MINI-REVIEW

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Regulation of EB1/3 proteins by classical MAPs in neurons

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Abbreviations: MTs, microtubules; +TIPs, microtubule plus-end tracking proteins; MAPs, microtubule-associated proteins; EBs, end binding proteins; MAP1B, microtubule associated protein 1B; MAP2, microtubule-associated protein 2; AIS, axon initial segment

Microtubules (MTs) are key cytoskeletal elements in developing and mature neurons. MT reorganization underlies the morphological changes that occur during neuronal development. Furthermore, MTs contribute to the maintenance of neuronal architecture, enable intracellular transport and act as scaffolds for signaling molecules. Thus, a fine-tuned regulation of MT dynamics and stability is crucial for the correct differentiation and functioning of neurons. Different types of proteins contribute to the regulation of the MT state, such as plus-end tracking proteins (+TIPs), which interact with the plus-ends of growing microtubules, and classical microtubule-associated proteins (MAPs), which bind along the microtubule lattice. Recent evidence indicates that MAPs interplay with End Binding Proteins (EBs), the core +TIPs, in neuronal cells. This might contribute to the orchestrated regulation of MT dynamics in neurons. In this mini-review article, we address recent research on the neuronal crosstalk between EBs and classical MAPs and speculate on its possible functional relevance.

Introduction

Neurons are highly polarized cells with a long and thin axon and several shorter and thicker dendrites. The achievement of this complex morphology and the correct formation of an intricate network of synaptic contacts are crucial for the proper transmission and reception of signals in the brain. The microtubular cytoskeleton plays fundamental roles in different aspects of neuronal biology both during development and in adult neurons. Thus, MTs are required for the morphological changes that occur in diverse developmental processes, such as: migration, polarization, neurite and axon outgrowth and navigation as well as dendritic spine formation.[1] In mature neurons, MTs are also involved in the maintenance and organization of cell structure and intracellular transport.[2] MTs interact with the actin cytoskeleton and with a plethora of signaling molecules, acting as dynamic and versatile elements that reorganize in response to diverse extracellular stimuli.[2] Thus, MTs should be seen not only as essential architectural elements in neurons but also as highly dynamic structures that change their dynamic or stable state depending on the cellular context.

MTs are polar structures, with a minus and a plus end.[1] MT polarity influences the binding of certain proteins (e.g., dynein or kinesin motor proteins).[2] In neurons, MTs are tightly packed in dense parallel arrays forming bundles that are constrained into the thin cylindrical structures of axons and dendrites.[1] which differ with respect to MT polarity. Thus, while axonal MTs present a uniform orientation, with their plus ends facing the distal tip of the axon, dendrites show a mixed MT orientation, with their plus-ends facing either the dendritic tip or the cell body.[1] Although in most cells MT minus-ends are anchored to the centrosome, a MT-organizing center (MTOC), in neurons MTs are nucleated in the centrosome and then released by the action of the severing protein katanin.[3,4] Short MT polymers are transported into neurites, dendrites and axon shafts by molecular motors.[5] On the other hand, MT plus-ends are unattached and free to undergo the so called "dynamic instability," periods of MT polymerization followed by phases of depolymerization.[6]

Regulation of MT dynamics and stability is performed by diverse types of proteins, such as MT plus-end tracking proteins (+TIPs) and classical MT-associated proteins (MAPs).[7-9] For a long time, classical MAPs have been considered the main regulators of MT stability and dynamics in neurons. However, +TIPs have lately emerged as important players in the regulation of dynamics of neuronal MTs. Recent reports show that classical MAPs modulate the action of EBs, the core +TIPs, in neurons.[10.11] These findings show that a complex set of functional interactions between microtubular proteins exists at multiple layers.

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MAPs vs. EBs: Regulators of MT Dynamics and Stability in Neurons

Classical or structural MAPs, which bind along the MT lattice, are involved in MT bundling and stabilization.[9] Neuronal MAPs, such as Tau, MAP1B, and MAP2, are direct MT regulators that promote MT nucleation, polymerization, and stabilization, in vitro and in vivo.[12-14] However, MAP1B is a weaker MT stabilizer than Tau and MAP2.[12-14] This is in agreement with the localization of these MAPs; while in cells, MAP1B is present both in cytosol and bound to dynamic MTs, Tau and MAP2 mostly localize along MTs, stabilizing them.[12,13,15] Moreover, Tau and MAP2 -but not MAP1B- induce bundle formation.[12] The three MAPs regulate MT dynamics as well.[9,15-18] While MAP1B and Tau mainly localize to axons, MAP2 is present in dendrites.[1] Consistent with their localization, MAP1B and Tau are required for proper axonogenesis whereas MAP2 is essential for dendritogenesis.[1] Furthermore, different phenotypes related to defects in brain development are found in mice deficient in classical MAPs.[19-23] In general, double knockout mice for two of these MAPs present more severe brain developmental phenotypes than single knockout mice.[23,24] MAP1B expression levels decrease during development and are reduced in mature neurons, while Tau and MAP2 levels remain high, contributing to MT stabilization in axons and dendrites in adult neurons.[9]

+TIPs accumulate specifically at the plus-ends of growing MTs and control diverse dynamic instability parameters (e.g., rates of MT growth, catastrophe, rescue, etc).[25] Early studies on neuronal +TIPs showed that MTs undergo dynamic instability in every neuronal compartment and that MT growth is slower in neurons than in non-neuronal cells.[26] +TIPs also mediate the interaction of MTs with actin cytoskeleton, cell cortex and organelles.[25] Many +TIPs interact with each other at MT plus-ends.[7] In fact, every known +TIP binds to End Binding Proteins (EBs), the core +TIPs that mark all growing MTs.[7] EBs also interact with diverse signaling molecules.[27] As a result, +TIPs form huge hubs of proteins at distal MT ends, with EB proteins at their epicenter. These protein platforms allow the transduction of signaling cascades into local MT reorganization that lead to morphological changes subjacent to neuronal differentiation and plasticity. It is thus not surprising that EBs are important players in the regulation of MT dynamics in developing and mature neurons.

The family of EB proteins has three members, EB1–3.[8] While EB1 is ubiquitous, EB3 is predominantly expressed in brain, mainly in neurons.[28] EB1 and EB3 accumulate at distal ends of growing MTs throughout the neuron.[26] Both EB1 and EB3 have been shown to be involved in neurite outgrowth.[29,30] Downregulation of EB1 leads to a reduction in neurite length in differentiating neuroblastoma cells in which EB1 regulates MT growth rate, growth distance and duration.[29] In *Drosophila* neurons, EB1 is required for uniform dendrite MT polarity and MT growth at dendrite branch points.[31] EB1 is enriched in the distal axon, recruiting the dynein activator dynactin in an ordered pathway, thus leading to the initiation of retrograde transport by the motor protein dynein.[32] EB3 interacts with different proteins that regulate the actin cytoskeleton, such as drebrin, in filopodia of advancing growth cones,[30] and p140Cap in dendritic spines.[33] EB3 interacts also with the postsynaptic density protein 95 (PSD-95), contributing to the modulation of MT dynamics during dendrite formation.[34] Thus, EB3 might act as a linker between MTs and the actin cytoskeleton during neurite extension, regulation of morphology of dendrites and dendritic spines, and synaptic plasticity. In addition, the three members of the EB family, EB1, EB2 and EB3, have been shown to interact with the N-terminal segment of the intracellular domain of Plexin-B3, a transmembrane receptor for Semaphorin 5 involved in neurite outgrowth.[35]

In mature neurons, EB1 and EB3 are concentrated and stabilized at the Axon Initial Segment (AIS), through their interaction with the scaffold protein ankyrin G.[36] Notably, EB1 and EB3 do not accumulate at MT plus-ends but bind along the MT lattice of the AIS, contributing to MT stabilization at this neuronal compartment[36] EB1 also interacts with the potassium channel Kv1, enriched at the AIS, and leads to its targeting to axons.[37] This interaction is negatively regulated by phosphorylation of the auxiliary Kvβ2 subunit of Kv1 channels, mediated by cyclin-dependent kinase (Cdk).[38] Thus, EB proteins play important roles in the maintenance of neuronal architecture and the correct localization and function of potassium channels, crucial for action potential initiation and propagation as well as neurotransmitter release.

MAPs as Modulators of EBs Actions in Neurons

EB1/3 have thus emerged as key regulators of MT dynamics and stability in neurons, rivaling in importance with structural MAPs. Recent findings provide evidence that EBs and MAPs should be considered as close cooperators in the task of regulating MT state. Notably, these studies show that classical MAPs act as direct regulators of the actions of EBs in neuronal cells, pointing to the existence of a functional interplay between these two types of microtubular proteins.[10,11]

Typical localization of classical MAPs and EBs on MTs differ: while EBs accumulate at MT plus-ends in a comet-like pattern, classical MAPs bind along MTs.[7,9] How can then EBs be directly regulated by MAPs? To envision such a scenario, different aspects have to be considered: (1) a pool of both EB proteins and MAPs can be found in the cytosol; (2) EB1/3 localize along MTs under certain conditions. This broadens the possibilities suggesting that the interaction between EBs and MAPs could take place either in the cytosol or at MT lattices. Moreover, as mentioned above, neuronal MAPs show specific localizations either in axons or dendrites. Below, we draw together and discuss studies that describe the crosstalk between MAPs and EBs in different neuronal compartments and subcellular locations (see **Fig. 1**).

MAP1B Sequesters EBs in the Cytosol of Extending Neurites/Axons of Developing Neuronal Cells

EB proteins reside shortly at MT plus-ends, since EB1/3 undergo a fast exchange on off MT growing ends.[39] Thus, there

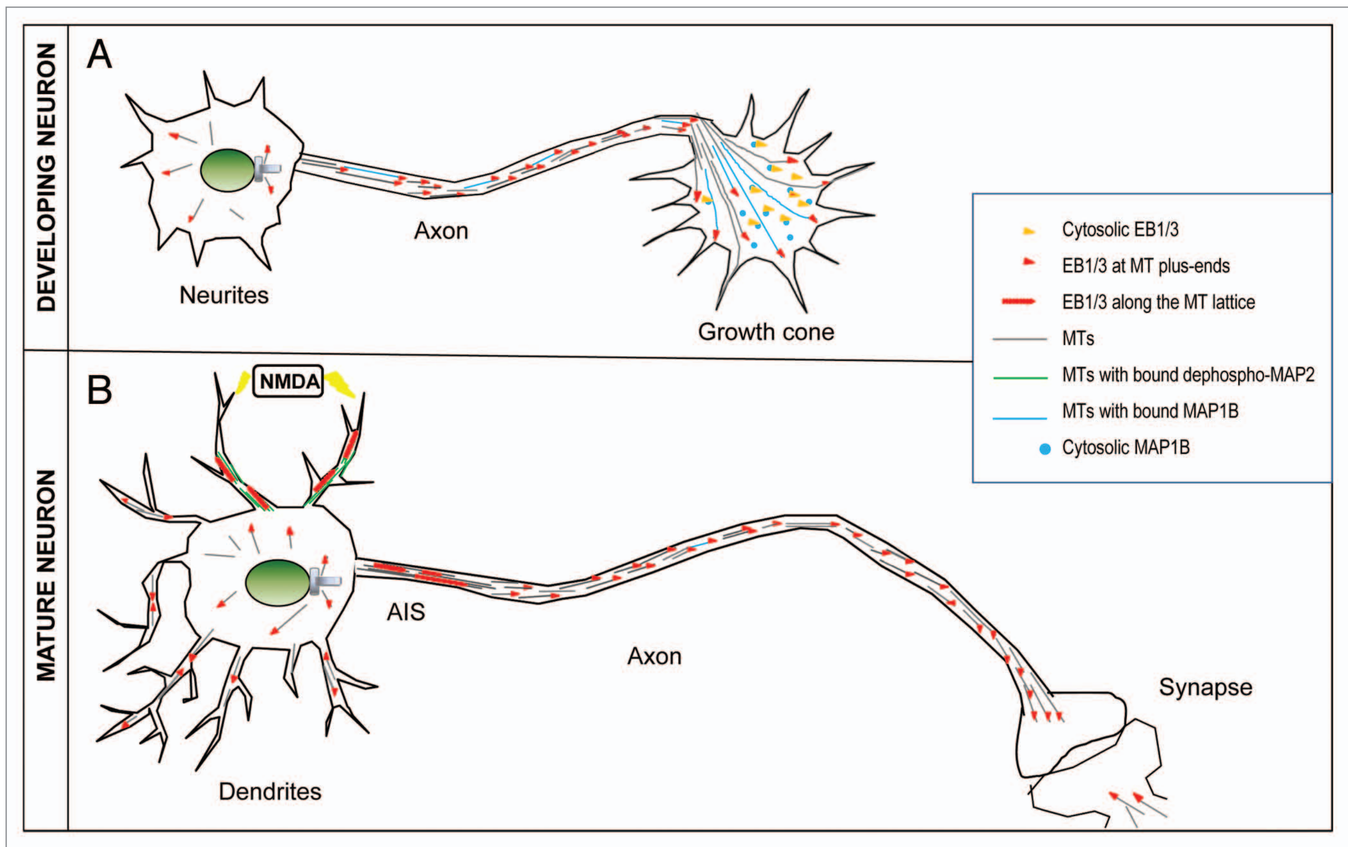

Figure 1. EB1/3 proteins are differentially regulated by classical MAPs in developing or mature neurons. (**A**) In differentiating neurons, MAP1B, which is expressed at high levels, sequesters EB1/3 in the cytosol (see detail in growth cone). This contributes to maintain MTs in a highly dynamic state during axon outgrowth. (**B**) In dendrites of mature neurons, neuronal activation (e.g., by NMDA) induces MAP2 dephosphorylation and binding to MTs, leading to MT bundling. Dephosphorylated MAP2 recruits EB1/3 to MT bundles, thus decreasing MT dynamics and increasing MT stability in dendrites. EB1/3 proteins are also found along the MT lattice at the AIS, interacting with ankyrin G and maybe with other MAPs.

is a pool of EB1/3 in the cytosol whose interaction with MTs can be subject of regulation. Of note, a considerable amount of some structural MAPs, such as MAP1B, is also present in the cytosol.[40] Moreover, expression of EB1/3 and MAP1B is enriched along extending neurites and axons.[10] As shown in the model presented in **Figure 1A**, we have recently shown that MAP1B interacts directly with EB1/3 and sequesters them in the cytosol of developing neuronal cells thereby regulating MT dynamics in a coordinated fashion.[10] We propose that MAP1B reduces the effective pool of cytosolic EBs available to interact with MT plus-ends, thus keeping the high MT dynamicity required during axonogenesis. In particular, the MAP1B/EBs crosstalk in growth cones contributes to growth cone remodeling and proper advance during axon outgrowth.

We showed that the effect of MAP1B on EB proteins is not due to the stabilizing actions of MAP1B on MTs and is specific for MAP1B since: (1) Tau, another classical axonal MAP, does not exert comparable effects on EB1/3 in developing neuronal cells, (2) a fragment of MAP1B, which does not interact with MTs, retains EB proteins in the cytosol in a similar way to full-length MAP1B.[10]

We showed that the interaction between MAP1B and EBs is negatively modulated by phosphorylation.[10] Phosphorylation also negatively regulates the binding of EBs to other protein partners,[38,41,42] as well as the binding of MAP1B to MTs.[15,43] This is probably due to the fact that both the MT lattice surface and the C-terminal partner-binding part of the EBs are negatively charged.[44] Usually, phosphorylation events occur upon triggering of signaling cascades in response to extracellular cues. Thus, it seems likely that assembly and disassembly of all these protein complexes in neurons, including the MAPs/EBs, will occur downstream of the activation of certain signal transduction pathways. Moreover, high levels of MAP1B would promote that a significant proportion of other +TIPs and/or signaling molecules that otherwise localized to MT plus-ends, would be retained in the cytosol bound to EB1/3. This adds an extra layer of complexity to the local regulation of MT dynamics during neuronal differentiation.

Our data also suggest that MAP1B may be hindering low-affinity binding sites for EB1/3 along MTs. It is tempting to speculate that as axons start growing and MAP1B levels increase, the putative localization of EBs at the MT lattice is impaired. Hence, we propose that MAP1B may regulate the interaction of EB proteins with MTs during neurite/axon extension in two different ways: by sequestration of EB1/3 in the cytosol and by prevention of their localization along MTs. Hence, MAP1B

contributes to avoid the overstabilization of MTs in neurites, axon shaft, and growth cone during differentiation.

MAP2 Recruits EB3 to MT Bundles in Dendrites of Mature Neurons

In mature neurons, EB1/3 accumulate at MT plus-ends in dendrites and certain regions of the axons.[26] This indicates that dynamic MTs are not only important during neuronal development but are also required to maintain neuronal morphology and function. The interaction of EB3 with MTs in adult neurons is modulated by neuronal activity.[11] Induction of long-term depression (LTD) by NMDA in primary rat hippocampal neurons, leads to the rapid removal of EB3 from MT plus-ends in dendrites and the subsequent attenuation of MT dynamics (see **Fig. 1B**).[11] However, this rapid NMDA effect is followed by a more prolonged response, during which EB3 is recruited along MAP2-positive MT bundles in the dendritic shaft. Notably, MAP2 interacts directly with EB3 and is necessary and sufficient for this activity-dependent redistribution of EB3 to MTs.[11] Remarkably, under basal conditions, EB3 and MAP2 are both abundantly present in dendrites but they interact with different populations of MTs; EB3 binds to the plus-ends of growing MTs and MAP2 decorates stable MTs.[11] Of note, as described for MAP1B, regulation of the interaction of MAP2 with EB3 is negatively regulated by phosphorylation. Thus, phosphorylation seems to be a common regulatory mechanism of the interaction between classical MAPs and EBs. It will be exciting to elucidate further the growth factors, signaling pathways, and protein kinases that control the assembly and/or disassembly of the MAPs/EBs complexes.

Kapitein et al.[11] suggest that relocalization of EB3 along MAP2-positive MT bundles would be a way to partially deplete the cytosolic pool of EB3 available to accumulate at MT plus-ends and to promote growth of dynamic MTs, required for maintenance of dendritic spine morphology. Alternatively, they propose that this might be a way to recruit molecules involved in specific signaling cascades to the MT lattice.[11] In this context, as occurs at the AIS,[36] EB1/3 proteins switch their function from being pure +TIPs to become classical MAPs (**Fig. 1B**). It is possible that EB1/3 interact with other classical MAPs along stable MTs localized at the AIS in mature neurons. Recruiting of EBs to MT bundles appears to be a way to enhance MT stability in specific regions of adult neurons (e.g., AIS) and/or under certain conditions (e.g., neuronal activation).

Summary and Future Perspectives

Here we have reviewed and discussed recent work on new mechanisms of regulation of EB1/3 proteins by direct interactions with classical MAPs in neurons. Neuronal MAPs show different developmental expression patterns, subcellular localization, and MT stabilizing capacity, providing wide possibilities of EBs regulation at different levels. Thus, axonal MAP1B is expressed at the beginning of axon extension and declines upon maturation whereas dendritic MAP2 is expressed later but remains high in adult neurons.[9] In this way, MAP1B locally modulates MT dynamics by trapping EB1/3 in the cytosol of extending neurites and/or axons.[10] In adult neurons, MAP2 recruits EB3 to stable MT bundles in response to neuronal activation, thereby reducing MT dynamics and enhancing MT stability in dendrites.[11] Both MAPs would, in different manners, regulate the amount of free diffuse EB proteins in the cytosol of neurons. It is likely that other classical MAPs regulate EB1/3 binding to MTs in neurons in a similar fashion. Given the wide expression of EBs and classical MAPs, it is plausible that a functional interplay between MAPs and EBs occurs in a variety of cell types, thus contributing to the regulation of MT dynamics in a number of cellular processes. The findings discussed above have only paved the way to start deciphering the molecular mechanisms involved in the modulation of the MAP1B/EBs interplay in neuronal cells. Further research will be required to fully understand the complex coordination of the actions of MAPs and EBs and its relevance in neuronal physiology.

Disclosure of Potential Conflicts of Interest

No potential conflict of interest was disclosed.

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References

1. Conde C, Cáceres A. Microtubule assembly, organization and dynamics in axons and dendrites. Nat Rev Neurosci 2009; 10:319-32; PMID:19377501; http://dx.doi.org/10.1038/nrn2631
2. Dent EW, Baas PW. Microtubules in neurons as information carriers. J Neurochem 2013; PMID:24266899; http://dx.doi.org/10.1111/jnc.12621
3. Ahmad FJ, Yu W, McNally FJ, Baas PW. An essential role for katanin in severing microtubules in the neuron. J Cell Biol 1999; 145:305-15; PMID:10209026; http://dx.doi.org/10.1083/jcb.145.2.305
4. Yu W, Solowska JM, Qiang L, Karabay A, Baird D, Baas PW. Regulation of microtubule severing by katanin subunits during neuronal development. J Neurosci 2005; 25:5573-83; PMID:15944385; http://dx.doi.org/10.1523/JNEUROSCI.0834-05.2005
5. Baas PW, Buster DW. Slow axonal transport and the genesis of neuronal morphology. J Neurobiol 2004; 58:3-17; PMID:14598366; http://dx.doi.org/10.1002/neu.10281
6. Mitchison T, Kirschner M. Dynamic instability of microtubule growth. Nature 1984; 312:237-42; PMID:6504138; http://dx.doi.org/10.1038/312237a0
7. Galjart N. Plus-end-tracking proteins and their interactions at microtubule ends. Curr Biol 2010; 20:R528-37; PMID:20620909; http://dx.doi.org/10.1016/j.cub.2010.05.022
8. Gouveia SM, Akhmanova A. Cell and molecular biology of microtubule plus end tracking proteins: end binding proteins and their partners. Int Rev Cell Mol Biol 2010; 285:1-74; PMID:21035097; http://dx.doi.org/10.1016/B978-0-12-381047-2.00001-3
9. Avila J, Domínguez J, Díaz-Nido J. Regulation of microtubule dynamics by microtubule-associated protein expression and phosphorylation during neuronal development. Int J Dev Biol 1994; 38:13-25; PMID:8074993
10. Tortosa E, Galjart N, Avila J, Sayas CL. MAP1B regulates microtubule dynamics by sequestering EB1/3 in the cytosol of developing neuronal cells. EMBO J 2013; 32:1293-306; PMID:23572079; http://dx.doi.org/10.1038/emboj.2013.76

11. Kapitein LC, Yau KW, Gouveia SM, van der Zwan WA, Wulf PS, Keijzer N, Demmers J, Jaworski J, Akhmanova A, Hoogenraad CC. NMDA receptor activation suppresses microtubule growth and spine entry. J Neurosci 2011; 31:8194-209; PMID:21632941; http://dx.doi.org/10.1523/JNEUROSCI.6215-10.2011
12. Takemura R, Okabe S, Umeyama T, Kanai Y, Cowan NJ, Hirokawa N. Increased microtubule stability and alpha tubulin acetylation in cells transfected with microtubule-associated proteins MAP1B, MAP2 or tau. J Cell Sci 1992; 103:953-64; PMID:1487506
13. Vandecandelaere A, Pedrotti B, Utton MA, Calvert RA, Bayley PM. Differences in the regulation of microtubule dynamics by microtubule-associated proteins MAP1B and MAP2. Cell Motil Cytoskeleton 1996; 35:134-46; PMID:8894283; http://dx.doi.org/10.1002/(SICI)1097-0169(1996)35:2<134::AID-CM6>3.0.CO;2-A
14. Brandt R, Lee G. Functional organization of microtubule-associated protein tau. Identification of regions which affect microtubule growth, nucleation, and bundle formation in vitro. J Biol Chem 1993; 268:3414-9; PMID:8429017
15. Goold RG, Owen R, Gordon-Weeks PR. Glycogen synthase kinase 3beta phosphorylation of microtubule-associated protein 1B regulates the stability of microtubules in growth cones. J Cell Sci 1999; 112:3373-84; PMID:10504342
16. Panda D, Samuel JC, Massie M, Feinstein SC, Wilson L. Differential regulation of microtubule dynamics by three- and four-repeat tau: implications for the onset of neurodegenerative disease. Proc Natl Acad Sci U S A 2003; 100:9548-53; PMID:12886013; http://dx.doi.org/10.1073/pnas.1633508100
17. Panda D, Goode BL, Feinstein SC, Wilson L. Kinetic stabilization of microtubule dynamics at steady state by tau and microtubule-binding domains of tau. Biochemistry 1995; 34:11117-27; PMID:7669769; http://dx.doi.org/10.1021/bi00035a017
18. Bunker JM, Wilson L, Jordan MA, Feinstein SC. Modulation of microtubule dynamics by tau in living cells: implications for development and neurodegeneration. Mol Biol Cell 2004; 15:2720-8; PMID:15020716; http://dx.doi.org/10.1091/mbc.E04-01-0062
19. Dawson HN, Ferreira A, Eyster MV, Ghoshal N, Binder LI, Vitek MP. Inhibition of neuronal maturation in primary hippocampal neurons from tau deficient mice. J Cell Sci 2001; 114:1179-87; PMID:11228161
20. Harada A, Oguchi K, Okabe S, Kuno J, Terada S, Ohshima T, Sato-Yoshitake R, Takei Y, Noda T, Hirokawa N. Altered microtubule organization in small-calibre axons of mice lacking tau protein. Nature 1994; 369:488-91; PMID:8202139; http://dx.doi.org/10.1038/369488a0
21. Fujio J, Hosono H, Ishiguro K, Ikegami S, Fujita SC. Tau phosphorylation in the mouse brain during aversive conditioning. Neurochem Int 2007; 51:200-8; PMID:17597257; http://dx.doi.org/10.1016/j.neuint.2007.04.024
22. Ikegami S, Harada A, Hirokawa N. Muscle weakness, hyperactivity, and impairment in fear conditioning in tau-deficient mice. Neurosci Lett 2000; 279:129-32; PMID:10688046; http://dx.doi.org/10.1016/S0304-3940(99)00964-7
23. Teng J, Takei Y, Harada A, Nakata T, Chen J, Hirokawa N. Synergistic effects of MAP2 and MAP1B knockout in neuronal migration, dendritic outgrowth, and microtubule organization. J Cell Biol 2001; 155:65-76; PMID:11581286; http://dx.doi.org/10.1083/jcb.200106025
24. Takei Y, Teng J, Harada A, Hirokawa N. Defects in axonal elongation and neuronal migration in mice with disrupted tau and map1b genes. J Cell Biol 2000; 150:989-1000; PMID:10973990; http://dx.doi.org/10.1083/jcb.150.5.989
25. Akhmanova A, Steinmetz MO. Tracking the ends: a dynamic protein network controls the fate of microtubule tips. Nat Rev Mol Cell Biol 2008; 9:309-22; PMID:18322465; http://dx.doi.org/10.1038/nrm2369
26. Stepanova T, Slemmer J, Hoogenraad CC, Lansbergen G, Dortland B, De Zeeuw CI, Grosveld F, van Cappellen G, Akhmanova A, Galjart N. Visualization of microtubule growth in cultured neurons via the use of EB3-GFP (end-binding protein 3-green fluorescent protein). J Neurosci 2003; 23:2655-64; PMID:12684451
27. Jiang K, Toedt G, Montenegro Gouveia S, Davey NE, Hua S, van der Vaart B, Grigoriev I, Larsen J, Pedersen LB, Bezstarosti K, et al. A Proteome-wide screen for mammalian SxIP motif-containing microtubule plus-end tracking proteins. Curr Biol 2012; 22:1800-7; PMID:22885064; http://dx.doi.org/10.1016/j.cub.2012.07.047
28. Nakagawa H, Koyama K, Murata Y, Morito M, Akiyama T, Nakamura Y. EB3, a novel member of the EB1 family preferentially expressed in the central nervous system, binds to a CNS-specific APC homologue. Oncogene 2000; 19:210-6; PMID:10644998; http://dx.doi.org/10.1038/sj.onc.1203308
29. Stepanova T, Smal I, van Haren J, Akinci U, Liu Z, Miedema M, Limpens R, van Ham M, van der Reijden M, Poot R, et al. History-dependent catastrophes regulate axonal microtubule behavior. Curr Biol 2010; 20:1023-8; PMID:20471267; http://dx.doi.org/10.1016/j.cub.2010.04.024
30. Geraldo S, Khanzada UK, Parsons M, Chilton JK, Gordon-Weeks PR. Targeting of the F-actin-binding protein drebrin by the microtubule plus-tip protein EB3 is required for neuritogenesis. Nat Cell Biol 2008; 10:1181-9; PMID:18806788; http://dx.doi.org/10.1038/ncb1778
31. Mattie FJ, Stackpole MM, Stone MC, Clippard JR, Rudnick DA, Qiu Y, Tao J, Allender DL, Parmar M, Rolls MM. Directed microtubule growth, +TIPs, and kinesin-2 are required for uniform microtubule polarity in dendrites. Curr Biol 2010; 20:2169-77; PMID:21145742; http://dx.doi.org/10.1016/j.cub.2010.11.050
32. Moughamian AJ, Osborn GE, Lazarus JE, Maday S, Holzbaur EL. Ordered recruitment of dynactin to the microtubule plus-end is required for efficient initiation of retrograde axonal transport. J Neurosci 2013; 33:13190-203; PMID:23926272; http://dx.doi.org/10.1523/JNEUROSCI.0935-13.2013
33. Jaworski J, Kapitein LC, Gouveia SM, Dortland BR, Wulf PS, Grigoriev I, Camera P, Spangler SA, Di Stefano P, Demmers J, et al. Dynamic microtubules regulate dendritic spine morphology and synaptic plasticity. Neuron 2009; 61:85-100; PMID:19146815; http://dx.doi.org/10.1016/j.neuron.2008.11.013
34. Sweet ES, Previtera ML, Fernández JR, Charych EI, Tseng CY, Kwon M, Starovoytov V, Zheng JQ, Firestein BL. PSD-95 alters microtubule dynamics via an association with EB3. J Neurosci 2011; 31:1038-47; PMID:21248129; http://dx.doi.org/10.1523/JNEUROSCI.1205-10.2011
35. Laht P, Pill K, Haller E, Veske A. Plexin-B3 interacts with EB-family proteins through a conserved motif. Biochim Biophys Acta 2012; 1820:888-93; PMID:22373814; http://dx.doi.org/10.1016/j.bbagen.2012.02.007
36. Leterrier C, Vacher H, Fache MP, d'Ortoli SA, Castets F, Autillo-Touati A, Dargent B. End-binding proteins EB3 and EB1 link microtubules to ankyrin G in the axon initial segment. Proc Natl Acad Sci U S A 2011; 108:8826-31; PMID:21551097; http://dx.doi.org/10.1073/pnas.1018671108
37. Gu C, Zhou W, Puthenveedu MA, Xu M, Jan YN, Jan LY. The microtubule plus-end tracking protein EB1 is required for Kv1 voltage-gated K+ channel axonal targeting. Neuron 2006; 52:803-16; PMID:17145502; http://dx.doi.org/10.1016/j.neuron.2006.10.022
38. Vacher H, Yang JW, Cerda O, Autillo-Touati A, Dargent B, Trimmer JS. Cdk-mediated phosphorylation of the Kvβ2 auxiliary subunit regulates Kv1 channel axonal targeting. J Cell Biol 2011; 192:813-24; PMID:21357749; http://dx.doi.org/10.1083/jcb.201007113
39. Dragestein KA, van Cappellen WA, van Haren J, Tsibidis GD, Akhmanova A, Knoch TA, Grosveld F, Galjart N. Dynamic behavior of GFP-CLIP-170 reveals fast protein turnover on microtubule plus ends. J Cell Biol 2008; 180:729-37; PMID:18283108; http://dx.doi.org/10.1083/jcb.200707203
40. Tögel M, Wiche G, Propst F. Novel features of the light chain of microtubule-associated protein MAP1B: microtubule stabilization, self interaction, actin filament binding, and regulation by the heavy chain. J Cell Biol 1998; 143:695-707; PMID:9813091; http://dx.doi.org/10.1083/jcb.143.3.695
41. Watanabe T, Noritake J, Kakeno M, Matsui T, Harada T, Wang S, Itoh N, Sato K, Matsuzawa K, Iwamatsu A, et al. Phosphorylation of CLASP2 by GSK-3beta regulates its interaction with IQGAP1, EB1 and microtubules. J Cell Sci 2009; 122:2969-79; PMID:19638411; http://dx.doi.org/10.1242/jcs.046649
42. Kumar P, Chimenti MS, Pemble H, Schönichen A, Thompson O, Jacobson MP, Wittmann T. Multisite phosphorylation disrupts arginine-glutamate salt bridge networks required for binding of cytoplasmic linker-associated protein 2 (CLASP2) to end-binding protein 1 (EB1). J Biol Chem 2012; 287:17050-64; PMID:22467876; http://dx.doi.org/10.1074/jbc.M111.316661
43. Ulloa L, Díaz-Nido J, Avila J. Depletion of casein kinase II by antisense oligonucleotide prevents neuritogenesis in neuroblastoma cells. EMBO J 1993; 12:1633-40; PMID:8467810
44. Honnappa S, John CM, Kostrewa D, Winkler FK, Steinmetz MO. Structural insights into the EB1-APC interaction. EMBO J 2005; 24:261-9; PMID:15616574; http://dx.doi.org/10.1038/sj.emboj.7600529