Microtubule-Associated Protein 1B Function during Normal Development, Regeneration, and Pathological Conditions in the Nervous System

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ABSTRACT: Microtubule-associated protein 1B is the first MAP to be expressed during the development of the nervous system. Several different approaches have revealed that MAP1B function is associated with microtubule and actin microfilament polymerization and dynamics. In recent years, the generation of molecular models to inactivate MAP1B function in invertebrates and mammals has sparked some controversy about the real role of MAP1B. Despite discrepancies between some studies, it is clear that MAP1B plays a principal role in the development of the nervous system. In this article, we summarize the evidence for MAP1B function in a wide variety of cellular processes implicated in the proper construction of the nervous system. We also discuss the role of MAP1B in pathological processes.
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INTRODUCTION

One hundred years ago, pioneer neurobiologist Santiago Ramon y Cajal described how a neuroblast differentiates into a neuron with a complicated morphology characterized by the presence of a long cytoplasmic process, the axon, and several other cytoplasmic extensions known as dendrites (Ramon y Cajal, 1904). Once these morphological changes are achieved, the so-called mature neuron is able to interact through synaptic contacts with other neurons or with different tissues, making possible the function of the specialized network known as the nervous system. This network can be altered by lesions that affect neuronal morphology. Unfortunately, it is still not possible to repair most of these lesions that affect the CNS.

In this article we will analyze the role of a group of cytoskeletal proteins, namely the microtubule-associated proteins (MAPs), focusing in particular on the participation of MAP1B in the development of neuronal cytoplasmic extensions, and more briefly on the making of synaptic contacts. Later on we will discuss the role for MAP1B in the regeneration of damaged neurons and its participation in some pathological conditions.

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A model for the morphological transformation of an immature neuroblast with a spherical form into a mature highly polarized neuron with different cytoplasmic extensions (including one axon and several dendrites) was proposed during the middles 80's by M. Kirschner and T. Mitchison (1986a,b). According to these authors, cell polarization, including that of neurons, was the consequence of a change in microtubule dynamics limited to selected regions of the cell (cell polarization by selective stabilization of microtubules). They suggested that the morphological change was, along with other factors, the consequence of a change in microtubule dynamics in some neuronal regions. In those regions, microtubules became more stable, and as consequence, a cytoplasmic extension occurred in that region. Therefore, an important factor influencing this extension is the existence of a protein that acts as a microtubule stabilizer. In fact, there are several such proteins present in neurons, and they have been collectively termed microtubule-associated proteins (MAPs). Of these neuronal MAPs, the best studied are MAP1A, MAP1B, MAP2, tau, doublecortin, and LIS1. Each of these proteins is encoded by a single gene and the RNA transcripts could be alternatively spliced into different isoforms. This is the case for tau (Himmler, 1989), MAP2 (Papandrikopoulou et al., 1989; Langkopf et al., 1994), and MAP1B (Kutschera et al., 1998). So far, the existence of transcripts generated by alternative splicing for MAP1A has not been reported.

However, the formation of axons and dendrites requires the participation of a coordinated and complex network of proteins that, in addition to MAP function, includes other factors. For instance, neurotrophins (Meiri and Burdick, 1991), actin and some of its associated proteins (Lanier and Gertler, 2000), molecular motors like dynein (Phillis et al., 1996) or CHO1/MKLP1 (Ferhat et al., 1998; Yu et al., 2000), or other proteins that decrease (CRMP2) (Inagaki et al., 2001; Fukata et al., 2002) or increase (stathmin/SCG10) (Matsuo et al., 1998; Moreno et al., 1999) microtubule instability could play a role in axonogenesis and dendrite arborization.

MAP1B

MAP1B was described by several independent groups during the middle 80's (Greene et al., 1983; Binder et al., 1984; Bloom et al., 1985; Calvert and Anderton, 1985; Riederer et al., 1986). It is the first MAP to be expressed during development of the nervous system (Tucker et al., 1988, 1989). Soon after its discovery, a smaller protein, termed light chain 1, (LC1) was found to be associated with MAP1B (Kuznetsov et al., 1986). MAP1B protein is encoded by a single gene that expresses a precursor protein that in turn expresses nine different exons (seven coding and two noncoding ones). The presence of these two noncoding exons has been shown to be responsible for the generation of alternative isoforms of the protein. These alternative isoforms of MAP1B lack the N-terminal domain encoded by exons 1 to 3 (Kutschera et al., 1998), but retain the functional domain of the protein, because the tubulin binding site has been mapped into exon 5. The protein containing the heavy chain, or properly MAP1B, and also the LC1, is encoded in a single mRNA that is further translated as a polyprotein, which is finally proteolytically processed giving rise to the functional MAP1B protein (Hammarback et al., 1991). There is another protein, LC3, that also binds to MAP1B, but it is codified by a different gene (Mann and Hammarback, 1994, 1996). MAP1B expression is at least under homeoprotein transcriptional control, by engrailed, *in vivo*, although the participation of other transcriptional regulators cannot be ruled out (Montesinos et al., 2001). The tubulin-binding domain on MAP1B is quite different from that found in MAP2, tau, and MAP4. It is composed of several repeats of four amino acids containing basic amino acidic residues (Noble et al., 1989). The presence of these basic motifs confers on MAP1A and MAP1B a different capability for binding and stabilizing microtubules *in vitro* (Vandecandelaere et al., 1996) and when expressed in eukaryotic cell lines (Takemura et al., 1992). However, an important difference between MAP1B and other neuronal MAPs, such as MAP2 and tau, is that its overexpression does not induce microtubule bundling even though its binds to microtubules and stabilizes them (Takemura et al., 1992). It has recently been suggested that light chains could be the bona fide tubulin binding domain for both MAP1A and MAP1B, and that heavy chains could act as regulatory units for light-chain binding to microtubules (Togel et al., 1998; Noiges et al., 2002). However, these results have only been described in non-neuronal cells, and so it is necessary to address the real physiological significance of these interactions in neuronal cells.

MAP1B has been shown to be the first of the neural MAPs to be expressed in neurons *in situ* (Crino et al., 1997; Cheng et al., 1999). Because the expression of MAP1B is down-regulated during brain development it was suggested that the protein could play a major role during neuron morphological differentiation, a role that disappears after neuron-neuron contacts are formed (Diaz-Nido and Avila, 1989; Schoenfeld et al., 1989).

MAP1B PHOSPHORYLATION

The biochemical properties and subcellular distribution of MAP1B can be modified by post-translational modifications, essentially protein phosphorylation, which can affect both its distribution and functions. Thus, phosphorylation of MAP1B can modify cross-bridges with MTs *in vitro* (Sato-Yoshitake et al., 1989). Additionally, MAP1B phosphorylation patterns are modified during development (Diaz-Nido et al., 1990, 1991; Fischer and Romano-Clarke, 1990; Riederer et al., 1993; Ulloa et al., 1993; Black et al., 1994; Riederer, 1995). Subsequently, it was shown that MAP1B phosphorylation patterns found during brain development could be reproduced in cell cultures (Diaz-Nido et al., 1990; Black et al., 1994; Ulloa et al., 1994). The study of MAP1B phosphorylation has indicated the existence of at least two major modes of MAP1B phosphorylation (Avila et al., 1994). Mode I MAP1B phosphorylation induces an important upward shift in the electrophoretic mobility of the protein and may be catalyzed by proline-directed protein kinases (such as gsk3 and cdk5) (Garcia-Perez et al., 1998). By contrast, mode II MAP1B phosphorylation does not modify its electrophoretic mobility and is catalyzed by casein kinase II. The presence of mode II has been shown to be essential for proper neurite development (Diaz-Nido et al., 1988; Ulloa et al., 1993; Avila et al., 1994). Phosphorylation levels of MAP1B are controlled by an equilibrium between the kinases and protein phosphatases. Mode I phosphorylation is regulated by protein phosphatases PP2A and PP2B (Ulloa et al., 1993; Gong et al., 2000), while mode II is regulated by PP1 and PP2A (Ulloa et al., 1993). Both modes of phosphorylation are independently regulated during brain development and have different subcellular distributions in developing neurons. Mode I phosphorylation is mainly present in the distal part of the axon, whereas mode II is present in all subcellular domains of the neuron, including the axon and the somatodendritic compartments (Ulloa et al., 1994) [Fig. 1(A)]. The differential behavior of both modes of phosphorylation suggests that mode I can be used as a marker of axonal growth. An explanation for such a role was suggested by inhibiting gsk3, an enzyme responsible for mode I phosphorylation in neuronal cell cultures. Thus, physiological inhibition of Wnt7a gave rise to decreased axonal length, alterations in the growth cone shape and size, and, more importantly, to an imbalance in the content of stable and dynamic microtubules (Lucas et al., 1998). Similar results were obtained by pharmacologically inhibiting the kinase with lithium chloride (Goold et al., 1999). Both experiments clearly suggest that as well as its role in the stabilization of microtubules, MAP1B, and especially the mode I phosphorylated form, is important for the control of microtubule dynamics. Recently, it has been confirmed by culturing hippocampal and dorsal root ganglia neurons derived from a MAP1B hypomorph mouse line that, in the absence of MAP1B, there is a decrease of tyrosinated microtubules in the distal part of the axons, while there is a shift of detyrosinated forms towards the distal part of the axon and the growth cone (Gonzalez-Billault et al., 2001, 2002) [Fig. 1(B,C)]. Similar studies were conducted in order to inactivate tau protein and then analyze the effect of tau suppression on the dynamics of microtubules in growing axons of cultured neurons. However, opposite to MAP1B results, acute inactivation of tau protein in sympathetic neurons did not interfere with axonal extension. Moreover, neurons effectively depleted of tau were able to extend axons that resemble those of control cells, and the axons contain normal-appearing microtubule arrays with normal dynamic behavior (Tint et al., 1998). The fact that MAP1B loss-of-function can alter microtubule dynamics might have severe consequences for those processes that depend on the dynamic properties of microtubules. In an elegant experiment, it was shown that microscale chromophore-assisted laser inactivation of phosphorylated MAP1B altered growth cone turning behavior in cultures of neurons (Mack et al., 2000). In such a way, MAP1B phosphorylated in mode I may be responsible for the dynamic changes occurring to a neuron in response to extracellular environmental cues. In support of this, cdk5 has been shown to be redistributed towards the axonal tips of neuronal cells in the presence of the extracellular matrix component, laminin. This redistribution is paralleled by an increase in mode I MAP1B phosphorylation, suggesting that MAP1B has an active role linking extracellular cues with changes in cytoskeleton dynamics (Pigino et al., 1997). Additionally, this increase of MAP1B phosphorylated by PDPKs was reported to be dependent on a rise in the expression pattern of a cdk5 activator, namely p35 (Paglini et al., 1998). It has been recently shown that the participation of MAP1B phosphorylated in mode I in the signaling cascades is responsible for radial and tangential neural migration (Gonzalez-Billault et al., unpublished).

However, MAP1B can interact not only with microtubules but also with actin microfilaments mainly in the growth cone, a highly dynamic neuronal actin subcellular domain (Mansfield et al., 1991; Garcia Rocha and Avila, 1995). Previous studies have shown

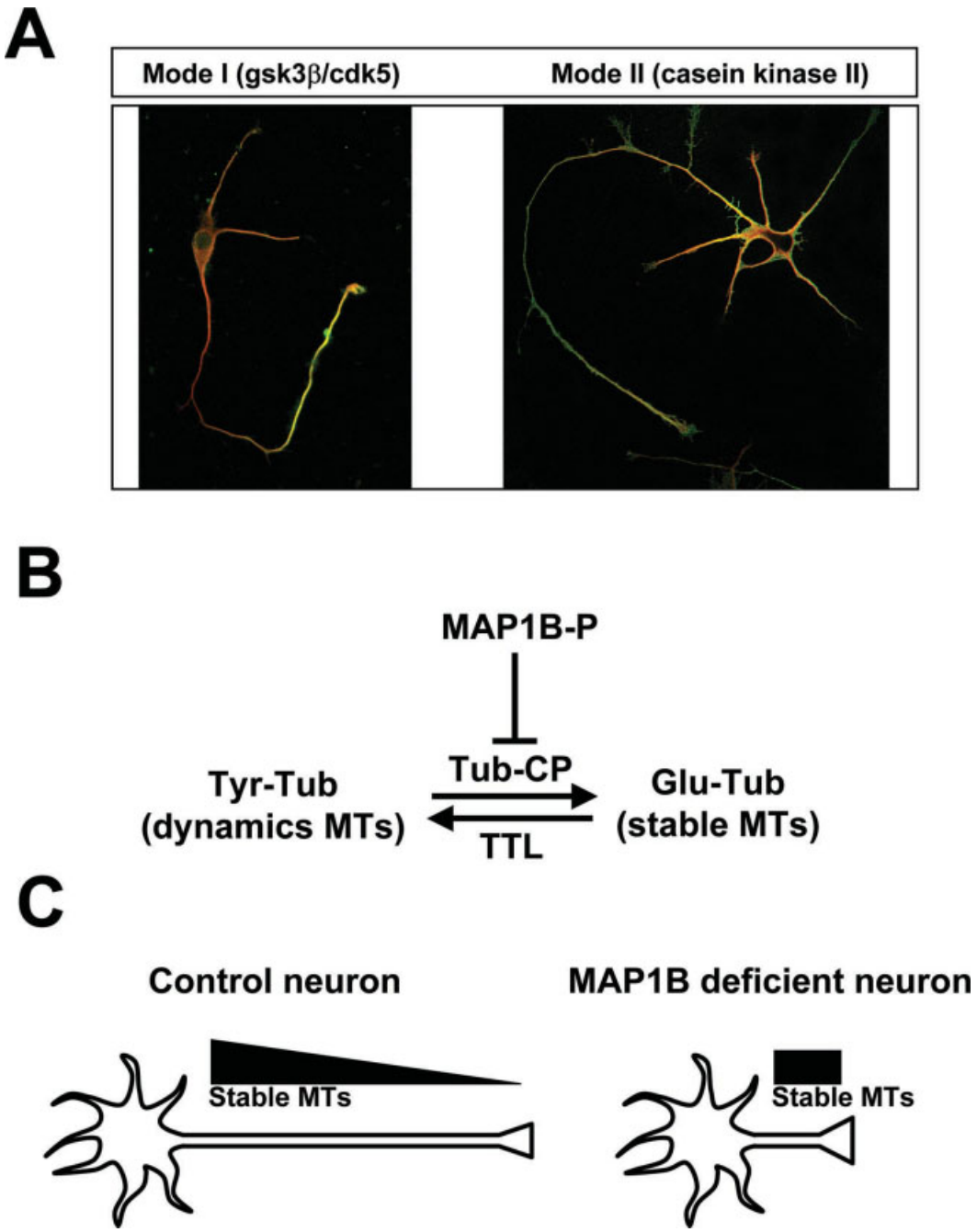

Figure 1 MAP1B phosphorylated in mode I may control the dynamic properties of neuronal microtubules. (A) Confocal micrograph of pyramidal hippocampal neurons in culture stained with an antibody that recognizes MAP1B phosphorylated in mode I (left panel) and an antibody that recognizes MAP1B phosphorylated in mode II (right panel). Observe the differential distribution of MAP1B. While MAP1B phosphorylated in mode I is mainly present in the distal part of axon, that phosphorylated in mode II is equally distributed in the axon and somatodendritic compartment. (B) MAP1B may contribute to the control of the transition between tyrosinated (dynamic) and detyrosinated (stable) microtubules in a mode-I-phosphorylation-dependent manner, by regulating either tubulin tyrosine ligase or tubulin carboxypeptidase. (C) MAP1B deficiency should thus be responsible for loss of the microtubule stability gradient, thereby contributing to the inhibition of axonal growth.

that MAP1B and, more specifically, the LC1 can bind to actin filaments *in vitro* (Pedrotti et al., 1996), and to stress fibers *in vivo* when it is ectopically expressed in non-neuronal cells (Togel et al., 1998). The fact that microtubules containing MAP1B penetrate into the peripheral domain of the growth cone and interact with actin filaments is evidence for the actin-binding properties of MAP1B (Bush et al., 1996). Consequently, the severe loss of function of MAP1B has been shown to alter actin dynamics in a still unknown manner, as shown by time-lapse video analyses of peripheral neurons lacking MAP1B (Gonzalez-Billault et al., 2002b). However, very recently it has been shown that neurons lacking MAP1B contain less active rac-GTP, and that the binding of Tiam1, a GEF protein controlling activity of rac1, to neuronal microtubules is also decreased (Rosso et al., unpublished observations).

These observations may turn out to be very important in light of previous studies showing that the growth of microtubules in fibroblasts can produce changes in the activity of GTPases such as rac1, leading to actin polymerization and formation of the lamellipodia (Waterman-Storer and Salmon, 1999; Waterman-Storer et al., 1999).

Similar to what has been described for fibroblasts, the growth of neuronal microtubules may increase actin assembly in the growth cones (Rochlin et al., 1999). Although the molecular mechanisms linking microtubule and actin microfilament dynamics have not yet been elucidated, it is tempting to suggest that MAP1B may participate in these events. In the case of microtubules, MAP1B could mediate the dynamics of MTs through direct interaction with other proteins controlling microtubule polymerization at the distal tip of the axon. The interaction of MAP1B with some known or as yet uncharacterized actin-associated proteins and the regulation of small GTPases through direct interaction or by modulating the action of GTPase-associated proteins (GEFs/GAPs) could explain the role of MAP1B in the control of actin dynamics.

ROLE OF MAP1B IN AXONOGENESIS

Several cell culture models using neuronlike cells, such as PC12, have been used to study the effect of the suppression of MAP1B. By using a specific antisense oligonucleotide, it was found that in the absence of MAP1B, there is no NGF-induced neurite outgrowth in PC12 cells, suggesting that this protein may be required for neuritogenesis (Brugg et al., 1993). Later on, it was indicated that MAP1B participation in process formation appears to be dependent on the substrate on which neurons are grown, being particularly prominent during laminin-enhanced axonal extension (DiTella et al., 1996). The generation of molecular genetic models of MAP1B inactivation has further contributed to explain its role in neurite formation. Thus, CNS and PNS neuronal cell cultures derived from a MAP1B hypomorphous mouse line gave raise to neurons bearing shorter axons than in wild-type controls. In these cases, axonogenesis was inhibited rather than impaired, suggesting that MAP1B itself is not a determinant of neurite polarity, and there is some compensational effect due to the presence of another structural MAP (Gonzalez-Billault et al., 2001, 2002). Compensation effects on MAP1B loss-of-function have indeed been described. Hence, hippocampal cells lacking MAP1B contained more MAP2 bound to their neuronal microtubules (Gonzalez-Billault et al., 2001). Furthermore, in recent years, two independent studies have shown that MAP1B and MAP2 may have some synergistic functions during laminin-enhanced neurite outgrowth. These studies used combined gene-targeting approaches to inactivate MAP1B and MAP2 (Teng et al., 2001) and a gene-trapping approach to inactivate the MAP1B gene in conjunction with MAP2 inhibition with antisense oligonucleotides (Gonzalez-Billault et al., 2002a). Some discrepancies between these two studies can be explained by differences in the severity of MAP1B inactivation in the two genetic ablation models (Gonzalez-Billault and Avila, 2000). As for tau and MAP1B redundancy, oligonucleotide inhibition of tau expression combined with MAP1B suppression in a hypomorph mutant line confirmed previous studies suggesting that axonal elongation may be dependent on tau or MAP1B according to the substrate on which neurons are plated (DiTella et al., 1996; Gonzalez-Billault et al., 2002a). However, it is clear that neuritogenesis is at least inhibited in the absence of MAP1B. Cell culture and mammalian molecular genetic approaches are not the unique demonstration of MAP1B function in neurite outgrowth. Molecular genetic ablation of futsch, a *Drosophila* MAP1B orthologue, indicated that the protein is essential for both dendritic and axonal development. Futsch protein expression was described as being negatively regulated in non-neuronal tissues, consistent with previously described observations for mammalian MAP1B. Furthermore, futsch is required for the proper establishment of neuronal cytoskeleton and regulates normal synaptic growth (Hummel et al., 2000; Roos et al., 2000).

MOLECULAR GENETIC MODELS

More recently, up to four different types of mice lacking MAP1B have been described. In one of these strains, mice that are homozygous for the *Map1b* gene die early during embryogenesis after blastocyst formation (Edelmann et al., 1996), raising the possibility that MAP1B is essential for neural development. In these mutant strains, heterozygous animals display severe neuronal defects that have not been reproduced in any of the heterozygous animals derived from the other three mutant models. Thus, the severity of the phenotype of heterozygous animals described by Edelman and colleagues is still a puzzling and unexplained issue.

In another strain, mutants reach adulthood and exhibit minor defects such as hypogenesis of the optic and sciatic nerve (Takei et al., 1997). The absence of lethality was explained as a function of discrete amounts of MAP1B expression in this hypomorphous mutant (Takei et al., 1997).

An intermediate phenotype was described by a third gene-targeting model. This mouse line was shown to be truly null for MAP1B expression. Homozygous lethality and abnormal development of nervous system were described (Meixner et al., 2000).

Finally, by using another molecular genetic approach, namely insertion of a gene trapping vector, another hypomorphous model was generated (Chowdhury et al., 1997; Gonzalez-Billault et al., 2000). In this model, MAP1B-deficient mice die perinatally and have gross abnormalities in the structure of their nervous system. The abnormalities were found in all laminated structures of brain, including the cerebral cortex, hippocampus, and cerebella, suggesting that MAP1B may play a novel role in neuronal migration and axonal guidance (Gonzalez-Billault et al., 2000; Meixner et al., 2000). These effects were confirmed in a genetic model designed to inactivate both tau and MAP1B genes (Takei et al., 2000). Although there are several known mechanisms that control neuronal migration and axonal guidance, the participation of MAP1B in these processes remains elusive.

MAP1B AND NEURAL REGENERATION

As mentioned above, mode-I-phosphorylated MAP1B is absent from many types of mature neurons, although it remains high in those brain regions where axonal growth persists into adulthood, such as olfactory axons, retina, and some territories in the PNS. Using these neural types, it was investigated whether mode-I- phosphorylated MAP1B plays a role during neuronal regeneration similar to that known to occur during neuron development. Several observations suggest that this could indeed be the case.

First, MAP1B was expressed during regeneration of mouse retinal explants in a way clearly reminiscent of that found during development (Bates et al., 1993). Second, regeneration of cat trochlear motoneurons proceeds with an increase of phosphorylated forms of MAP1B, while MAP2 is clearly diminished. These studies suggest that neuronal regeneration of CNS and PNS axons may occur in a similar manner (Book et al., 1996). Third, sciatic nerve regeneration also proceeds with an increase of phosphorylated MAP1B recognized by a mode I phosphorylation antibody (Bush et al., 1996a,b; Tonge et al., 1996; Soares et al., 2002) with no variation in the other variants of MAP1B phosphorylation (Ramon-Cueto and Avila, 1999). A comprehensive study dealing with the phosphorylation patterns of MAP1B in the adult rat nervous system demonstrated that, in addition to a differential subcellular localization for both modes of phosphorylation, the presence of the slow-migrating MAP1B isoforms in sites with a potential regeneration ability was important (Ramon-Cueto and Avila, 1997). Fourth, phosphorylated MAP1B was increased in the retina during regeneration of fish optic nerve, during both development and regeneration of retinal ganglion cells. These findings confirm that mode I phosphorylation is maintained after development in those regions with high neuronal plasticity (Vecino et al., 1996, 1998; Vecino and Avila, 2001).

The mechanism by which MAP1B affects axon regeneration is not clearly understood. Besides neuronal expression, higher levels of MAP1B can be found in oligodendrocytes, both in culture (Fischer et al., 1990; Vouyiouklis and Brophy, 1993; Ulloa et al., 1994) and *in situ* during active myelination (Wu et al., 2001). Additionally, MAP1B has been found to be highly expressed in Schwann cells during nerve regeneration (Ma et al., 1999). The phosphorylation pattern found in Schwann cells seems to be quite different from that found in neurons during regeneration (Ma et al., 1999; Ramon-Cueto and Avila, 1999). MAP1B is absent from GFAP-positive astrocytes (Fischer et al., 1990). Another glial cell type involved in neuronal regeneration is present in the olfactory bulb. Thus, ensheathing glia has been shown to promote axonal regeneration in the CNS *in vitro* and *in vivo* (Ramon-Cueto et al., 2000). The presence of MAP1B in these glial cells has been studied and the results suggest that ensheathing glia have a differential expression pattern of MAP1B isoforms from other

glial cells types such as astrocytes, oligodendrocytes, and Schwann cells (Gonzalez-Billault et al., unpublished observations).

Some MAP1B isoforms and related proteins (e.g., claustrin) are known to be associated with the cell membrane (Tanner et al., 2000). It has also been shown that MAP1B binds to myelin-associated glycoprotein (MAG), a protein expressed in myelinating oligodendrocytes and Schwann cells (Franzen et al., 2001). Interestingly, MAG binding to MAP1B depends on its phosphorylation state. Thus, it can bind only to mode-I-phosphorylated MAP1B, a mode that is specifically found in neurons, and not in the abovementioned glial cells (Franzen et al., 2001). It is not known whether this interaction has any consequence for the regulation of axon regeneration, although myelination problems have been described in at least two molecular genetic models with an inactive *Map1b* gene (Takei et al., 1997; Meixner et al., 1999). A possible explanation to consider is that the MAG-MAP1B interaction may provide a structural link between the periaxonal membrane of the myelin-forming cell and the axonal cytoskeleton, thereby contributing to the known capacity of myelin to affect structure and stability of myelinated axons.

MAP1B FUNCTION IN PATHOLOGICAL CONDITIONS

Although the participation of MAP1B in nervous system pathologies occurring during normal development or during genetic or sporadic neurodegenerative disorders has not been thoroughly analyzed, there is some evidence pointing to a role for MAP1B in such processes (Fig. 2). MAP1B phosphorylated in mode I, a mode that is prominent during development, has been found to decorate and colocalize with neurofibrillary tangles, a common hallmark for Alzheimer disease (Ulloa et al., 1994). Concordant with this fact, it has very recently been proposed that full length MAP1B could act as an effector of cell death in neurodegenerative disorders triggered by amyloid-β deposition, such as Alzheimer disease (Uchida, 2002).

Another role for MAP1B in pathological conditions is related to its interaction with gigaxonin, a protein responsible for giant axonal neuropathy (GAN), an autosomal recessive disorder characterized cytopathologically by cytoskeletal abnormality. The interaction between gigaxonin and MAP1B can be verified through its LC1 subunit. Transfected cells expressing both proteins enhanced the microtubule stability required for long-distance axonal transport (Ding et al., 2002). Interestingly, at least two different mutations identified in GAN patients (Bomont et al., 2000) led to loss of gigaxonin-MAP1B interaction (Ding et al., 2002).

Deregulation of MAP1B expression could also be related to the onset of pathological conditions. Hence, a decrease of MAP1B staining in the inner half of the molecular layer, especially in a portion where Purkinje cells are absent, has been shown to occur during human olivocerebellar degeneration (OCD). This reduction of MAP1B staining suggests that normal interaction of Purkinje cells and climbing fibers could be vulnerable to nervous system insults such as ischemia or hypoxia, and that retrograde transynaptic degeneration of the inferior olivary nuclei could then be induced (Ohyu and Takashima, 1998).

Finally, a *Drosophila* model for human Fragile X syndrome (dFXR) has revealed that futsch may be a target for dFXR translational regulation in the *Drosophila* nervous system. The evidence presented in this study clearly demonstrates that dFXR specifically binds to futsch mRNA, controlling futsch protein levels (Zhang et al., 2001). Although the interaction described here has not been shown to occur in humans, we might expect similar results to be found.

As mentioned above, the severe MAP1B deficiencies reported in the molecular genetic models produced aberrant organization in the CNS and PNS, associated with failures in neuronal migration and axonal guidance processes. Although the exact molecular contribution of MAP1B remains elusive, it is reasonable to suggest that MAP1B may participate in an as yet unknown human disorder related to neuronal migration defects.

CONCLUSION

In this article, we have summarized the evidence that implicates MAP1B participation in a wide variety of normal and pathological processes occurring during the development and aging of the nervous system. Although the exact molecular mechanisms for most of the processes described here have not yet been fully elucidated, it is clear that MAP1B function does have a principal role in those processes. Cumulative evidence derived from classic biochemistry experiments, histological analyses, cell-culture approaches, and molecular genetics in invertebrates and mammals suggests that by controlling microtubule and actin dynamics, MAP1B should be a critical point for axonal out-

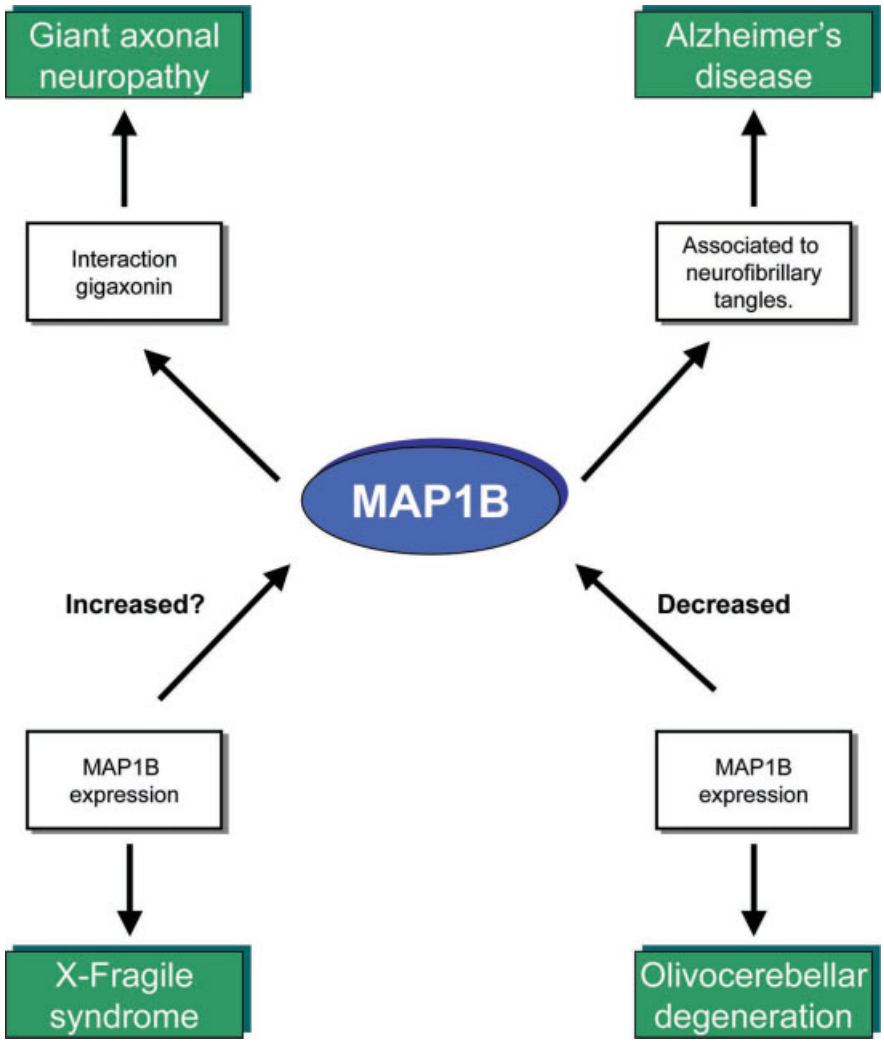

Figure 2 MAP1B in pathological conditions. Pathological processes where MAP1B could be involved through its integration with other proteins, or a change (increase or decrease) in its expression.

growth, neuronal migration, and axonal guidance. Additionally, nervous system dysfunction may also be related to changes in MAP1B expression and function. Therefore, it is tempting to speculate that by being the first MAP to be expressed in the development of the nervous system, MAP1B could control the settling and correct development of the nervous system. Lessons from molecular genetic models have taught us that functional redundancy between MAPs does indeed exist, although not in a complete fashion. We may look forward to the role of MAP1B in the aforementioned process being clarified in the near future, and we should expect that its being the first to be expressed during the development of the nervous system is not merely a stochastic event.

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