The search and prime hypothesis for growth cone turning

Søren S.L. Andersen

Summary
In the fields of axonal and dendritic guidance, there is now a significant accumulation of knowledge of how extracellular signaling molecules activate their cognate growth cone receptors. Relatively little is known about the subsequent activation of intracellular signaling pathways and actin reorganization, and very little is known about how microtubules (MTs) reorganize during growth cone turning. I hypothesize that dynamic MTs are required in order to catalyze the polarized actin assembly necessary for growth cone turning, that MTs and actin filaments promote each other's assembly through positive feedback, that MT stability is enhanced further through the formation of membrane-associated MT attachment sites, and that these MT stabilization events subsequently accelerate axonal/dendritic shaft formation. ***BioEssays*** **27:86–90, 2005.**

Introduction

In the developing brain, a myriad of neurons send out processes that eventually find their target with which they make synaptic connections, and which ultimately lead to a functional brain.[1] At the molecular level, in the last decade much has been discovered about how axons and dendrites find their targets. Those studies have focussed on extracellular signaling molecules and their cognate membrane receptors. There is a gap currently in our understanding of how extracellular signals translate into intracellular reorganization of the actin and the microtubule (MT) cytoskeleton, with most of the work focussed on actin.[2–6]

This review concentrates on MTs which are traditionally portrayed as passive followers of the growth cone. However, direct real-time observations of MTs in growing neurons showed that, when a growth cone receives a signal to turn, within a few minutes the dynamic growth cone MTs orient in the direction to which the growth cone ultimately turns.[7,8] In order to explain these observations, I here propose the "search and prime" working hypothesis (Fig. 1). The hypothesis has three premises which in temporal order are: (1) when the growth cone receives a signal to turn, the actin assembly machinery is 'primed' for turning but *requires* MTs to deliver (by motors and/or MT dynamics) components required for proper polar actin assembly, (2) the area of primed actin positively promotes MT stability, and (3) primed actin and MTs positively promote each other's assembly leading to turning. Central to the hypothesis is my proposal that, without dynamic MTs, a growth cone is incapable of properly sensing a guidance signal, and hence explicitly stipulating that dynamic MTs are active principal players in regulating axon guidance, and not just passive followers. There is direct evidence for such an active role for dynamic MTs, as addition of low concentrations of Vinblastine,[9] which destabilizes MTs, or low concentrations of taxol,[10] which stabilizes MTs, to neuronal cultures leads to randomly walking growth cones.

E-mail: soren1@sorenandersen1.org
DOI 10.1002/bies.20154
Published online in Wiley InterScience (www.interscience.wiley.com).

How is MT assembly locally regulated during turning?

When an axon/dendrite extends, it follows the lead of its growth cone. The growth cone is extremely sensitive in detecting externally applied signals.[11] The integrated sum of spatially asymmetric turning signals that a growth cone receives from the outside, ultimately determines the direction to which a growth cone turns. When not receiving any external spatially asymmetric signals, the path taken by the growth cone is that of a random zig-zag walk with a small amplitude.

At the intracellular molecular level, I suggest that, in a growth cone receiving a turning signal, an early event is a local change in the global growth cone "MT polymerization potential" (P_{MT}) toward a more positive value (Fig. 1 (blue circle)). The P_{MT} is defined as the tendency of the MT-building block tubulin to polymerize into dynamic MTs; a positive value indicates that more MT polymer mass will form, whereas a negative value indicates that MTs will depolymerize.[12] A locally more positive P_{MT} will result in the polymerization, and increased stability, of dynamic MTs. Consequently, the local positive increase in the growth cone's global P_{MT} leads to local stabilization of dynamic pioneer MTs, which are constantly exploring the edges of the entire growth cone periphery.[13,14]

To generate the positive P_{MT}, phosphorylation-dependent changes occur in the activities of molecules that interact with and regulate the pool of polymerizable tubulin dimers, as well as in the activities of molecules that interact directly with the MTs.[12] Candidates for such molecules are the proteins

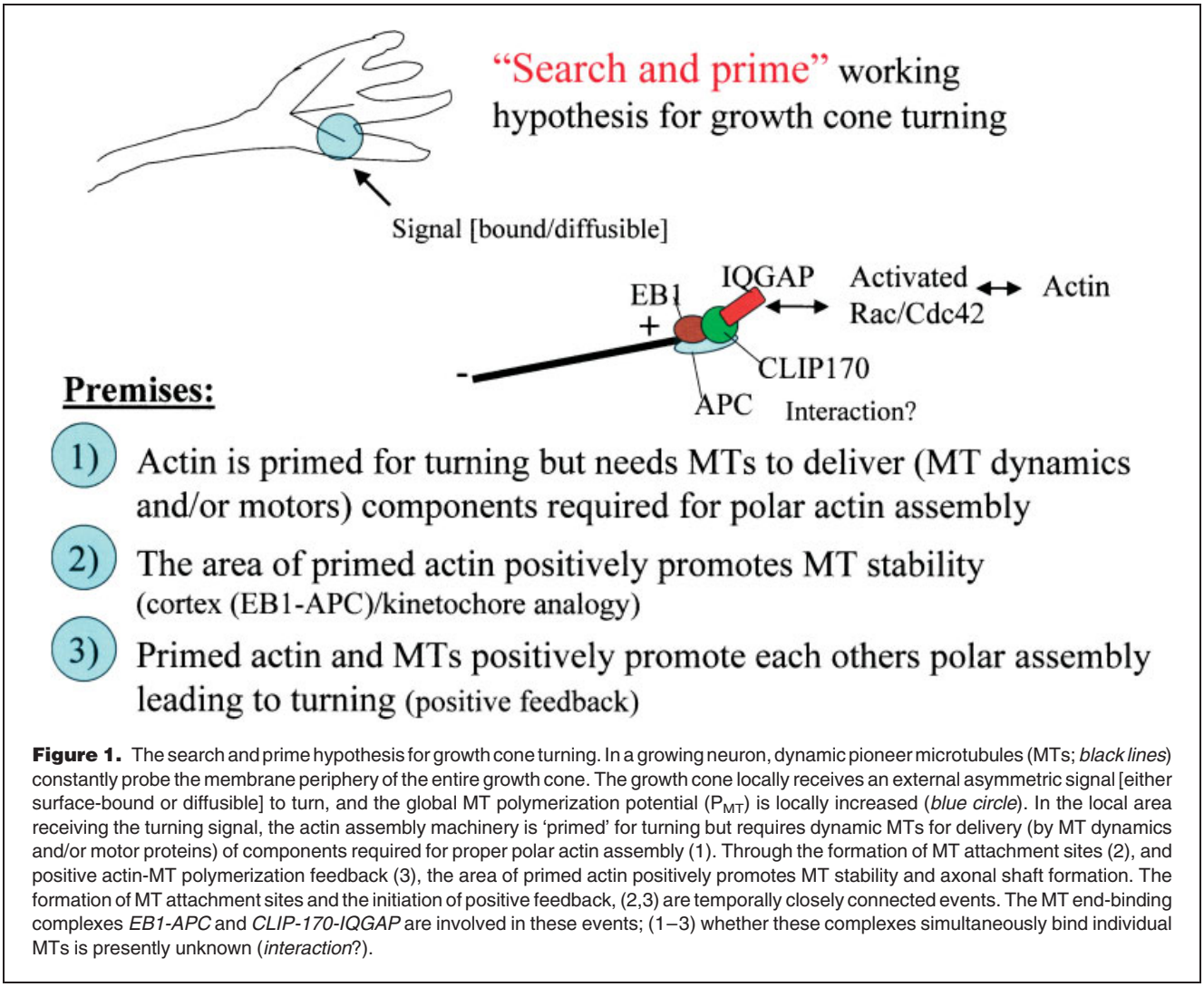

Figure 1. The search and prime hypothesis for growth cone turning. In a growing neuron, dynamic pioneer microtubules (MTs; *black lines*) constantly probe the membrane periphery of the entire growth cone. The growth cone locally receives an external asymmetric signal [either surface-bound or diffusible] to turn, and the global MT polymerization potential (P_{MT}) is locally increased (*blue circle*). In the local area receiving the turning signal, the actin assembly machinery is 'primed' for turning but requires dynamic MTs for delivery (by MT dynamics and/or motor proteins) of components required for proper polar actin assembly (1). Through the formation of MT attachment sites (2), and positive actin-MT polymerization feedback (3), the area of primed actin positively promotes MT stability and axonal shaft formation. The formation of MT attachment sites and the initiation of positive feedback, (2,3) are temporally closely connected events. The MT end-binding complexes *EB1-APC* and *CLIP-170-IQGAP* are involved in these events; (1–3) whether these complexes simultaneously bind individual MTs is presently unknown (*interaction*?).

Stathmin/Op18, SCG10, CRMP2 and MAP1B. Stathmin/Op18 and its neuronal homolog SCG10 are both present in neurons, interact with tubulin dimers and negatively regulate MT assembly; upon phosphorylation, these molecules' inhibitory effect on MT assembly is turned off.[12,15] CRMP2 (for Collapsin Response Mediator Protein-2) was recently discovered to bind tubulin dimers, like Stathmin/Op18 and SCG10. Unlike the latter, CRMP2 promotes MT assembly,[16] and local recruitment and regulation of CRMP2 is probably a key event in locally increasing the P_{MT}. MAP1B is present in axons and stabilizes MTs. Interestingly, a MAP1B knockout mouse has more stable MTs than a wild-type mouse.[17,18] Phosphorylation-dependent regulation of MAP1B's activity appears to be required to sustain dynamic MTs in the growth cone. Hence, a certain level of MAP1B phosphorylation appears to permit dynamic MTs, whereas too much or too little phosphorylation either abolishes or enhances its MT-stabilizing activity. In addition to these proteins, other tubulin and MT-interacting proteins (i.e. motors) are involved in locally regulating the P_{MT}. However, rather than compiling an exhaustive list of potential candidates, the goal here is to outline the principles at work during growth cone turning.

Why are dynamic MTs required for turning?

The external asymmetric turning signals are decoded by receptors in the growth cone membrane and conveyed to the growth cone's intracellular milieu and cytoskeleton.[2,3,11] I suggest the reason that MTs are so important for guidance, is that growing dynamic MTs actively deliver effector molecules that are required for polarized actin assembly, so that directional growth cone turning can ensue (Fig. 1 (1)). One can imagine that such actin-effector molecules, which I suggest use the MTs as transport vehicle to reach their target destination, are attached to MTs through adaptor proteins and/or

motor proteins. A candidate(s) for such an adaptor is the MT end-binding protein CLIP-170[19,20] that has been shown to interact with IQGAP.[21] IQGAP in turn interacts with activated Rac and Cdc42, which belong to the Rho family of small GTPases and are involved in the regulation of the formation of lammellipodia and filopodia, respectively.[2,3] IQGAP is an effector of Rac and Cdc42[22] and, through binding to the MT-associated CLIP-170, I posit that a mechanism is secured whereby a growing dynamic (pioneer) MT can deliver key components (e.g. activated Rac, Cdc42) for proper actin assembly to the focalized site of the growth cone receiving the turning signal (Fig. 1). Thus, I suggest that, in the area of the growth cone receiving a turning signal, growing MTs are essential for turning because they mediate the co-localization of key regulatory actin assembly components in a focal spot that are required for actin reorganization, filopodia formation and growth cone turning.

Axonal shaft formation: further stabilization of MTs during turning

When the first pioneer MTs have started to 'accumulate' at the site of turning, additional mechanisms stabilize MTs and further promote polarized actin assembly in the direction of the growth cone turn. In a way, growth cone turning can be viewed as a regulated change in tissue morphology, and hence as a morphogenetic process. From the morphogenesis of organs, the polarization of cells and the generation of transient cellular apparatuses, one has learned that morphological changes involve stabilizing anchor points, like the kinetochores in the mitotic spindle. Hence, in a ''Kar9ochore'' yeast polarization analogy,[23] I suggest that, in later-early stages of growth cone turning, MTs become physically stabilized through binding to membrane-associated MT attachment sites. In a Kar9ochore analogy, I propose that two key molecules in this process are the MT end-binding proteins EB1 and APC.[24,25] Hence, following nuclear division in budding yeast, transport of the daughter nucleus into the nascent budding daughter cell occurs on MT tracks anchored with their minus ends at the spindle pole body, and with their plus ends attached/anchored at a cortical site in the membrane of the budding daughter cell.[26] The cortical MT attachment site in yeast has been shown to contain Kar9p (APC homologue) and the MT-associated protein Bim1p (EB1 homologue).[27] I suggest that, when a growth cone receives a signal to turn, the actin network and/or the plasma membrane locally assembles a molecular complex equivalent to the yeast cortical MT attachment site and, consisting of at least the MT end-binding proteins EB1 and APC (Fig. 1(2)). Such a focal site for MT attachment and stabilization will promote more MTs to grow and persist, in that area of the growth cone (cortex/kinetochore analogy), and also accelerate the process of laying down the MT bundles,[7,9] which is one of the directly visible early events of axonal shaft formation.

Do individual MTs have multiple end-binding complexes associated?

An intriguing question, linked to but separate from the growth-cone-turning question itself, is whether MTs with multiple end-binding complexes exist, or whether several different populations of MTs with different end-binding complexes are prevalent. Thus, one can imagine one population of MTs with CLIP-170 associated and which recruits IQGAP and Rac/Cdc42, and yet another population of MTs with the EB1-APC complex associated. As proposed in Fig. 1, it is possible that MTs exist with both the CLIP-170 and EB1 complexes simultaneously associated. Indeed, association of multiple end-binding complexes to individual MTs would ensure that key components for actin assembly and MT stability were simultaneously conveyed, spatially and temporally, to the site of the growth cone receiving the turning signal.

Positive feedback

Once the first pioneer MTs have become stabilized in the area of the growth cone receiving a signal to turn, the actin-MT network is locally set up for autocatalytic positive feedback,[28] which further promotes MT stabilization and assembly as well as more polarized actin assembly (Fig. 1(3)). Positive feedback between MT and actin assembly has, for example, been demonstrated in the context of the leading edge of migrating tissue-culture cells and involves (at least) the molecules Rac, the kinase PAK, and Stathmin/Op18.[14,29]

Repulsive growth cone turning

The model presented here addresses growth cone attraction, but how is growth cone repulsion mediated? The answer to this question very likely should be found in the observation that a growth cone not receiving an asymmetric external turning signal continuously is doing zig-zag miniturns. This is because the random attempts to turn cancel each other out over time, and because there is constant symmetric force equilibrium across the growth cone.[30–35] Hence, I suggest an attractive turning response is caused when 'the set point' for actin and MT polymer polymerization is increased more on the side receiving the asymmetric turning signal than on the opposite side. By inference, a repulsive signal starts with inactivation/inhibition/collapse of the actin assembly apparatus on the side of the growth cone receiving the repulsive turning signal. Recent research has demonstrated that this collapse in particular invokes the activation the Rho GTPase and, depending on the context, also inactivation of other members of the Rho family of small GTPases.[2,3] As a result of the actin collapse, the searching pioneer MTs in that area of the growth cone no longer receive stimulating/stabilizing positive feedback signals, whereas the pioneer MTs on the side of the growth cone not receiving the repulsive signal still have intact the ''baseline'' activity of actin assembly. Hence, I suggest inhibition of cytoskeletal assembly on one side of the growth cone will

cause outgrowth on and turning to the other side, because of the latter's intact baseline cytoskeletal assembly activity, and because the symmetry of the growth cone[28] is locally broken by the repulsive turning signal's negative effect on actin assembly. Thus, as a result of the intrinsic baseline activity, the side not receiving the repulsive signal will quickly enter into a positive feedback state because it no longer is in competition with the opposite (repulsed) side. Thus, I suggest that turning will subsequently ensue as for an attractive turning cue.

Coincidentally, while this article was in review, a genetic study[36] appeared suggesting that a Slit[2]-mediated repulsive turning response operates through "activation"[36] of the MT end-binding protein CLASP (CLIP-ASsociated Protein).[37,38] "Activation" of CLASP, presumably through phosphorylation by the Abl kinase,[39] is suggested to result in inhibition of MT polymerization on the side of the growth cone receiving the repulsive signal and, consequently, growth cone turning to the opposite side.[36] However, Abl kinase has been demonstrated to regulate many actin assembly effector molecules,[36] and has a long history of involvement in axonal guidance.[39] A direct (e.g. biochemical) link between Abl and CLASP, notably the mechanism of CLASP "activation", has not been demonstrated.[36] It follows from the hypothesis presented here, that attraction could be mediated by "inactivation" of CLASP which, however, already is thought "inactive"[36] in the resting growth cone not receiving a turning signal.[36] Hence, the Abl-CLASP pathway and, in particular, the extent to which Slit repulsion[2] is mediated by the Abl kinase's[39] "activation" of CLASP remain unclear.

In a larger picture, the recent neuronal MT-CLASP study[36] renders support to the hypothesis presented here. Directly, by acknowledging and providing evidence for an active role of MT polymerization in axonal guidance. Indirectly, I suggest, as the above discussed positive feedback mechanism is providing the actual driving force for the repulsive turning response. However, the study[36] diverges from the hypothesis in this paper in that it invokes a specialized, or even guidance-cue-specific, intracellular pathway for growth cone repulsion, and neither explicitly nor implicitly mechanistically ties together attractive and repulsive growth cone responses. In contrast, I am proposing a unified hypothesis for attraction and repulsion and, in essence, suggest that the growth cone will turn to the side of the growth cone where the actin-MT interactions/cross-talks are the strongest, or still intact, and that this process involves an actin-MT assembly core machinery (Fig. 1).

Testing the hypothesis

There is already strong pharmacological evidence that dynamic MTs are required for growth cone turning.[9,10] Moreover, recent pharmacological experiments have shown that *local* regulation of MT assembly can directly regulate growth cone turning. Hence, caged u.v.-activatable taxol was cleverly used to show that, once taxol was locally uncaged on one side of the growth cone, it turned to that side, and without the growth cone otherwise receiving any external cues. In contrast, local application of the MT-destabilizing drug nocodazole caused a repulsive response.[40] Hence, these pharmacological experiments suggest that the growth cone turns to the side of the growth cone having the more stable MTs. Under physiological conditions, growth cone MTs are dynamic[7–9,13] and, as formulated in this exposé, I suggest that actin and MTs obligatorily and mutually regulate each others assembly during growth cone turning (Fig. 1).

The pharmacological experiments[9,10,40] now need be investigated at the molecular protein level. Based on the hypothesis proposed in this paper, I suggest this issue should be addressed by abolishing the function of members of the EB1,[24,41] CLIP-170[19–21] and/or CLASP[37,38] related proteins, and subsequently observing whether growth cones can turn or not. Unfortunately, systemic disruption of such proteins in an entire organism may cause pleiotropic effects, embryonic lethality, abnormal growth or other defects. Thus, as with any perturbation experiment involving cellular players, one will have to experiment to find the best way to disrupt the function of the EB1 and CLIP-170 family member proteins in neurons. Fortunately, many tools are available to interfere with specific gene products and, in our so-called "post-genomic era", the toolbox is expanding at a steady pace.[42] Amongst the new tools available, and continuously under development, to interfere with gene products, are inducible RNAi (RNA interference) vectors for mammalian systems,[42] combinatorial chemistry-derived small-molecule-protein-specific inhibitors, and micro-scale Chromophore-Assisted Laser Inactivation (micro-CALI), of which the latter can be applied to inactivate a specific protein within a 10 μm region in the growth cone.[35] Hence, the experimentalist can feel confident that, by picking the right tools, one can interfere specifically, both temporally and spatially, with any gene product. As a beginning, it appears likely that partial or complete abolishment of EB1,[41] or its neuronal homolog EB3,[43,44] should be possible, at least in neuronal cell cultures, for example by the usage of antisense techniques. Knockdown, or knockout, in an entire organism of EB3 and/or EB1 should be attempted in order to obtain in vivo data. Similar approaches can be applied to the CLIP-170 and CLASP-type proteins. Encouragingly, a CLIP-115[45] knockout mouse is viable, and without gross morphological defects.[46]

It would be of interest to monitor carefully the kinetics of attractive and repulsive turning responses. Hence, grounded in the mechanism proposed here, one could expect a repulsive turning response to take slightly longer than an attractive response. Pending the results of such kinetic analysis, one will be able to gain further insights into the mechanisms of attraction and repulsion, and to what extent they are mechanistically identical events revolving around a local change of the set-point for MT and actin assembly.

Acknowledgments

The paper was first presented as a special seminar in January 2004 at the MRC Centre for Developmental Neurobiology, King's College in London, and subsequently as a talk in August 2004 at the Gordon Research Conference on Macromolecular Organization and Cell Function, Queen's College Oxford. Both audiences are gratefully acknowledged for their interest in this subject, and the latter for stimulating the potential foundation of the guidosomics field.

References

1. Swanson LW. 2003. Brain architecture: understanding the basic plan. Oxford University Press, Oxford. 263pp.
2. Guan KL, Rao Y. 2003. Signalling mechanisms mediating neuronal responses to guidance cues. Nat Rev Neurosci 4:941–956.
3. Dickson BJ. 2002. Molecular mechanisms of axon guidance. Science 298:1959–1964.
4. Kim S, Chiba A. 2004. Dendritic guidance. Trends Neurosci 27:194–202.
5. Horck FPG, Weinl C, Holt CE. 2004. Retinal axon guidance: novel mechanisms for steering. Curr Opin Neurobiol 14:61–66.
6. Strasser GA, Rahim NA, VanderWaal KE, Gertler FB, Lanier LM. 2004. Arp2/3 is a negative regulator of growth cone translocation. Neuron 43:81–94.
7. Tanaka EM, Kirschner MW. 1991. Microtubule behavior in the growth cones of living neurons during axon elongation. J Cell Biol 115:345–363.
8. Tanaka E, Kirschner MW. 1995. The role of microtubules in growth cone turning at substrate boundaries. J Cell Biol 128:127–137.
9. Tanaka E, Ho T, Kirschner MW. 1995. The role of microtubule dynamics in growth cone motility and axonal growth. J Cell Biol 128:139–155.
10. Williamson T, Gordon-Weeks PR, Schachner M, Taylor J. 1996. Microtubule reorganization is obligatory for growth cone turning. Proc Natl Acad Sci USA 93:15221–15226.
11. Rosoff WJ, Urbach JS, Esrick MA, McAllister RG, Richards LJ, et al. 2004. A new chemotaxis assay shows the extreme sensitivity of axons to molecular gradients. Nat Neurosci 7:678–682. [Erratum: Nat Neurosci, 2004;7:785].
12. Andersen SSL. 2000. Spindle assembly and the art of regulating microtubule dynamics by MAPs and Stathmin/Op18. Trends Cell Biol 10:261–267.
13. Schaefer AW, Kabir N, Forscher P. 2002. Filopodia and actin arcs guide the assembly and transport of two populations of microtubules with unique dynamic parameters in neuronal growth cones. J Cell Biol 158: 139–152.
14. Rodriguez OC, Schaefer AW, Mandato CA, Forscher P, Bement WM, et al. 2003. Conserved microtubule-actin interactions in cell movement and morphogenesis. Nat Cell Biol 5:599–609.
15. Grenningloh G, Soehrman S, Bondallaz P, Ruchti E, Cadas H. 2004. Role of the microtubule destabilizing proteins SCG10 and stathmin in neuronal growth. J Neurobiol 58:60–69.
16. Arimura N, Menager C, Fukata Y, Kaibuchi K. 2004. Role of CRMP-2 in neuronal polarity. J Neurobiol 58:34–47.
17. Dehmelt L, Halpain S. 2004. Actin and microtubules in neurite initiation: are MAPs the missing link? J Neurobiol 58:18–33.
18. Gordon-Weeks PR. 2004. Microtubules and growth cone function. J Neurobiol 58:70–83.
19. Rickard JE, Kreis TE. 1990. Identification of a novel nucleotide-sensitive microtubule-binding protein in HeLa cells. J Cell Biol 110:1623–1633.
20. Pierre P, Scheel J, Rickard JE, Kreis TE. 1992. CLIP-170 links endocytic vesicles to microtubules. Cell 70:887–890.
21. Fukata M, Watanabe T, Noritake J, Nakagawa M, Yamaga M, et al. 2002. Rac1 and Cdc42 capture microtubules through IQGAP1 and CLIP-170. Cell 109:873–885.
22. Briggs MW, Sacks DB. 2003. IQGAP proteins are integral components of cytoskeletal regulation. EMBO Rep 4:571–574.
23. Bloom K. 2000. It's a kar9ochore to capture microtubules. Nat Cell Biol 2:E96–98.
24. Gundersen GG, Gomes ER, Wen Y. 2004. Cortical control of microtubule stability and polarization. Curr Opin Cell Biol 16:106–112.
25. Gundersen GG. 2002. Evolutionary conservation of microtubule-capture mechanisms. Nat Rev Mol Cell Biol 3:296–304.
26. Liakopoulos D, Kusch J, Grava S, Vogel J, Barral Y. 2003. Asymmetric loading of Kar9 onto spindle poles and microtubules ensures proper spindle alignment. Cell 112:561–574.
27. Gundersen GG, Bretscher A. 2003. Microtubule asymmetry. Science 300:2040–2041.
28. Andersen SSL, Bi GQ. 2000. Axon formation: a molecular model for the generation of neuronal polarity. Bioessays 22:172–179.
29. Wittmann T, Bokoch GM, Waterman-Storer CM. 2004. Regulation of microtubule destabilizing activity of Op18/stathmin downstream of Rac1. J Biol Chem 279:6196–6203.
30. Lamoureux P, Ruthel G, Buxbaum RE, Heidemann SR. 2002. Mechanical tension can specify axonal fate in hippocampal neurons. J Cell Biol 159: 499–508.
31. Heidemann SR, Lamoureaux P, Buxbaum RE. 2000. Opposing views on tensegrity as a structural framework for understanding cell mechanics. J Appl Physiol 89:1670–1678.
32. Lamoureux P, Buxbaum RE, Heidemann SR. 1998. Axonal outgrowth of cultured neurons is not limited by growth cone competition. J Cell Sci 111:3245–3252.
33. Heidemann SR. 1996. Cytoplasmic mechanisms of axonal and dendritic growth in neurons. Int Rev Cytol 165:235–296.
34. Lamoureux P, Zheng J, Buxbaum RE, Heidemann SR. 1992. A cytomechanical investigation of neurite growth on different culture surfaces. J Cell Biol 118:655–661.
35. Wang F-S, Liu C-W, Diefenbach TJ, Jay DG. 2003. Modeling the role of myosin 1c in neuronal growth cone turning. Biophys J 85:3319–3328.
36. Lee H, Engel U, Rusch J, Scherrer S, Sheard K, et al. 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.
37. Akhmanova A, Hoogenraad CC, Drabek K, Stepanova T, Dortland B, et al. 2001. CLASPs are CLIP-115 and -170 associating proteins involved in the regional regulation of microtubule dynamics in motile fibroblasts. Cell 104:923–935.
38. Maiato H, Fairley EAL, Rieder CL, Swedlow JR, Sunkel CE, et al. 2003. Human CLASP1 is an outer kinetochore component that regulates spindle microtubule dynamics. Cell 113:891–904.
39. Hu S, Reichardt LF. 1999. From membrane to cytoskeleton: enabling a connection. Neuron 22:419–422.
40. Buck KB, Zheng JQ. 2002. Growth cone turning induced by direct local modification of microtubule dynamics. J Neurosci 22:9358–9367.
41. Rogers SL, Rogers GC, Sharp DJ, Vale RD. 2002. Drosophila EB1 is important for proper assembly, dynamics and positioning of the mitotic spindle. J Cell Biol 158:873–884.
42. Prawitt D, Brixel L, Spangenberg C, Eshkind L, Heck R, et al. 2004. RNAi knock-down mice: an emerging technology for post-genomic functional genetics. Cytogenet Genome Res 105:412–421.
43. Nakagawa H, Koyama K, Murata Y, Morito M, Akiyama T, et al. 2000. EB3, a novel member of the EB1 family preferentially expressed in the central nervous system, binds to a CNS-specific APC homologue. Oncogene 19:210–216.
44. Stepanova T, Slemmer J, Hoogenraad CC, Lansbergen G, Dortland B, et al. 2003. Visualization of microtubule growth in cultured neurons via the use of EB3-GFP (end-binding protein 3-green fluorescent protein). J Neurosci 23:2655–2664.
45. De Zeeuw CI, Hoogenraad CC, Goedknegt E, Hertzberg E, Neubauer A, et al. 1997. CLIP-115, a novel brain-specific cytoplasmic linker protein, mediates the localization of dendritic lamellar bodies. Neuron 19:1187–1199.
46. Hoogenraad CC, Akhmanova A, Galjart N, De Zeeuw CI. 2004. LIMK1 and CLIP-115: linking cytoskeletal defects to Williams syndrome. BioEssays 26:141–150.