity to promote kinetochore microtubule

dynamics and turnover [Manning et al., 2010]. Another example is the direct association of EB1 family members with MCAK, a potent microtubule depolymerase [Lee et al., 2008]. In an in vitro reconstitution system, EB3, which facilitates tubulin assembly, targets MCAK to the growing microtubule ends and enhances the capacity of MCAK to induce catastrophes, resulting in increase of overall microtubule dynamicity in the system [Montenegro Gouveia et al., 2010]. In cells, overall effects exerted by +TIP complexes on microtubule ends might vary as the situation demands. Thus, the fate of microtubule ends and the resulting impact on microtubule-related events are controlled differentially and precisely at each microtubule anchor site, so that cells establish asymmetric and complex microtubule networks to carry out given functions.

Construction and Function of Microtubule Networks in Various Processes

Examples of actual cell architectures with various microtubule organization patterns showing highlighted plus and minus ends are presented in Fig. 4. Microtubule organizing mechanisms and their biological functions during the morphogenesis of different cell types are described below.

Cell-to-Substrate Adhesion

The ECM provides signaling cues that regulate cell functions, and that could be the first signals adherent cells receive. The composition of the ECM, its three-dimensional organization and its stiffness are major determinants of microenvironmental signaling. The relationship between microtubule plus ends and cell-substratum adhesions was first described in migrating fish fibroblasts, in which microtubule ends targeted to focal adhesions (FAs) were visualized by vinculin staining using live cell fluorescence microscopy [Kaverina et al., 1998]. It has also been reported that fibronectin-mediated stimulation of focal adhesion kinase induces localized stabilization of microtubules by Rho signaling in migrating mouse fibroblasts [Palazzo et al., 2004]. Once attached to the basal cortex, microtubules regulate FA turnover, and thereby facilitate cell migration in concert with endocytic processes [Ezratty et al., 2005; Small and Kaverina, 2003]. Adenomatous polyposis coli (APC) tumor suppressor protein appears to be one of several factors linking FA and microtubule plus end dynamics [Matsui et al., 2008; Matsumoto et al., 2010]. On the other hand, in human MCF-10A mammary epithelial cells, the CLASP-LL5 complex anchors microtubule plus ends to non-FA cell-substratum adhesion sites composed of deposited laminin and laminin receptor integrins [Hotta et al., 2010]. Interestingly, upon epithelial-mesenchymal transition (EMT) during chicken embryo gastrulation, microtubules near the basal cortex are disrupted and the loss of the basal microtubules causes basement membrane breakdown [Nakaya et al., 2008]. This provides evidence of microtubule-ECM communication. Overall, it is likely that microtubules can be targeted to different types of cell-substratum adhesion sites through distinct pathways to regulate cell adhesion, but the molecular linkage between the ECM and microtubules has not yet been precisely dissected and is not understood in detail.

Directional Migration

Directional cell migration is an important process that occurs in tissue development, chemotaxis and wound healing. During directional migration the plus ends of microtubules are stabilized near the leading edges [Waterman-Storer and Salmon, 1997] (Fig. 4A). Microtubule outgrowth from the centrosome shows no directional bias. However, dynamic instability is highly polarized; most microtubules in leading edges are stabilized with a reduced frequency of growth/shortening, while in trailing edges the dynamicity, the sum of the growth and shortening distance per unit time, is increased [Salaycik et al., 2005]. Rho family GTPases, in particular Rac1, RhoA and Cdc42, phosphatidylinositol-3,4,5-triphosphate (PIP3) signaling, and PAR (partitioning-defective) gene products are implicated in the polarization of microtubules [Wittmann and Waterman-Storer, 2001; Etienne-Manneville and Hall, 2002].

Among +TIPs, CLASPs, actin crosslinking family 7 (ACF7, also known as MACF1) and APC tumor suppressor protein localize to the cell cortex near migrating cell edges and attach EB1-positive microtubule plus ends to the cortex to facilitate directional migration (Fig. 3A-b) [Akhmanova et al., 2001; Kodama et al., 2003; Etienne-Manneville et al., 2005; Mimori-Kiyosue et al., 2007]. The molecular linkages that have been reported at the cell cortex are depicted in Fig. 3B. APC promotes persistent growth of microtubule ends and guides them to the front of the lamellipodia [Näthke et al., 1996; Kita et al., 2006]. APC remains attached to the extending microtubule ends with the help of plus end-directed motor activities [Mimori-Kiyosue et al., 2000; Jimbo et al., 2002; Jaulin and Kreitzer, 2010], which results in accumulation of APC at the ends of pioneering microtubules (Fig. 3A-b). In contrast, CLASPs, immobilized on LL5-containing cortical patches formed at the base of lamellipodia, keep the microtubule ends within this narrow area for a longer time period, although individual microtubule ends exhibit repetitive short distance growth/shortening (Figs. 2A-a and 3A-b) [Mimori-Kiyosue et al., 2005; Hotta et al., 2010]. The site of APC localization relies on the Par6-aPKC-Cdc42 complex [Etienne-Manneville et al., 2005], while the CLASP-LL5 complex requires the PI3K pathway, activated by ECM-integrin association, for localization to the basal cell cortex [Hotta et al., 2010]. The affinity of APC and CLASPs to the microtubules is partly regulated by GSK-3β, which phosphorylates MAPs to release microtubules and is inactivated through Rac1- or Cdc42-dependent phosphorylation, which occurs specifically at the leading

edge of migrating cells [Etienne-Manneville and Hall, 2003; Wittmann and Waterman-Storer, 2005].

In extending nerve processes, microtubule behavior and the regulatory mechanisms controlling this behavior are similar to that reported for the leading edge of other types of migrating cells. For example, the involvement of APC and CLASPs, under the control of nerve growth factor signaling and Abelson (Abl) tyrosine kinase, respectively, have been described [Lee et al., 2004; Zhou et al., 2004]. During synaptogenesis, microtubules decorated with EB1 can enter synapses and modulate spine morphology by interacting with p140Cap/SNIP, a regulator of Src tyrosine kinase, through the regulation of the actin cytoskeleton [Jaworski et al., 2009]. Microtubule orientation is unique in neurites: in axons microtubules are aligned unidirectionally, with all the plus ends pointing toward the growth cone, while microtubules are aligned nonuniformly in differentiated dendrites, with dynamic plus ends pointing both distally and toward the cell body (Fig. 4B). The precise mechanisms governing this unique microtubule organization in nerve processes are still obscure, and current knowledge has been reviewed by Conde and Caceres [2009].

Epithelial Cell Polarization

Epithelial cells contain stable microtubules that are not associated with centrosomes, and these microtubules are required for epithelial polarization. At the early stage of epithelial polarization, cadherin-mediated contact interactions initiate a signaling pathway that alters microtubule organization by stabilizing microtubule ends indirectly via an as yet unknown pathway [Chausovsky et al., 2000]. A minus end-binding protein, Nezha/Patronin, may contribute to the stabilization of free minus ends in the cytoplasm [Meng et al., 2008; Goodwin and Vale, 2010] (Fig. 2B-d). Furthermore, cadherin-mediated cell–cell interactions provide extracellular cues that induce nucleus and centrosome off-centering toward cell–cell contacts, and promote orientation of the nucleus–centrosome axis toward free cell edges [Dupin et al., 2009].

Apicobasal polarization of epithelial cells involves a dramatic reorganization of microtubules (Fig. 4C-a). The radial array of microtubules focused on a centrally located centrosome is lost or greatly reduced, and a non-centrosomal apicobasal array develops (Fig. 4C-b) [Bre et al., 1987; Buendia et al., 1990], while a subset of microtubules still grow toward apical membranes [Jaulin et al., 2007]. Concomitantly, minus end-capping and end-anchoring factors, such as γ-tubulin, ninein and Nezha, relocate to the apical anchoring sites [Meads and Schroer, 1995; Mogensen et al., 2000; Meng et al., 2008]. At the basal sites, +TIPs, including APC and CLASP-LL5 complex, are localized to retain microtubule plus ends at the basal cortex [Reilein and Nelson, 2005; Hotta et al., 2010]. These observations are consistent with the notion that the minus and plus end-anchoring molecules are recruited to the apical and basal region, respectively, to align microtubules along the apicobasal axis (Fig. 4C-a).

Recent studies have uncovered intriguing relationships between microtubules and septins in the formation of apicobasal microtubule arrays. Septins are filamentous guanine triphosphates (GTPases) that can bind to microtubules [reviewed by Kinoshita, 2006; Weirich et al., 2008; Spiliotis, 2010]. In epithelial cells undergoing polarization, septin 2 associated with bundled microtubules guides microtubule growth dynamics and microtubule-microtubule interactions toward the establishment of the apical microtubule meshwork [Bowen et al., 2011]. The septin tracks also facilitate post-Golgi vesicle transport by antagonizing MAP4, which has an inhibitory role in vesicle transport. This regulatory step is required for columnar-shaped epithelial morphogenesis [Spiliotis et al., 2008].

Similar to epithelial morphogenesis, microtubule alignment is important for development of the vertebrate central nervous system (CNS). The different cell types in the CNS develop from a common pool of progenitor cells. The nuclei of progenitors move between the apical and basal surfaces of the neuroepithelium in phase with their cell cycle, a process termed interkinetic nuclear migration (INM), which may have a role in regulating cell cycle and proliferation [Del Bene et al., 2008]. During INM, the plus end-directed motor dynein and the minus end-directed motor kinesin are required for apical and basal migration of the nucleus, respectively [Tsai et al., 2010; Kosodo et al., 2011].

In the mouse epidermis, which is a stratified squamous epithelium composed of proliferating basal and differentiated suprabasal keratinocytes, microtubules stereotypically reorganize as they differentiate. In basal cells microtubules form a cytoplasmic network emanating from an apical centrosome, while in suprabasal cells microtubules concentrate at cell-cell junctions. During epidermal differentiation ninein and Lis1/Ndel1, which are centrosomal proteins required for microtubule anchoring, are lost from the centrosome and is recruited to desmosomes by desmoplakin, resulting in the relocation of microtubules to the cell cortex [Lechler and Fuchs, 2007; SumiGray et al., 2011].

Planar Cell Polarity

In some types of epithelia, such as the *Drosophila* wing epidermis, a global polarity cue induces a second axis within a plane, known as planar cell polarity (PCP), which is perpendicular to apical/basal polarity [Goodrich and Strutt, 2011] (Fig. 4D). Wnt signalling components, including Frizzled and Disheveled and non-classical cadherins Fat, Dachsous and Flamingo, are involved in PCP development. In the apical area of the *Drosophila* wing epidermis, microtubules are aligned along the proximal-distal axis with a small but significant excess of plus end-distal microtubules [Shimada et al., 2006; Harumoto

et al., 2010]. This characteristic alignment and asymmetry of microtubule growth is controlled in part by atypical cadherins, Dachsous and Fat, as well as by PAR-1, which appears to contribute to the distal redistribution of the core PCP mediator, Frizzled.

In mammals, motile cilia cover many organs and produce large-scale fluid flows crucial for development and physiology and that act in concert with the PCP pathway [reviewed by Wallingford, 2010; Gray et al., 2011]. Cilia are microtubule-based organelles that protrude from the cell and consist of nine outer microtubule doublets with/without an inner microtubule doublet ("9 + 2" or "9 + 0" configuration, respectively). Defects in ciliary motility cause a range of disease symptoms including bronchiectasis, hydrocephalus, and situs inversus [reviewed by Gerdes et al., 2009]. A recent finding linked Frizzled to septins in ciliogenesis as well as to collective cell movement during vertebrate embryogenesis [Kim et al., 2010]. Septins appear to be key mediators connecting microtubule systems to higher-order tissue polarities. Septin 2 also forms a diffusion barrier at the base of the ciliary membrane [Hu et al., 2010].

Mitotic Spindle Assembly and Orientation

Microtubule end-binding factors play critical roles during mitotic spindle assembly and orientation along the division axis, at centrosomes, kinetochores and the cell cortex and in the spindle checkpoint that controls cell-cycle progression (Fig. 2C-c, Fig. 4C-c, Table I). For detailed discussions on the role of MAPs in mitosis and spindle orientation during asymmetric cell division, please refer to other eminent reviews Kline-Smith and Walczak, 2004; Maiato et al., 2004; and Siller and Doe, 2009, respectively.

From a biological perspectives, asymmetric cell division, in which proteins or RNA determinants are segregated differentially into two daughter cells, is essential for generating diverse cell types during development of multicellular organisms [Gonczy, 2008], for example controlling the self-renewal versus differentiation decision in skin [Fuchs, 2008], neuroblasts [Chia et al., 2008], and cancer cells [Knoblich, 2010]. Among the MAPs being highlighted in this review, cortical APC has been implicated in spindle orientation in dividing *Drosophila* male germline stem cells [Yamashita et al., 2003].

Muscle Cell Differentiation

Skeletal muscle is generated by the fusion of precursor cells called myoblasts to form multinucleated syncytial myotubes, a process that requires microtubules and EB1 family proteins [Guo et al., 1986; Straube et al., 2003]. While myoblasts carry typical radial centrosomal microtubule networks, in myotubes microtubules form linear arrays parallel to the long cell axis and microtubule-nucleating material clusters (pericentriolar proteins), which include γ-tubulin, ninein and pericentrin, are redistributed around the nuclei (Fig. 4E). At later stages of differentiation, during myofibrillogenesis, precursors of myosin filaments display microtubule plus end directed movements to the cell membrane and form sarcomeric myosin filaments [Pizon et al., 2005].

In *Drosophila* tendon cells, a compact microtubule array, in which the microtubules are oriented in the same direction, is formed at a unique subcellular domain that connects the muscle-tendon junction and the cuticle. The *Drosophila* ACF7 homologue, Shot, and the EB1-APC1 complex are involved in the formation of this essential compact microtubule network [Subramanian et al., 2003]. In tendon cells with reduced Shot activity, EB1-APC1 dissociates from the muscle-tendon junction and the microtubule array elongates. The resulting tendon cells lose their stress resistance and elongate.

Yeast Growth

Yeasts, being single-celled organisms, only carry a few microtubules, whose behavior along the growth axis is strictly controlled during progression of the cell cycle (Fig. 4F) [Hayles and Nurse, 2001; Chang and Martin, 2009]. Budding yeast and fission yeast are highly tractable model eukaryotes, and investigation of the molecular differences and similarities among these yeast species and higher eukaryotes have contributed to our understanding of cell polarity [reviewed by Gundersen, 2002].

In fission yeast, cell polarization relies largely on microtubules, which deliver polarity factors to the cell tips, where they function to recruit protein complexes involved in actin assembly. In contrast, in budding yeast, spatial cues are dependent on septins and actin. In multicellular organisms, all these cytoskeletal components may cooperate spatially within a cell to generate more complex shapes. In addition, although certain molecules, such as the EB1 family members and the dynein-dynacitn complex, are highly conserved in all eukaryotic organisms, including plants, yeasts adopt unique mechanisms to target molecules to microtubule ends. For example, budding yeast dynein and Bik1p (CLIP-170), as well as fission yeast Tip1p (CLIP-170), are targeted to microtubule ends by kinesin-mediated motility [Busch et al., 2004; Carvalho et al., 2004], and Bim1p (EB1 family)-accumulated microtubule plus ends are targeted to the bud tip by myosin walking along the actin cable extending from the tip (Fig. 2A-c) [Hwang et al., 2003]. Despite minor differences, the discovery of basic modules and principles of cell morphogenesis derived from the genetic dissection of the yeast models have provided important novel insight into how more complex cells are shaped.

Conclusions and Perspectives

The molecular basis for microtubule patterning is being rapidly unveiled in the modern era of molecular cell biology by

application of approaches such as cultured cell systems and in vitro reconstitution systems combined with sophisticated technologies, such as live-cell and single molecule imaging, physical manipulation and computer modeling. The fundamental concepts explaining microtubule patterning and its importance, at least at the cultured cell level, appear to be established. However, our knowledge of the upstream signals that induce the formation of microtubule-anchoring structures that have different purpose at distinct sites within cells to generate highly shaped microtubule patterns is still limited. Moreover, compared to the abundance of data from cultured cells, little is known about the detailed organization and dynamics of microtubules in mammalian cells located in their innate tissue environments, in which various physiological requirements may recruit microtubule ends to appropriate sites. On the other hand, recent progress in comprehensive genetic analysis technologies has revealed the physiological relevance of microtubule systems in various human diseases. Furthermore, tools such as embryonic stem cells or induced pluripotent stem cells are now available that are able to differentiate into a variety of cell types and tissues in vitro. With such tools in hand, the focus for the field will be to understand the biological significance of the regulation of microtubules in terms of cell differentiation, organ development and maintenance, as well as disease.

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References

Akhmanova A, Hoogenraad CC, Drabek K, Stepanova T, Dortland B, Verkerk T, Vermeulen W, Burgering BM, De Zeeuw CI, Grosveld F, Galjart N. 2001. Clasps are CLIP-115 and -170 associating proteins involved in the regional regulation of microtubule dynamics in motile fibroblasts. Cell 104:923–935.

Akhmanova A, Steinmetz MO. 2008. Tracking the ends: a dynamic protein network controls the fate of microtubule tips. Nat Rev Mol Cell Biol 9:309–322.

Amos LA, Schlieper D. 2005. Microtubules and maps. Adv Protein Chem 71:257–298.

Banks JD, Heald R. 2004. Adenomatous polyposis coli associates with the microtubule-destabilizing protein XMCAK. Curr Biol 14: 2033–2038.

Bartolini F, Gundersen GG. 2006. Generation of noncentrosomal microtubule arrays. J Cell Sci 119:4155–4163.

Berry RW,Shelansk.Ml. 1972. Interactions of Tubulin with Vinblastine and Guanosine Triphosphate. J Mol Biol 71:71–80.

Bieling P, Laan L, Schek H, Munteanu EL, Sandblad L, Dogterom M, Brunner D, Surrey T. 2007. Reconstitution of a microtubule plus-end tracking system in vitro. Nature 450:1100–1105.

Bowen JR, Hwang D, Bai X, Roy D, Spiliotis ET. 2011. Septin GTPases spatially guide microtubule organization and plus end dynamics in polarizing epithelia. J Cell Biol 194(2):187–197.

Bre MH, Kreis TE, Karsenti E. 1987. Control of microtubule nucleation and stability in Madin-Darby canine kidney cells: the occurrence of noncentrosomal, stable detyrosinated microtubules. J Cell Biol 105:1283–1296.

Brouhard GJ, Stear JH, Noetzel TL, Al-Bassam J, Kinoshita K, Harrison SC, Howard J, Hyman AA. 2008. XMAP215 is a processive microtubule polymerase. Cell 132:79–88.

Buendia B, Bre MH, Griffiths G, Karsenti E. 1990. Cytoskeletal control of centrioles movement during the establishment of polarity in Madin-Darby canine kidney cells. J Cell Biol 110:1123–1135.

Bugnard E, Zaal KJ, Ralston E. 2005. Reorganization of microtubule nucleation during muscle differentiation. Cell Motil Cytoskeleton 60:1–13.

Busch KE, Hayles J, Nurse P, Brunner D. 2004. Tea2p Kinesin is involved in spatial microtubule organization by transporting tip1p on microtubules. Dev Cell 6:831–843.

Buttrick GJ, Millar JB. 2011. Ringing the changes: emerging roles for DASH at the kinetochore-microtubule interface. Chromosome Res 19:393–407.

Carvalho P, Gupta ML, Hoyt MA, Pellman D. 2004. Cell cycle control of kinesin-mediated transport of Bik1 (CLIP-170) regulates microtubule stability and dynein activation. Dev Cell 6:815–829.

Cassimeris L. 2002. The oncoprotein 18/stathmin family of microtubule destabilizers. Curr Opin Cell Biol 14:18–24.

Chang F, Martin SG. 2009. Shaping fission yeast with microtubules. Cold Spring Harb Perspect Biol 1:a001347.

Chausovsky A, Bershadsky AD, Borisy GG. 2000. Cadherin-mediated regulation of microtubule dynamics. Nat Cell Biol 2:797–804.

Chen CR, Chen J, Chang EC. 2000. A conserved interaction between Moe1 and Mal3 is important for proper spindle formation in Schizosaccharomyces pombe. Mol Biol Cell 11:4067–4077.

Chen CR, Li YC, Chen J, Hou MC, Papadaki P, Chang EC. 1999. Moe1, a conserved protein in Schizosaccharomyces pombe, interacts with a Ras effector, Scd1, to affect proper spindle formation. Proc Natl Acad Sci U S A 96:517–522.

Chia W, Somers WG, Wang HY. 2008. Drosophila neuroblast asymmetric divisions: cell cycle regulators, asymmetric protein localization, and tumorigenesis. J Cell Biol 180:267–272.

Conde C, Caceres A. 2009. Microtubule assembly, organization and dynamics in axons and dendrites. Nat Rev Neurosci 10:319–332.

Del Bene F, Wehman AM, Link BA, Baier H. 2008. Regulation of neurogenesis by interkinetic nuclear migration through an apical-basal Notch gradient. Cell 134:1055–1065.

des Georges A, Katsuki M, Drummond DR, Osei M, Cross RA, Amos LA. 2008. Mal3, the Schizosaccharomyces pombe homolog of EB1, changes the microtubule lattice. Nature Struct Mol Biol 15:1102–1108.

Dujardin DL, Vallee RB. 2002. Dynein at the cortex. Curr Opin Cell Biol 14:44–49.

Dupin I, Camand E, Etienne-Manneville S. 2009. Classical cadherins control nucleus and centrosome position and cell polarity. J Cell Biol 185:779–786.

Efimov A, Kharitonov A, Efimova N, Loncarek J, Miller PM, Andreyeva N, Gleeson P, Galjart N, Maia AR, McLeod IX and

others. 2007. Asymmetric CLASP-dependent nucleation of noncentrosomal microtubules at the trans-Golgi network. Dev Cell 12: 917–930.

Elie-Caille C, Severin F, Helenius J, Howard J, Muller DJ, Hyman AA. 2007. Straight GDP-tubulin protofilaments form in the presence of taxol. Curr Biol 17:1765–1770.

Ems-McClung SC, Walczak CE. 2010. Kinesin-13s in mitosis: Key players in the spatial and temporal organization of spindle microtubules. Semin Cell Dev Biol 21:276–282.

Etienne-Manneville S, Hall A. 2002. Rho GTPases in cell biology. Nature 420:629–635.

Etienne-Manneville S, Hall A. 2003. Cdc42 regulates GSK-3beta and adenomatous polyposis coli to control cell polarity. Nature 421:753–756.

Etienne-Manneville S, Manneville JB, Nicholls S, Ferenczi MA, Hall A. 2005. Cdc42 and Par6-PKCzeta regulate the spatially localized association of Dlg1 and APC to control cell polarization. J Cell Biol 170:895–901.

Ezratty EJ, Partridge MA, Gundersen GG. 2005. Microtubule-induced focal adhesion disassembly is mediated by dynamin and focal adhesion kinase. Nat Cell Biol 7:581–590.

Flory MR, Morphew M, Joseph JD, Means AR, Davis TN. 2002. Pcp1p, an Spc110p-related calmodulin target at the centrosome of the fission yeast Schizosaccharomyces pombe. Cell Growth Differ 13:47–58.

Fodde R, Kuipers J, Rosenberg C, Smits R, Kielman M, Gaspar C, van Es JH, Breukel C, Wiegant J, Giles RH and others. 2001. Mutations in the APC tumour suppressor gene cause chromosomal instability. Nat Cell Biol 3:433–438.

Fuchs E. 2008. Skin stem cells: rising to the surface. Journal of Cell Biology 180:273–284.

Fukata M, Watanabe T, Noritake J, Nakagawa M, Yamaga M, Kuroda S, Matsuura Y, Iwamatsu A, Perez F, Kaibuchi K. 2002. Rac1 and Cdc42 capture microtubules through IQGAP1 and CLIP-170. Cell 109:873–885.

Garcia MA, Koonrugsa N, Toda T. 2002. Spindle-kinetochore attachment requires the combined action of Kin I-like Klp5/6 and Alp14/Dis1-MAPs in fission yeast. Embo J 21:6015–6024.

Geraldo S, Khanzada UK, Parsons M, Chilton JK, Gordon-Weeks PR. 2008. Targeting of the F-actin-binding protein drebrin by the microtubule plus-tip protein EB3 is required for neuritogenesis. Nat Cell Biol 10:1181–1189.

Gerdes JM, Davis EE, Katsanis N. 2009. The vertebrate primary cilium in development, homeostasis, and disease. Cell 137:32–45.

Goldstone S, Reyes C, Gay G, Courtheoux T, Dubarry M, Tournier S, Gachet Y. 2010. Tip1/CLIP-170 protein is required for correct chromosome poleward movement in fission yeast. PLoS One 5: e10634.

Gonczy P. 2008. Mechanisms of asymmetric cell division: flies and worms pave the way. Nat Rev Mol Cell Biol 9:355–366.

Goodrich LV, Strutt D. 2011. Principles of planar polarity in animal development. Development 138:1877–1892.

Goodwin SS, Vale RD. 2010. Patronin regulates the microtubule network by protecting microtubule minus ends. Cell 143:263–274.

Grallert A, Beuter C, Craven RA, Bagley S, Wilks D, Fleig U, Hagan IM. 2006. S. pombe CLASP needs dynein, not EB1 or CLIP170, to induce microtubule instability and slows polymerization rates at cell tips in a dynein-dependent manner. Genes Dev 20:2421–2436.

Gray RS, Roszko I, Solnica-Krezel L. 2011. Planar cell polarity: coordinating morphogenetic cell behaviors with embryonic polarity. Dev Cell 21:120–133.

Grohmann A, Tanneberger K, Alzner A, Schneikert J, Behrens J. 2007. AMER1 regulates the distribution of the tumor suppressor APC between microtubules and the plasma membrane. J Cell Sci 120:3738–3747.

Gundersen GG. 2002. Evolutionary conservation of microtubule-capture mechanisms. Nat Rev Mol Cell Biol 3:296–304.

Gundersen GG, Cook TA. 1999. Microtubules and signal transduction. Curr Opin Cell Biol 11:81–94.

Guo J, Yang Z, Song W, Chen Q, Wang F, Zhang Q, Zhu X. 2006. Nudel contributes to microtubule anchoring at the mother centriole and is involved in both dynein-dependent and -independent centrosomal protein assembly. Mol Biol Cell 17:680–689.

Guo JX, Jacobson SL, Brown DL. 1986. Rearrangement of tubulin, actin, and myosin in cultured ventricular cardiomyocytes of the adult rat. Cell Motil Cytoskeleton 6:291–304.

Gupta ML, Jr. Carvalho P, Roof DM, Pellman D. 2006. Plus end-specific depolymerase activity of Kip3, a kinesin-8 protein, explains its role in positioning the yeast mitotic spindle. Nat Cell Biol 8: 913–923.

Harumoto T, Ito M, Shimada Y, Kobayashi TJ, Ueda HR, Lu B, Uemura T. 2010. Atypical cadherins Dachsous and fat control dynamics of noncentrosomal microtubules in planar cell polarity. Dev Cell 19:389–401.

Hayles J, Nurse P. 2001. A journey into space. Nat Rev Mol Cell Biol 2:647–656.

Helfant AH. 2002. Composition of the spindle pole body of Saccharomyces cerevisiae and the proteins involved in its duplication. Curr Genet 40:291–310.

Hirokawa N. 1998. Kinesin and dynein superfamily proteins and the mechanism of organelle transport. Science 279:519–526.

Hotani H, Horio T. 1988. Dynamics of microtubules visualized by darkfield microscopy: treadmilling and dynamic instability. Cell Motil Cytoskeleton 10:229–236.

Hotta A, Kawakatsu T, Nakatani T, Sato T, Matsui C, Sukezane T, Akagi T, Hamaji T, Grigoriev I, Akhmanova A and others. 2010. Laminin-based cell adhesion anchors microtubule plus ends to the epithelial cell basal cortex through LL5alpha/beta. J Cell Biol 189: 901–917.

Howard J, Hyman AA. 2007. Microtubule polymerases and depolymerases. Curr Opin Cell Biol 19:31–35.

Howard J, Hyman AA. 2009. Growth, fluctuation and switching at microtubule plus ends. Nat Rev Mol Cell Biol 10:569–574.

Hsu KS, Toda T. 2011. Ndc80 internal loop interacts with Dis1/TOG to ensure proper kinetochore-spindle attachment in fission yeast. Curr Biol 21:214–220.

Hu Q, Milenkovic L, Jin H, Scott MP, Nachury MV, Spiliotis ET, Nelson WJ. 2010. A septin diffusion barrier at the base of the primary cilium maintains ciliary membrane protein distribution. Science 329:436–439.

Hwang E, Kusch J, Barral Y, Huffaker TC. 2003. Spindle orientation in Saccharomyces cerevisiae depends on the transport of microtubule ends along polarized actin cables. J Cell Biol 161:483–488.

Jacobs M, Smith H, Taylor EW. 1974. Tubulin - nucleotide binding and enzymic activity. J Mol Biol 89:455–468.

Jang CY, Wong J, Coppinger JA, Seki A, Yates JR, III, Fang G. 2008. DDA3 recruits microtubule depolymerase Kif2a to spindle poles and controls spindle dynamics and mitotic chromosome movement. J Cell Biol 181:255–267.

Janke C, Kneussel M. 2010. Tubulin post-translational modifications: encoding functions on the neuronal microtubule cytoskeleton. Trends Neurosci 33:362–372.

Jaulin F, Kreitzer G. 2010. KIF17 stabilizes microtubules and contributes to epithelial morphogenesis by acting at MT plus ends with EB1 and APC. J Cell Biol 190:443–460.

Jaulin F, Xue X, Rodriguez-Boulan E, Kreitzer G. 2007. Polarization-dependent selective transport to the apical membrane by KIF5B in MDCK cells. Dev Cell 13:511–522.

Jaworski J, Kapitein LC, Gouveia SM, Dortland BR, Wulf PS, Grigoriev I, Camera P, Spangler SA, Di Stefano P, Demmers J, et al. 2009. Dynamic microtubules regulate dendritic spine morphology and synaptic plasticity. Neuron 61:85–100.

Jimbo T, Kawasaki Y, Koyama R, Sato R, Takada S, Haraguchi K, Akiyama T. 2002. Identification of a link between the tumour suppressor APC and the kinesin superfamily. Nat Cell Biol 4:323–327.

Kaplan KB, Burds AA, Swedlow JR, Bekir SS, Sorger PK, Näthke IS. 2001. A role for the Adenomatous Polyposis Coli protein in chromosome segregation. Nat Cell Biol 3:429–432.

Kardon JR, Vale RD. 2009. Regulators of the cytoplasmic dynein motor. Nat Rev Mol Cell Biol 10:854–865.

Kaverina I, Rottner K, Small JV. 1998. Targeting, capture, and stabilization of microtubules at early focal adhesions. J Cell Biol 142: 181–190.

Kilmartin JV, Goh PY. 1996. Spc110p: assembly properties and role in the connection of nuclear microtubules to the yeast spindle pole body. Embo J 15:4592–4602.

Kim SK, Shindo A, Park TJ, Oh EC, Ghosh S, Gray RS, Lewis RA, Johnson CA, Attie-Bittach T, Katsanis N, et al. 2010. Planar cell polarity acts through septins to control collective cell movement and ciliogenesis. Science 329(5997):1337–1340.

Kimura A, Onami S. 2005. Computer simulations and image processing reveal length-dependent pulling force as the primary mechanism for C. elegans male pronuclear migration. Dev Cell 8: 765–775.

Kimura A, Onami S. 2007. Local cortical pulling-force repression switches centrosomal centration and posterior displacement in C. elegans. J Cell Biol 179:1347–1354.

Kinoshita K, Noetzel TL, Arnal I, Drechsel DN, Hyman AA. 2006. Global and local control of microtubule destabilization promoted by a catastrophe kinesin MCAK/XKCM1. J Muscle Res Cell Motil 27:107–114.

Kinoshita M. 2006. Diversity of septin scaffolds. Curr Opin Cell Biol 18:54–60.

Kirschner M, Mitchison T. 1986. Beyond self-assembly: from microtubules to morphogenesis. Cell 45:329–342.

Kita K, Wittmann T, Näthke IS, Waterman-Storer CM. 2006. Adenomatous polyposis coli on microtubule plus ends in cell extensions can promote microtubule net growth with or without EB1. Mol Biol Cell 17:2331–2345.

Kline-Smith SL, Walczak CE. 2004. Mitotic spindle assembly and chromosome segregation: Refocusing on microtubule dynamics. Molecular Cell 15:317–327.

Knoblich JA. 2010. Asymmetric cell division: recent developments and their implications for tumour biology. Nature Reviews Molecular Cell Biology 11:849–860.

Knowlton AL, Vorozhko VV, Lan W, Gorbsky GJ, Stukenberg PT. 2009. ICIS and Aurora B coregulate the microtubule depolymerase Kif2a. Curr Biol 19:758–763.

Kodama A, Karakesisoglou I, Wong E, Vaezi A, Fuchs E. 2003. ACF7: an essential integrator of microtubule dynamics. Cell 115: 343–354.

Kodani A, Tonthat V, Wu B, Sutterlin C. 2010. Par6 alpha interacts with the dynactin subunit p150 Glued and is a critical regulator of centrosomal protein recruitment. Mol Biol Cell 21: 3376–3385.

Kollman JM, Polka JK, Zelter A, Davis TN, Agard DA. 2010. Microtubule nucleating gamma-TuSC assembles structures with 13-fold microtubule-like symmetry. Nature 466:879–882.

Korinek WS, Copeland MJ, Chaudhuri A, Chant J. 2000. Molecular linkage underlying microtubule orientation toward cortical sites in yeast. Science 287:2257–2259.

Kosodo Y, Suetsugu T, Suda M, Mimori-Kiyosue Y, Toida K, Baba SA, Kimura A, Matsuzaki F. 2011. Regulation of interkinetic nuclear migration by cell cycle-coupled active and passive mechanisms in the developing brain. Embo J 30:1690–1704.

Lansbergen G, Grigoriev I, Mimori-Kiyosue Y, Ohtsuka T, Higa S, Kitajima I, Demmers J, Galjart N, Houtsmuller AB, Grosveld F and others. 2006. CLASPs attach microtubule plus ends to the cell cortex through a complex with LL5beta. Dev Cell 11:21–32.

Lechler T, Fuchs E. 2007. Desmoplakin: an unexpected regulator of microtubule organization in the epidermis. J Cell Biol 176:147–154.

Lee H, Engel U, Rusch J, Scherrer S, Sheard K, Van Vactor D. 2004. The microtubule plus end tracking protein Orbit/MAST/CLASP acts downstream of the tyrosine kinase Abl in mediating axon guidance. Neuron 42:913–926.

Lee L, Tirnauer JS, Li J, Schuyler SC, Liu JY, Pellman D. 2000. Positioning of the mitotic spindle by a cortical-microtubule capture mechanism. Science 287:2260–2262.

Lee MJ, Gergely F, Jeffers K, Peak-Chew SY, Raff JW. 2001. Msps/XMAP215 interacts with the centrosomal protein D-TACC to regulate microtubule behaviour. Nat Cell Biol 3:643–649.

Lee T, Langford KJ, Askham JM, Bruning-Richardson A, Morrison EE. 2008. MCAK associates with EB1. Oncogene 27:2494–2500.

Ligon LA, Karki S, Tokito M, Holzbaur ELF. 2001. Dynein binds to beta-catenin and may tether microtubules at adherens junctions. Nature Cell Biology 3:913–917.

Louie RK, Bahmanyar S, Siemers KA, Votin V, Chang P, Stearns T, Nelson WJ, Barth AI. 2004. Adenomatous polyposis coli and EB1 localize in close proximity of the mother centriole and EB1 is a functional component of centrosomes. J Cell Sci 117(Pt 7):1117–1128.

Luders J, Stearns T. 2007. Microtubule-organizing centres: a re-evaluation. Nat Rev Mol Cell Biol 8:161–167.

Lundin VF, Leroux MR, Stirling PC. 2010. Quality control of cytoskeletal proteins and human disease. Trends Biochem Sci 35: 288–297.

Maffini S, Maia AR, Manning AL, Maliga Z, Pereira AL, Junqueira M, Shevchenko A, Hyman A, Yates JR, III, Galjart N, et al. 2009. Motor-independent targeting of CLASPs to kinetochores by CENP-E promotes microtubule turnover and poleward flux. Curr Biol 19: 1566–1572.

Maiato H, Sampaio P, Sunkel CE. 2004. Microtubule-associated proteins and their essential roles during mitosis. Int Rev Cytol 241: 53–153.

Manneville JB, Jehanno M, Etienne-Manneville S. 2010. Dlg1 binds GKAP to control dynein association with microtubules, centrosome positioning, and cell polarity. J Cell Biol 191:585–598.

Manning AL, Bakhoum SF, Maffini S, Correia-Melo C, Maiato H, Compton DA. 2010. CLASP1, astrin and Kif2b form a molecular switch that regulates kinetochore-microtubule dynamics to promote mitotic progression and fidelity. Embo J 29:3531–3543.

Matsui C, Kaieda S, Ikegami T, Mimori-Kiyosue Y. 2008. Identification of a link between the SAMP repeats of APC (adenomatous polyposis coli) tumor suppressor and the SH3 domain of DDEF. J Biol Chem 283:33006–33020.

Matsumoto S, Fumoto K, Okamoto T, Kaibuchi K, Kikuchi A. 2010. Binding of APC and dishevelled mediates Wnt5a-regulated focal adhesion dynamics in migrating cells. Embo J 29:1192–1204.

McNiven MA, Wang M, Porter KR. 1984. Microtubule polarity and the direction of pigment transport reverse simultaneously in surgically severed melanophore arms. Cell 37:753–765.

Meads T, Schroer TA. 1995. Polarity and nucleation of microtubules in polarized epithelial cells. Cell Motil Cytoskeleton 32:273–288.

Meng W, Mushika Y, Ichii T, Takeichi M. 2008. Anchorage of microtubule minus ends to adherens junctions regulates epithelial cell-cell contacts. Cell 135:948–959.

Miller RK, D'Silva S, Moore JK, Goodson HV. 2006. The CLIP-170 orthologue Bik1p and positioning the mitotic spindle in yeast. Curr Top Dev Biol 76:49–87.

Mimori-Kiyosue Y, Grigoriev I, Lansbergen G, Sasaki H, Matsui C, Severin F, Galjart N, Grosveld F, Vorobjev I, Tsukita S, et al. 2005. CLASP1 and CLASP2 bind to EB1 and regulate microtubule plus-end dynamics at the cell cortex. J Cell Biol 168:141–153.

Mimori-Kiyosue Y, Matsui C, Sasaki H, Tsukita S. 2007. Adenomatous polyposis coli (APC) protein regulates epithelial cell migration and morphogenesis via PDZ domain-based interactions with plasma membranes. Genes Cells 12:219–233.

Mimori-Kiyosue Y, Shiina N, Tsukita S. 2000. Adenomatous polyposis coli (APC) protein moves along microtubules and concentrates at their growing ends in epithelial cells. J Cell Biol 148:505–518.

Mimori-Kiyosue Y, Tsukita S. 2003. "Search-and-capture" of microtubules through plus-end-binding proteins (+TIPs). J Biochem 134:321–326.

Mitchison T, Kirschner M. 1984. Dynamic instability of microtubule growth. Nature 312:237–242.

Mogensen MM, Malik A, Piel M, Bouckson-Castaing V, Bornens M. 2000. Microtubule minus-end anchorage at centrosomal and non-centrosomal sites: the role of ninein. J Cell Sci 113 (Pt 17): 3013–3023.

Molk JN, Salmon ED, Bloom K. 2006. Nuclear congression is driven by cytoplasmic microtubule plus end interactions in *S. cerevisiae*. J Cell Biol 172:27–39.

Montenegro Gouveia S, Leslie K, Kapitein LC, Buey RM, Grigoriev I, Wagenbach M, Smal I, Meijering E, Hoogenraad CC, Wordeman L, et al. 2010. In vitro reconstitution of the functional interplay between MCAK and EB3 at microtubule plus ends. Curr Biol 20:1717–1722.

Moss DK, Bellett G, Carter JM, Liovic M, Keynton J, Prescott AR, Lane EB, Mogensen MM. 2007. Ninein is released from the centrosome and moves bi-directionally along microtubules. J Cell Sci 120(Pt 17):3064–3074.

Nakaya Y, Sukowati EW, Wu Y, Sheng GJ. 2008. RhoA and microtubule dynamics control cell-basement membrane interaction in EMT during gastrulation. Nature Cell Biology 10:765–775.

Näthke IS, Adams CL, Polakis P, Sellin JH, Nelson WJ. 1996. The adenomatous polyposis coli tumor suppressor protein localizes to plasma membrane sites involved in active cell migration. J Cell Biol 134:165–179.

Nédélec FJ, Surrey T, Maggs AC, Leibler S. 1997. Self-organization of microtubules and motors. Nature 389:305–308.

Niethammer P, Bastiaens P, Karsenti E. 2004. Stathmin-tubulin interaction gradients in motile and mitotic cells. Science 303: 1862–1866.

Ortiz J, Funk C, Schafer A, Lechner J. 2009. Stu1 inversely regulates kinetochore capture and spindle stability. Genes Dev 23: 2778–2791.

Palazzo AF, Eng CH, Schlaepfer DD, Marcantonio EE, Gundersen GG. 2004. Localized stabilization of microtubules by integrin- and FAK-facilitated Rho signaling. Science 303:836–839.

Pizon V, Gerbal F, Diaz CC, Karsenti E. 2005. Microtubule-dependent transport and organization of sarcomeric myosin during skeletal muscle differentiation. Embo J 24:3781–3792.

Radulescu AE, Cleveland DW. 2010. NuMA after 30 years: the matrix revisited. Trends Cell Biol 20:214–222.

Reilein A, Nelson WJ. 2005. APC is a component of an organizing template for cortical microtubule networks. Nat Cell Biol 7: 463–473.

Rivero S, Cardenas J, Bornens M, Rios RM. 2009. Microtubule nucleation at the cis-side of the Golgi apparatus requires AKAP450 and GM130. Embo J 28:1016–1028.

Rodionov VI, Borisy GG. 1997. Self-centring activity of cytoplasm. Nature 386:170–173.

Rodriguez OC, Schaefer AW, Mandato CA, Forscher P, Bement WM, Waterman-Storer CM. 2003. Conserved microtubule-actin interactions in cell movement and morphogenesis. Nat Cell Biol 5: 599–609.

Rogers GC, Rogers SL, Schwimmer TA, Ems-McClung SC, Walczak CE, Vale RD, Scholey JM, Sharp DJ. 2004. Two mitotic kinesins cooperate to drive sister chromatid separation during anaphase. Nature 427:364–370.

Roll-Mecak A, McNally FJ. 2010. Microtubule-severing enzymes. Curr Opin Cell Biol 22:96–103.

Saito TT, Okuzaki D, Nojima H. 2006. Mcp5, a meiotic cell cortex protein, is required for nuclear movement mediated by dynein and microtubules in fission yeast. J Cell Biol 173:27–33.

Salaycik KJ, Fagerstrom CJ, Murthy K, Tulu US, Wadsworth P. 2005. Quantification of microtubule nucleation, growth and dynamics in wound-edge cells. J Cell Sci 118(Pt 18):4113–4122.

Samejima I, Miller VJ, Groocock LM, Sawin KE. 2008. Two distinct regions of Mto1 are required for normal microtubule nucleation and efficient association with the gamma-tubulin complex in vivo. J Cell Sci 121(Pt 23):3971–3980.

Sanchez-Perez I, Renwick SJ, Crawley K, Karig I, Buck V, Meadows JC, Franco-Sanchez A, Fleig U, Toda T, Millar JB. 2005. The DASH complex and Klp5/Klp6 kinesin coordinate bipolar chromosome attachment in fission yeast. Embo J 24:2931–2943.

Sardar HS, Luczak VG, Lopez MM, Lister BC, Gilbert SP. 2010. Mitotic kinesin CENP-E promotes microtubule plus-end elongation. Curr Biol 20:1648–1653.

Sato M, Vardy L, Angel Garcia M, Koonrugsa N, Toda T. 2004. Interdependency of fission yeast Alp14/TOG and coiled coil protein Alp7 in microtubule localization and bipolar spindle formation. Mol Biol Cell 15:1609–1622.

Schmoranzer J, Fawcett JP, Segura M, Tan S, Vallee RB, Pawson T, Gundersen GG. 2009. Par3 and dynein associate to regulate local microtubule dynamics and centrosome orientation during migration. Curr Biol 19:1065–1074.

Schuyler SC, Pellman D. 2001. Microtubule "plus-end-tracking proteins": The end is just the beginning. Cell 105:421–424.

Shimada Y, Yonemura S, Ohkura H, Strutt D, Uemura T. 2006. Polarized transport of Frizzled along the planar microtubule arrays in Drosophila wing epithelium. Dev Cell 10:209–2022.

Siller KH, Doe CQ. 2009. Spindle orientation during asymmetric cell division. Nat Cell Biol 11:365–374.

Small JV, Kaverina I. 2003. Microtubules meet substrate adhesions to arrange cell polarity. Curr Opin Cell Biol 15:40–47.

Spiliotis ET. 2010. Regulation of microtubule organization and functions by septin GTPases. Cytoskeleton (Hoboken) 67:339–345.

Spiliotis ET, Hunt SJ, Hu Q, Kinoshita M, Nelson WJ. 2008. Epithelial polarity requires septin coupling of vesicle transport to polyglutamylated microtubules. J Cell Biol 180:295–303.

Splinter D, Tanenbaum ME, Lindqvist A, Jaarsma D, Flotho A, Yu KL, Grigoriev I, Engelsma D, Haasdijk ED, Keijzer N, et al. 2010. Bicaudal D2, dynein, and kinesin-1 associate with nuclear pore complexes and regulate centrosome and nuclear positioning during mitotic entry. PLoS Biol 8:e1000350.

Sproul LR, Anderson DJ, Mackey AT, Saunders WS, Gilbert SP. 2005. Cik1 targets the minus-end kinesin depolymerase kar3 to microtubule plus ends. Curr Biol 15:1420–1427.

Straube A, Brill M, Oakley BR, Horio T, Steinberg G. 2003. Microtubule organization requires cell cycle-dependent nucleation at dispersed cytoplasmic sites: polar and perinuclear microtubule organizing centers in the plant pathogen Ustilago maydis. Mol Biol Cell 14:642–657.

Stumpff J, von Dassow G, Wagenbach M, Asbury C, Wordeman L. 2008. The kinesin-8 motor Kif18A suppresses kinetochore movements to control mitotic chromosome alignment. Dev Cell 14:252–262.

Subramanian A, Prokop A, Yamamoto M, Sugimura K, Uemura T, Betschinger J, Knoblich JA, Volk T. 2003. Shortstop recruits EB1/APC1 and promotes microtubule assembly at the muscle-tendon junction. Curr Biol 13:1086–1095.

Sumigray KD, Chen H, Lechler T. 2011. Lis1 is essential for cortical microtubule organization and desmosome stability in the epidermis. J Cell Biol 194:631–642.

Toya M, Sato M, Haselmann U, Asakawa K, Brunner D, Antony C, Toda T. 2007. Gamma-tubulin complex-mediated anchoring of spindle microtubules to spindle-pole bodies requires Msd1 in fission yeast. Nat Cell Biol 9:646–653.

Tsai JW, Lian WN, Kemal S, Kriegstein AR, Vallee RB. 2010. Kinesin 3 and cytoplasmic dynein mediate interkinetic nuclear migration in neural stem cells. Nature Neurosci 13:1463–1471.

Urrutia R, McNiven MA, Albanesi JP, Murphy DB, Kachar B. 1991. Purified kinesin promotes vesicle motility and induces active sliding between microtubules in vitro. Proc Natl Acad Sci U S A 88:6701–6705.

Usui T, Maekawa H, Pereira G, Schiebel E. 2003. The XMAP215 homologue Stu2 at yeast spindle pole bodies regulates microtubule dynamics and anchorage. Embo J 22:4779–4793.

Vallee RB, Sheetz MP. 1996. Targeting of motor proteins. Science 271:1539–1544.

van der Vaart B, Manatschal C, Grigoriev I, Olieric V, Gouveia SM, Bjelic S, Demmers J, Vorobjev I, Hoogenraad CC, Steinmetz MO and others. 2011. SLAIN2 links microtubule plus end-tracking proteins and controls microtubule growth in interphase. J Cell Biol 193:1083–1099.

Varga V, Helenius J, Tanaka K, Hyman AA, Tanaka TU, Howard J. 2006. Yeast kinesin-8 depolymerizes microtubules in a length-dependent manner. Nat Cell Biol 8:957–962.

Wallingford JB. 2010. Planar cell polarity signaling, cilia and polarized ciliary beating. Curr Opin Cell Biol 22:597–604.

Watanabe T, Noritake J, Kakeno M, Matsui T, Harada T, Wang S, Itoh N, Sato K, Matsuzawa K, Iwamatsu A and others. 2009. Phosphorylation of CLASP2 by GSK-3beta regulates its interaction with IQGAP1, EB1 and microtubules. J Cell Sci 122(Pt 16):2969–2979.

Watanabe T, Wang S, Noritake J, Sato K, Fukata M, Takefuji M, Nakagawa M, Izumi N, Akiyama T, Kaibuchi K. 2004. Interaction with IQGAP1 links APC to Rac1, Cdc42, and actin filaments during cell polarization and migration. Dev Cell 7:871–883.

Waterman-Storer CM, Salmon ED. 1997. Actomyosin-based retrograde flow of microtubules in the lamella of migrating epithelial cells influences microtubule dynamic instability and turnover and is associated with microtubule breakage and treadmilling. J Cell Biol 139:417–434.

Watson P, Stephens DJ. 2006. Microtubule plus-end loading of p150(Glued) is mediated by EB1 and CLIP-170 but is not required for intracellular membrane traffic in mammalian cells. J Cell Sci 119:2758–2767.

Weirich CS, Erzberger JP, Barral Y. 2008. The septin family of GTPases: architecture and dynamics. Nat Rev Mol Cell Biol 9:478–489.

Weisenberg RC, Borisy GG, Taylor EW. 1968. The colchicine-binding protein of mammalian brain and its relation to microtubules. Biochemistry 7:4466–4479.

Weisenberg RC, Deery W. 1976. Tubulin-Nucleotide Reactions during Polymerization and Depolymerization. Journal of Cell Biology 70:A225–A225.

Wen Y, Eng CH, Schmoranzer J, Cabrera-Poch N, Morris EJ, Chen M, Wallar BJ, Alberts AS, Gundersen GG. 2004. EB1 and APC bind to mDia to stabilize microtubules downstream of Rho and promote cell migration. Nat Cell Biol 6:820–830.

Wilkie TM, Kinch L. 2005. New roles for Galpha and RGS proteins: communication continues despite pulling sisters apart. Curr Biol 15:R843–R854.

Wittmann T, Waterman-Storer CM. 2001. Cell motility: can Rho GTPases and microtubules point the way? J Cell Sci 114(Pt 21): 3795–3803.

Wittmann T, Waterman-Storer CM. 2005. Spatial regulation of CLASP affinity for microtubules by Rac1 and GSK3beta in migrating epithelial cells. J Cell Biol 169:929–939.

Wloga D, Gaertig J. 2010. Post-translational modifications of microtubules. J Cell Sci 123:3447–3455.

Wolyniak MJ, Blake-Hodek K, Kosco K, Hwang E, You L, Huffaker TC. 2006. The regulation of microtubule dynamics in Saccharomyces cerevisiae by three interacting plus-end tracking proteins. Mol Biol Cell 17:2789–2798.

Wordeman L. 2005. Microtubule-depolymerizing kinesins. Curr Opin Cell Biol 17:82–88.

Yamamoto A, Hiraoka Y. 2003. Cytoplasmic dynein in fungi: insights from nuclear migration. J Cell Sci 116(Pt 22):4501–4512.

Yamashita A, Yamamoto M. 2006. Fission yeast Num1p is a cortical factor anchoring dynein and is essential for the horse-tail nuclear movement during meiotic prophase. Genetics 173:1187–1196.

Yamashita YM. 2009. Regulation of asymmetric stem cell division: spindle orientation and the centrosome. Front Biosci 14:3003–3011.

Yamashita YM, Jones DL, Fuller MT. 2003. Orientation of asymmetric stem cell division by the APC tumor suppressor and centrosome. Science 301:1547–1550.

Yan X, Habedanck R, Nigg EA. 2006. A complex of two centrosomal proteins, CAP350 and FOP, cooperates with EB1 in microtubule anchoring. Mol Biol Cell 17:634–644.

Zaichick SV, Metodiev MV, Nelson SA, Durbrovskyi O, Draper E, Cooper JA, Stone DE. 2009. The mating-specific Galpha interacts with a kinesin-14 and regulates pheromone-induced nuclear migration in budding yeast. Mol Biol Cell 20:2820–2830.

Zanic M, Stear JH, Hyman AA, Howard J. 2009. EB1 recognizes the nucleotide state of tubulin in the microtubule lattice. PLoS One 4:e7585.

Zhou FQ, Zhou J, Dedhar S, Wu YH, Snider WD. 2004. NGF-induced axon growth is mediated by localized inactivation of GSK-30 and functions of the microtubule plus end binding protein APC. Neuron 42:897–912.