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The role of microtubule-associated protein 1B in axonal growth and neuronal migration in the central nervous system☆

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Abstract

In this review, we discuss the role of microtubule-associated protein 1B (MAP1B) and its phosphorylation in axonal development and regeneration in the central nervous system. MAP1B exhibits similar functions during axonal development and regeneration. MAP1B and phosphorylated MAP1B in neurons and axons maintain a dynamic balance between cytoskeletal components, and regulate the stability and interaction of microtubules and actin to promote axonal growth, neural connectivity and regeneration in the central nervous system.

Key Words: microtubule-associated protein 1B; central nervous system; axonal regeneration; axonal development; axon guidance; neuronal migration

Abbreviations: CNS, central nervous system; MAP1B, microtubule-associated protein 1B; GSK3β, glycogen synthase kinase 3β; PI3K, phosphatidylinositol-3 kinase; JNK, c-Jun N-terminal kinase

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INTRODUCTION

Although recent evidence indicates that axonal regeneration and neural pathway reconstruction can occur following central nervous system (CNS) injury, brain and spinal axons cannot rapidly or effectively traverse the site of injury. Glial scar formation, in particular, hinders axonal regeneration and CNS self-repair[1]. Consequently, trauma, ischemia and degenerative disease can result in permanent and severe disability. Microtubule-associated protein 1B (MAP1B) is one of the first MAPs expressed in neuroblasts, and is essential for axonal development and regeneration. It can induce cytoskeletal rearrangements by regulating actin and microtubule dynamics, and promote axonal growth, development, branching and regeneration[2-3]. Moreover, it plays an important role in axon guidance and neuronal migration[4].

A variety of signaling molecules are associated with axonal development and regeneration or axonal guidance, such as netrins[5], neurotrophic factor[6-7] and Wnt[8], and signaling molecules associated with neuronal migration, such as Reelin[9], modulate MAP1B function. However, the signaling pathways that regulate MAP1B function and the underlying molecular mechanisms remain poorly understood. Here, we review recent advances in our understanding of MAP1B function and regulation. An appreciation of the underlying molecular mechanisms should help researchers in their efforts to promote CNS repair and axonal regeneration, and lead to effective methods for neurological functional recovery following CNS injury.

MAP1B

MAP1B is a high-molecular-weight protein. The precursor polypeptide undergoes proteolytic processing to generate the C-terminal-derived light chain and the N-terminal-derived heavy chain[10]. The C-terminal product is a small protein, called MAP1B light chain 1[10], which contains a microtubule and actin binding domain and can regulate interactions between microtubules and microfilaments[11]. The MAP1B heavy chain contains a microtubule-binding domain and mediates binding of MAP1B light chain 1 to microtubules[12]. Cueille *et al* [13] found that the MAP1B heavy chain binds actin and regulates interactions between microtubules and actin. This indicates that MAP1B can regulate microtubule stability, interactions between microtubules and actin, and axonal extension[14]. MAP1B heavy chain is mainly involved in axonal longitudinal growth, microtubule stability and local actin dynamics, while MAP1B light chain 1 may

enhance growth cone dynamics by providing nodes for F-actin assembly[13].
Protein bioactivity and distribution vary with post-translational modification. MAP1B contains at least 33 phosphorylation sites[15], and differential phosphorylation modulates function. Phosphorylated MAP1B is categorized as type I or type II, *i.e.* P1-MAP1B or P2-MAP1B. The balance between MAP1B and phosphorylated MAP1B is regulated by protein kinases and protein phosphatases. P1-MAP1B is generated by phosphorylation by various protein kinases, such as glycogen synthase kinase 3β (GSK3β) and cyclin-dependent kinase 5. Dephosphorylation of P1-MAP1B is controlled by protein phosphatase 2A and 2B. P2-MAP1B is generated by phosphorylation by casein kinase. It is dephosphorylated by protein phosphatase 1 and 2A[16-17].
The functions and subcellular distributions of P1-MAP1B and P2-MAP1B are different. P1-MAP1B mainly aggregates in distal axons and growth cones during neural development to respond to extracellular factors. It regulates microtubule and actin dynamics and axonal extension[18]. P1-MAP1B gradually disappears following axonal maturation, and is used as a marker of axonal growth[19]. P2-MAP1B is mainly localized in subcellular structures of neurons throughout postnatal development[20]

MAP1B AND AXONAL DEVELOPMENT

Proteomics shows that MAP1B accumulates in the growth cone during axonal development to a greater extent than in elongating axons[18, 21]. In addition, inhibiting MAP1B function significantly slows axonal development, indicating the importance of MAP1B in axonogenesis and elongation. Cultured neurons from a mouse line deficient in MAP1B showed that axonal elongation was significantly reduced, indicating inhibition of MAP1B function can partly suppress axonal growth[22], consistent with another study[23] showing that other MAPs also promote axonogenesis. Knockout of MAP1B and MAP2 or MAP1B and tau significantly impairs axonal sprouting, but knockout of MAP2 and tau does not[24-25], suggesting that although the functions of the various MAP family members partly overlap, MAP2 and tau cannot replace MAP1B in axonal development. The quantity of MAP1B in neurons is tightly controlled, because low or high MAP1B levels can result in delayed axonal sprouting, pathological axonogenesis and reduced axonal growth[26-27].
MAP1B contains microtubule and actin binding domains; thus, it can regulate microtubule and actin stability[11-13]. Neuronal cultures from MAP1B knockout mice exhibit delayed neuronal migration and suppressed neurite elongation, but microtubule extension into growth cones is increased[24, 28]. Inhibiting MAP1B phosphorylation increases the size of growth cones and leads to shortened and thickened axons[29]. These results indicate that MAP1B can stabilize microtubules and induce the formation of microfilaments.
Immunodepletion of MAP1B significantly increases the sensitivity of microtubules in the distal axon and growth cone to nocodazole-induced depolymerization[23, 29], indicating that MAP1B increases the ability of microtubules to resist depolymerization. This may be related to the ability of MAP1B to induce microtubule protein acetylation and reduce levels of tyrosinated microtubules, thereby increasing microtubule stability[30-31]. In addition, MAP1B has been shown to regulate growth cone guidance and inhibit branching of regenerating axons[3], but Kuo *et al* [2] demonstrated that axonal branching is increased following MAP1B depletion.
MAP1B in distal axons and growth cones can interact with tubulin-tyrosine ligase to promote microtubule tyrosination and regulate microtubule dynamics, but MAP1B phosphorylation does not affect this interaction[32]. MAP1B binding to dynamic microtubules increases axonal elongation[33]. MAP1B cannot induce microtubule tyrosination because the tubulin-tyrosine ligase binding site is shielded[32]. These results indicate that MAP1B function depends on its location along the axon. MAP1B in axon terminals and growth cones promotes microtubule tyrosination, thereby regulating microtubule dynamics and stimulating axonal elongation. In contrast, MAP1B at other sites along the axon primarily stabilizes microtubules and prevents microtubule depolymerization.
Previous studies have shown that axons are thickened and shortened, and growth cone extension is increased following inhibition of MAP1B phosphorylation, while deletion of MAP1B or increasing the MAP1B/P-MAP1B ratio increases microtubule stability[28-29]. Moreover, phosphorylated MAP1B mainly regulates microtubule dynamics in growth cones and growing axons[29, 34], indicating that it contributes to microtubule stability and dynamics and plays an important role in regulating microtubule stability, because extensive promotion or inhibition of microtubule stability can affect axonal growth and development[35]. Microtubules and the associated MAP1B extend into growth cones, and microtubules within the growth cone can bind actin[33]. This indirectly indicates that MAP1B binds actin, thereby regulating the interaction between microtubules and actin.
Phosphorylated MAP1B can enhance growth cone motility by regulating actin dynamics in the growth cone[28]. In the initial stage of axonogenesis, phosphorylated MAP1B is at very low levels, but its levels increase with axonal development and elongation[36]. P1-MAP1B levels are highest in the growth cone, where it binds axonal terminal microtubules[27, 37]. There, it primarily regulates axonal elongation by modulating microtubule dynamics and interactions between microtubules and actin[23, 35, 38]. P2-MAP1B also participates in dendrite and synapse formation[14].
GSK3β phosphorylates MAP1B to regulate microtubule

dynamics[29, 39]. Nerve growth factor in primary neurons promotes axonal growth through the GSK3β-MAP1B pathway[6, 40]. Nerve growth factor interacts with tropomyosin-related tyrosine kinase to activate the mitogen-activated protein kinase/extracellular regulated kinase pathway, which in turn indirectly stimulates GSK3β phosphorylation through other kinases[7]. Other proteins, such as dystroglycan, can also interact with MAP1B and modulate GSK3β-mediated MAP1B phosphorylation[41]. GSK3β-mediated MAP1B phosphorylation results in microtubule sensitivity to depolymerization and increases the quantity of unstable microtubules[42], thereby promoting axonal elongation[19]. Reduced MAP1B phosphorylation by inhibiting GSK3β activity through the Wnt pathway thickens and shortens axons, and enlarges growth cones and stabilizes microtubules[8].

Nerve growth factor activates phosphatidylinositol-3 kinase (PI3K) and induces GSK3β phosphorylation at ser-9, which blocks the ability of GSK3β to activate primed substrate, *i.e.* substrate that is pre-phosphorylated at certain residues[40, 43]. Two types of GSK3β phosphorylation sites, primed and non-primed, are found in MAP1B[34, 44]. Therefore, nerve growth factor can negatively regulate P1-MAP1B following PI3K activation, *i.e.* nerve growth factor can regulate P1-MAP1B levels through the MAPK and PI3K pathways.

In PC12 cells, nerve growth factor activates neuron-specific p35 by activating the MAPK-ERK1/2 pathway. Subsequently, p35 binds Cdk5 to form an active complex that phosphorylates MAP1B to generate P1-MAP1B[45]. Cdk5 is distributed throughout the cytoplasm and axons, while p35 is only found in axon terminals and growth cones[46]. Therefore, Cdk5 can only be activated in axon terminals and growth cones, possibly contributing to the large amount of P1-MAP1B at these sites[27, 37], which plays crucial roles in microtubule dynamics, axonal elongation and growth cone guidance[46].

The c-Jun N-terminal kinase (JNK) phosphorylates a variety of cytoskeletal proteins, including MAP1B and MAP2. Blocking the JNK pathway reduces MAP1B phosphorylation[47-49], resulting in axonal degeneration and cytoskeletal defects. Moreover, JNK in certain neuronal cell types can promote axonal sprouting[47]. Tanner *et al* [50] reported that MAP1B may also regulate interactions between the cytoskeleton and the cell membrane, and between the cytoskeleton and the extracellular matrix or adhesion molecules. During synaptogenesis at the end stage of axonal development, MAP1B promotes axonal development through three pathways: (1) MAP1B promotes membrane skeleton assembly through interactions with F-actin; (2) MAP1B interacts with phospholipids; (3) MAP1B crosses the plasma membrane and functions as a type I membrane protein[51-52]. At least one form of MAP1B located at presynaptic and postsynaptic regions has been demonstrated to interact with cell membranes and synapsin, contributing to synapse formation and function in the later stages of axonal development[53]. The responsible subtype may be P2-MAP1B. However, this hypothesis requires further investigation.

MAP1B AND AXONAL REGENERATION

CNS functional recovery mainly depends on axonal regeneration and reconstruction of neural circuitry. The injured corticospinal tract forms new connections with spinal neurons, which aids neurological functional recovery to an extent[1]. Peripheral nerve injury can induce sprouting of dorsal root ganglia into the posterior horn[54]. These results indicate that the CNS internal environment supports axonal regeneration.

MAP1B mRNA and protein expression are significantly increased in cortical infarct foci and surrounding regions, promoting sensory and motor functional recovery[55-56]. This indicates that MAP1B plays an important role in nervous system repair. MAP1B can regulate interactions between microtubules and actin[23, 35, 38], and microtubules aggregate only in the presence of MAP1B[57-58]. Cueille *et al* [13] proposed that interactions between microtubules and actin play important roles not only in neurogenesis and differentiation, but also in axonal regeneration and neuronal connectivity in adults, indicating that MAP1B promotes axonal regeneration by regulating interactions between microtubules and actin and that high expression of MAP1B in the CNS contributes to neural plasticity.

Similar to axonal development, the ability of MAP1B to promote axonal regeneration and neuronal connectivity are highly correlated with MAP1B phosphorylation. Following traumatic brain injury, MAP1B and phosphorylated MAP1B exhibit a brief period of high expression in the hippocampus, cortex and thalamus, which has been demonstrated to associate with cytoskeletal protein stability[37]. Soares *et al* [59] reported that levels of phosphorylated MAP1B rapidly increase in newly generated axons near the spinal cord lesion, and neurons highly express phosphorylated MAP1B in the spinal cord following injury and periphery nerve injury, which promotes axonal reconstruction. P1-MAP1B and P2-MAP1B have distinct functions during axonal regeneration. Upregulated P1-MAP1B expression is associated with axonal regeneration, and upregulated P2-MAP1B expression is associated with synaptic plasticity after injury[60].

MAP1B and phosphorylated MAP1B are associated with axonal regeneration in the mature CNS. The JNK pathway has been shown to play an important role in axonal regeneration in JNK gene-deficient mice[61]. Phosphorylated JNK aggregates in distal axons during axonal regeneration, and promotes microtubule elongation and axonal sprouting by inducing MAP1B phosphorylation. Following spinal cord injury, JNK pathway activity is increased, which promotes axonal

sprouting and regeneration associated with MAP1B phosphorylation[59].

Similar to processes in axonal development, the JNK pathway can catalyze MAP1B phosphorylation during axonal regeneration. However, the correlation between CNS axonal regeneration and development, and the precise roles of MAP1B and phosphorylated MAP1B in CNS axonal generation and functional recovery require further investigation.

ROLE OF MAP1B IN AXONAL GUIDANCE

During axonal growth, the growth cone is responsible for signal perception and directing axon elongation. Microtubule and actin dynamics are important for growth cone directional motility[62]. Actin is regarded as the main skeletal component for growth cone genesis and guidance, but studies have demonstrated that dynamic microtubules surrounding the growth cone play a major role in regulating growth cone guidance[63-64]. The growth cone responds to the axon guidance factor Netrin-1 and other extracellular guidance cues by transducing these signals into changes in microtubule structure[62], and microtubule stability and growth is the structural basis of axon guidance. Buck *et al* [62] demonstrated that changes in local microtubular stability, growth and polymerization/depolymerization mediate growth cone navigation. Therefore, microtubular instability is essential for axon and growth cone guidance[65]. The regulation of microtubule dynamics and microtubule and actin interactions allows MAP1B to mediate growth cone migration, which is related to the netrin signaling pathway[4, 66]. MAP1B deletion can increase lateral branch sprouting and perturb growth cone guidance[3, 22, 24].

Netrin-1 is an important guidance molecule and induces intracellular signaling cascades by binding receptor deleted in colorectal cancer[63-64]. MAP1B is involved in Netrin-1 signal transduction[5]. Netrin-1 can enhance MAP1B expression through Cdk5 and Gsk3[5], and it can deactivate phosphorylated MAP1B in growth cones, resulting in impaired growth cone guidance[66].

MAP1B regulates microtubule stability and promotes axon elongation. P1-MAP1B mediates axon elongation to facilitate the formation of neural connections with target tissues or organs. Therefore, MAP1B and P1-MAP1B maintain microtubule dynamic balance and regulate subcellular distribution to promote axonal growth and guide migration.

MAP1B AND NEURONAL MIGRATION

MAP1B can also guide neuronal migration. Similar to its role in axon guidance, MAP1B regulates neuronal migration[9], and the dynamic balance between MAP1B and P1-MAP1B regulates neuronal morphology and promotes neuronal directional movement.

MAP1B gene defects result in delayed neuronal migration, ectopic localization, cortical plate defects and abnormal CNS development[24], indicating that the protein is involved in axonal elongation and neuronal migration, which is associated with actin and microtubule dynamics[24]. During neuronal migration, MAP1B regulates interactions between actin and microtubules[65]. CNS neuronal migration depends on the dynamic balance between stable and dynamic microtubules[26], which is mediated by MAP1B and P1-MAP1B[32, 67].

MAP1B can induce dynein, a protein involved in cell migration, to bind lissencephaly-related protein 1[68]. Deletion of MAP1B can attenuate their interaction, indicating the important role of MAP1B in neuronal migration[68]. Bouquet *et al* [3, 65] proposed that MAP1B exerted similar effects through related mechanisms in different types of cells (Figure 1).

Reelin may promote nervous system development through phosphorylation of MAP1B and other MAPs (such as lissencephaly-related protein 1)[68]. Reelin is an extracellular matrix protein that regulates neuronal migration and localization in the CNS by modulating MAP1B function. Reelin induces disabled 1 phosphorylation through very low density lipoprotein receptor and apolipoprotein receptor 2. Activated disabled 1 activates GSK3 and Cdk5, which synergistically increase levels of P1-MAP1B. The PI3K pathway regulates P1-MAP1B levels by inhibiting GSK3 activity[9, 43] to maintain microtubular instability and promote neuronal migration[9, 35].

Netrin-1 stimulates MAP1B phosphorylation by activating GSK3β and Cdk5 to produce P1-MAP1B, which regulates interaction of microtubules and actin, to mediate neuronal migration[5]. In addition, Netrin-1 interacts with its receptor, deleted in colorectal cancer, to activate the Rho GTPase Rac1[69]. Rac1 regulates MAP1B activity and indirectly controls microtubule dynamics and cell migration[38]. This also demonstrates that Netrin-1 can regulate neuronal migration through MAP1B. Thus, the Netrin-1-Rac1-GSK3β/Cdk5-MAP1B pathway may be an effective means of controlling neuronal migration, but this idea requires verification.

Kawauchi *et al* [67] reported that the T-cell lymphoma invasion and metastasis 1 (TIAM1)-Rac1-JNK pathway plays an important role in neuronal migration. TIAM1 activates Rac1 and stimulates neuronal migration by regulating actin cytoskeleton dynamics, and JNK regulates microtubule dynamics by stimulating MAP1B phosphorylation to control neuronal migration[67]. Rac1 regulates MAP1B activity, and MAP1B enhances Rac1 activity by interacting with TIAM1[38, 52]. The effects of Cdk5, GSK3β and JNK on microtubule dynamics must be tightly regulated to maintain the balance between microtubule stability and instability. Otherwise, cytoskeletal dynamics would be impaired, perturbing neuronal migration[9, 35]. Therefore, Reelin[68] and Netrin-1[5] play important roles in neuronal migration through effects on MAP1B.

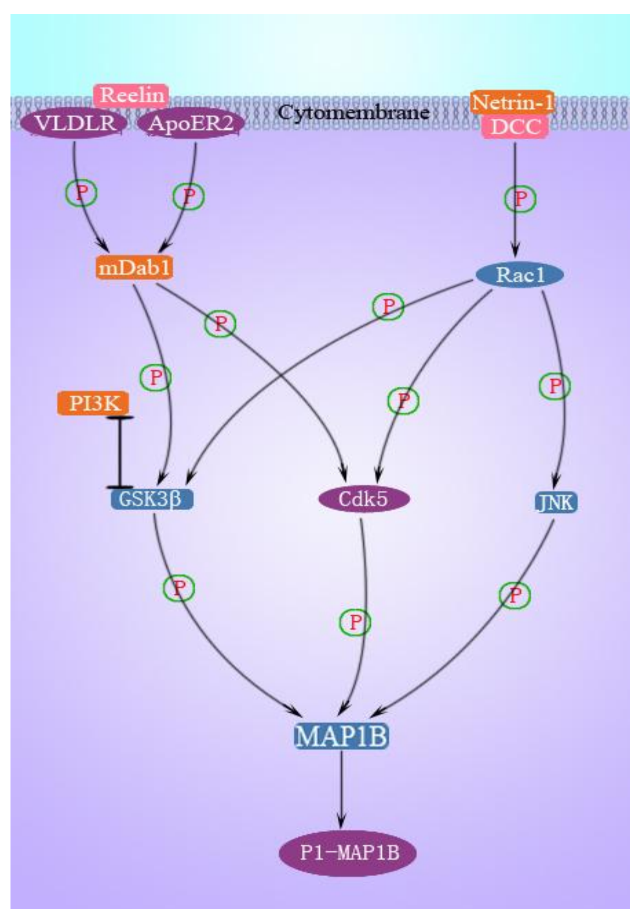

Figure 1 The main pathways that regulate MAP1B phosphorylation during neuronal migration. The Reelin pathway modulates MAP1B function to promote neuronal migration.

The axon guidance molecule Netrin-1 regulates MAP1B to indirectly promote neuronal migration. These two pathways promote MAP1B phosphorylation through GSK3β and Cdk5.

PI3K has been reported to inhibit GSK3β activity and negatively regulate MAP1B phosphorylation, thereby influencing neuronal migration.

MAP1B: Microtubule-associated protein 1B; GSK3β: glycogen synthase kinase 3β; JNK: c-Jun N-terminal kinase.

CONCLUSION

MAP1B and phosphorylated MAP1B maintain dynamic balance in CNS neurons and axons. They regulate microtubule stability and dynamics, maintain balance between microtubules and actin, and control their interaction to promote axonal growth, connectivity, and regeneration post-injury. Further studies are needed on MAP1B to investigate treatments to rapidly and effectively ameliorate CNS injury and improve the quality of patient's life.

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REFERENCES

[1] Sharma H, Alilain WJ, Sadhu A, et al. Reatments to restore respiratory function after spinal cord injury and their implications for regeneration, plasticity and adaptation. Exp Neurol. 2011.

[2] Kuo TY, Hong CJ, Hsueh YP. Bcl11A/CTIP1 regulates expression of DCC and MAP1b in control of axon branching and dendrite outgrowth. Mol Cell Neurosci. 2009;42(3):195-207.

[3] Bouquet C, Soares S, von Boxberg Y, et al. Microtubule-associated protein 1B controls directionality of growth cone migration and axonal branching in regeneration of adult dorsal root ganglia neurons. J Neurosci. 2004;24(32):7204-7213.

[4] Meixner A, Haverkamp S, Wässle H, et al. MAP1B is required for axon guidance and Is involved in the development of the central and peripheral nervous system. J Cell Biol. 2000;151(6): 1169-1178.

[5] Del Río JA, González-Billault C, Ureña JM, et al. MAP1B is required for Netrin 1 signaling in neuronal migration and axonal guidance. Curr Biol. 2004;14(10):840-850.

[6] Goold RG, Gordon-Weeks PR. NGF activates the phosphorylation of MAP1B by GSK3beta through the TrkA receptor and not the p75(NTR) receptor. J Neurochem. 2003;87(4):935-946.

[7] Goold RG, Gordon-Weeks PR. The MAP kinase pathway is upstream of the activation of GSK3beta that enables it to phosphorylate MAP1B and contributes to the stimulation of axon growth. Mol Cell Neurosci. 2005;28(3):524-534.

[8] Ciani L, Krylova O, Smalley MJ, et al. A divergent canonical WNT-signaling pathway regulates microtubule dynamics: dishevelled signals locally to stabilize microtubules. J Cell Biol. 2004;164(2):243-253.

[9] González-Billault C, Del Río JA, Ureña JM, et al. A role of MAP1B in Reelin-dependent neuronal migration. Cereb Cortex. 2005;15(8):1134-1145.

[10] Mei X, Sweatt AJ, Hammarback JA. Regulation of microtubule-associated protein 1B (MAP1B) subunit composition. J Neurosci Res. 2000;62(1):56-64.

[11] Noiges R, Eichinger R, Kutschera W, et al. Microtubule-associated protein 1A (MAP1A) and MAP1B: light chains determine distinct functional properties. J Neurosci. 2002;22(6): 2106-2114.

[12] 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(3):695-707.

[13] Cueille N, Blanc CT, Popa-Nita S, et al. Characterization of MAP1B heavy chain interaction with actin. Brain Res Bull. 2007; 71(6):610-618.

[14] Riederer BM. Microtubule-associated protein 1B, a growth-associated and phosphorylated scaffold protein. Brain Res Bull. 2007;71(6):541-558.

[15] Yu L, Coba MP, Husi H, et al. Proteomic analysis of in vivo phosphorylated synaptic proteins.Collins MOJ Biol Chem. 2005; 280(7):5972-5982.

[16] Ulloa L, Díaz-Nido J, Avila J. Depletion of casein kinase II by antisense oligonucleotide prevents neuritogenesis in neuroblastoma cells. EMBO J. 1993;12(4):1633-1640.

[17] Gong CX, Wegiel J, Lidsky T, et al. Regulation of phosphorylation of neuronal microtubule-associated proteins MAP1b and MAP2 by protein phosphatase-2A and -2B in rat brain. Brain Res. 2000; 853(2):299-309.

[18] Black MM, Slaughter T, Fischer I. Microtubule-associated protein 1b (MAP1b) is concentrated in the distal region of growing axons. J Neurosci. 1994;14(2):857-870.

[19] Trivedi N, Marsh P, Goold RG, et al. Glycogen synthase kinase-3beta phosphorylation of MAP1B at Ser1260 and Thr1265 is spatially restricted to growing axons. J Cell Sci. 2005;118(Pt 5): 993-1005.

[20] Gonzalez-Billault C, Jimenez-Mateos EM, Caceres A, et al. Microtubule-associated protein 1B function during normal development, regeneration, and pathological conditions in the nervous system. J Neurobiol. 2004;58(1):48-59.

[21] Nozumi M, Togano T, Takahashi-Niki K, et al. Identification of functional marker proteins in the mammalian growth cone. Proc Natl Acad Sci U S A. 2009;106(40):17211-17216.

[22] González-Billault C, Engelke M, Jiménez-Mateos EM, et al. Participation of structural microtubule-associated proteins (MAPs) in the development of neuronal polarity. J Neurosci Res. 2002; 67(6):713-719.

[23] Tint I, Fischer I, Black M. Acute inactivation of MAP1b in growing sympathetic neurons destabilizes axonal microtubules. Cell Motil Cytoskeleton. 2005;60(1):48-65.

[24] Takei Y, Teng J, Harada A, et al. Defects in axonal elongation and neuronal migration in mice with disrupted tau and map1b genes. J Cell Biol. 2000;150(5):989-1000.

[25] Teng J, Takei Y, Harada A, et al. Synergistic effects of MAP2 and MAP1B knockout in neuronal migration, dendritic outgrowth, and microtubule organization. J Cell Biol. 2001;155(1):65-76.

[26] Gonzalez-Billault C, Avila J, Cáceres A. Evidence for the role of MAP1B in axon formation. Mol Biol Cell. 2001;12(7):2087-2098.

[27] Jiménez-Mateos EM, Paglini G, González-Billault C, et al. End binding protein-1 (EB1) complements microtubule-associated protein-1B during axonogenesis. J Neurosci Res. 2005;80(3): 350-359.

[28] Gonzalez-Billault C, Owen R, Gordon-Weeks PR, et al. Microtubule-associated protein 1B is involved in the initial stages of axonogenesis in peripheral nervous system cultured neurons. Brain Res. 2002;943(1):56-67.

[29] 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(Pt 19):3373-3384.

[30] Bergstrom RA, Sinjoanu RC, Ferreira A. Agrin induced morphological and structural changes in growth cones of cultured hippocampal neurons. Neuroscience. 2007;149(3):527-536.

[31] Li W, Xia JT, Feng Y. Microtubule stability and MAP1B upregulation control neuritogenesis in CAD cells. Acta Pharmacol Sin. 2006;27(9):1119-1126.

[32] Utreras E, Jiménez-Mateos EM, Contreras-Vallejos E, et al. Microtubule-associated protein 1B interaction with tubulin tyrosine ligase contributes to the control of microtubule tyrosination. Dev Neurosci. 2008;30(1-3):200-210.

[33] Tymanskyj SR, Scales TM, Gordon-Weeks PR. MAP1B enhances microtubule assembly rates and axon extension rates in developing neurons. Mol Cell Neurosci. 2011;49(2):110-119.

[34] Scales TM, Lin S, Kraus M, et al. Nonprimed and DYRK1A-primed GSK3 beta-phosphorylation sites on MAP1B regulate microtubule dynamics in growing axons. J Cell Sci. 2009;122(Pt 14):2424-2435.

[35] Gordon-Weeks PR. Microtubules and growth cone function. J Neurobiol. 2004;58(1):70-83.

[36] Larsen KE, Pacheco M, Roth J, et al. Increased MAP1B expression without increased phosphorylation in manganese-treated PC12Mn cells. Exp Cell Res. 1998;245(1):105-115.

[37] Emery DL, Raghupathi R, Saatman KE, et al. Bilateral growth-related protein expression suggests a transient increase in regenerative potential following brain trauma. J Comp Neurol. 2000;424(3):521-531.

[38] Montenegro-Venegas C, Tortosa E, et al. MAP1B regulates axonal development by modulating Rho-GTPase Rac1 activity. Mol Biol Cell. 2010;21(20):3518-3528.

[39] Wood-Kaczmar A, Kraus M, Ishiguro K, et al. An alternatively spliced form of glycogen synthase kinase-3beta is targeted to growing neurites and growth cones. Mol Cell Neurosci. 2009; 42(3):184-194.

[40] Goold RG, Gordon-Weeks PR. Glycogen synthase kinase 3beta and the regulation of axon growth. Biochem Soc Trans. 2004; 32(Pt 5):809-811.

[41] Bhanot K, Young KG, Kothary R. MAP1B and clathrin are novel Interacting partners of the giant cyto-linker dystonin. J Proteome Res. 2011;10(11):5118-5127.

[42] Ishitani T, Ishitani S, Matsumoto K, et al. Nemo-like kinase is involved in NGF-induced neurite outgrowth via phosphorylating MAP1B and paxillin. J Neurochem. 2009;111(5):1104-1118.

[43] Zhou FQ, Snider WD. Cell Biology. GSK-3 beta and microtubule assembly in axons. Science. 2005;308(5719):211-214.

[44] Tymanskyj SR, Lin S, Gordon-Weeks PR. Evolution of the spatial distribution of MAP1B phosphorylation sites in vertebrate neurons. J Anat. 2010;216(6):692-704.

[45] Harada T, Morooka T, Ogawa S, et al. ERK induces p35, a neuron-specific activator of Cdk5, through induction of Egr1. Nat Cell Biol. 2001;3(5):453-459.

[46] Hahn CM, Kleinholz H, Koester MP, et al. Role of cyclin-dependent kinase 5 and its activator P35 in local axon and growth cone stabilization. Neuroscience. 2005;134(2):449-465.

[47] Pereira AC, Leite FG, Brasil BS, et al. A Vaccinia Virus-Driven Interplay between the MKK4/7-JNK1/2 Pathway and Cytoskeleton Reorganization. J Virol. 2012;86(1):172-184.

[48] Yamasaki T, Kawasaki H, Arakawa S, et al. Stress-activated protein kinase MKK7 regulates axon elongation in the developing cerebral cortex. J Neurosci. 2011;31(46):16872-16883.

[49] Eto K, Kawauchi T, Osawa M, et al. Role of dual leucine zipper-bearing kinase (DLK/MUK/ZPK) in axonal growth. Neurosci Res. 2010;66(1):37-45.

[50] Tanner SL, Franzen R, Jaffe H, et al. Evidence for expression of some microtubule-associated protein 1B in neurons as a plasma membrane glycoprotein. J Neurochem. 2000;75(2):553-562.

[51] Moritz A, Scheschonka A, Beckhaus T, et al. Metabotropic glutamate receptor 4 interacts with microtubule-associated protein 1B. Biochem Biophys Res Commun. 2009;390(1):82-86.

[52] Tortosa E, Montenegro-Venegas C, Benoist M, et al. Microtubule-associated protein 1B (MAP1B) is required for dendritic spine development and synaptic maturation. J Biol Chem. 2011;286(47):40638-40648.

[53] Kawakami S, Muramoto K, Ichikawa M, et al. Localization of microtubule-associated protein (MAP) 1B in the postsynaptic densities of the rat cerebral cortex. Cell Mol Neurobiol. 2003;23(6): 887-894.
[54] Soares S, von Boxberg Y, Lombard MC, et al. Phosphorylated MAP1B is induced in central sprouting of primary afferents in response to peripheral injury but not in response to rhizotomy. Eur J Neurosci. 2002;16(4):593-606.
[55] Müller HD, Neder A, Sommer C, et al. Different postischemic protein expression of the GABA(A) receptor alpha2 subunit and the plasticity-associated protein MAP1B after treatment with BDNF versus G-CSF in the rat brain. Restor Neurol Neurosci. 2009;27(1):27-39.
[56] Ayuso MI, García-Bonilla L, Martín ME, et al. Assessment of protein expression levels after transient global cerebral ischemia using an antibody microarray analysis. Neurochem Res. 2010; 35(8):1239-1247.
[57] Pedrotti B, Islam K. Microtubule associated protein 1B (MAP1B) promotes efficient tubulin polymerisation in vitro. FEBS Lett. 1995; 371(1):29-31.
[58] Shimamura M, Sato N, Sata M, et al. Delayed postischemic treatment with fluvastatin improved cognitive impairment after stroke in rats. Stroke. 2007;38(12):3251-3258.
[59] Soares S, Barnat M, Salim C, et al. Extensive structural remodeling of the injured spinal cord revealed by phosphorylated MAP1B in sprouting axons and degenerating neurons. Eur J Neurosci. 2007;26(6):1446-1461.
[60] Ramón-Cueto A, Avila J. Differential expression of microtubule-associated protein 1B phosphorylated isoforms in the adult rat nervous system. Neuroscience. 1997;77(2):485-501.
[61] Barnat M, Enslen H, Propst F, et al. Distinct roles of c-Jun N-terminal kinase isoforms in neurite initiation and elongation during axonal regeneration. J Neurosci. 2010;30(23):7804-7816.
[62] Buck KB, Zheng JQ. Growth cone turning induced by direct local modification of microtubule dynamics. J Neurosci. 2002;22(21): 9358-9367.
[63] Eriksson M, Samuelsson H, Björklund S, et al. MAP1B binds to the NMDA receptor subunit NR3A and affects NR3A protein concentrations. Neurosci Lett. 2010;475(1):33-37.
[64] Lee H, Engel U, Rusch J, et al. The microtubule plus end tracking protein Orbit/MAST/CLASP acts downstream of the tyrosine kinase Abl in mediating axon guidance. Neuron. 2004;42(6): 913-926.
[65] Bouquet C, Ravaille-Veron M, Propst F, et al. MAP1B coordinates microtubule and actin filament remodeling in adult mouse Schwann cell tips and DRG neuron growth cones. Mol Cell Neurosci. 2007;36(2):235-247.
[66] Mack TG, Koester MP, Pollerberg GE. The microtubule-associated protein MAP1B is involved in local stabilization of turning growth cones. Mol Cell Neurosci. 2000;15(1):51-65.
[67] Kawauchi T, Chihama K, Nabeshima Y, et al. The in vivo roles of STEF/Tiam1, Rac1 and JNK in cortical neuronal migration. EMBO J. 2003;22(16):4190-4201.
[68] Jiménez-Mateos EM, Wandosell F, Reiner O, et al. Binding of microtubule-associated protein 1B to LIS1 affects the interaction between dynein and LIS1. Biochem J. 2005;389(Pt 2):333-341.
[69] Antoine-Bertrand J, Ghogha A, Luangrath V, et al. The activation of ezrin-radixin-moesin proteins is regulated by netrin-1 through Src kinase and RhoA/Rho kinase activities and mediates netrin-1-induced axon outgrowth. Mol Biol Cell. 2011;22(19): 3734-3746.

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