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The MAP1B Case: An Old MAP That is New Again

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ABSTRACT: The functions of microtubule-associated protein 1B (MAP1B) have historically been linked to the development of the nervous system, based on its very early expression in neurons and glial cells. Moreover, mice in which MAP1B is genetically inactivated have been used extensively to show its role in axonal elongation, neuronal migration, and axonal guidance. In the last few years, it has become apparent that MAP1B has other cellular and molecular functions that are not related to its microtubule-stabilizing properties in the embryonic and adult brain. In this review, we present a systematic review of the canonical and novel functions of MAP1B and propose that, in addition to regulating the polymerization of microtubule and actin microfilaments, MAP1B also acts as a signaling protein involved in normal physiology and pathological conditions in the nervous system. © 2014 Wiley Periodicals, Inc. Develop Neurobiol 74: 953–971, 2014

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The function of the nervous system relies on the ability of neurons to couple information received in the form of an electrochemical signal in one part of the cell, mainly dendrites, with a response in the axon, which communicates with effector cells, generating networks with a directional flux of information. This morphological asymmetry, or neuronal polarity, is generated and maintained by several factors (Arimura and Kaibuchi, 2007; Cheng and Poo, 2012). One of the main effectors involved in polarity acquisition and maintenance is the neuronal cytoskeleton and its associated proteins (Bradke and Dotti, 1999; Conde and Caceres, 2009).

MAPs (microtubule-associated proteins) are a group of proteins with either enzymatic or structural activity, which can interact with tubulin polymers. Members of this family include, among others, the well-characterized MAP2 and tau proteins (Dehmelt and Halpain, 2005) and also members of the MAP1 family, a class comprised of MAP1A, MAP1B, and MAP1S. All these proteins, to a greater or lesser extent, have the ability to bind and stabilize microtubules (Halpain and Dehmelt, 2006). MAP1 proteins are differentially expressed, both with respect to time and cell type. Here, we focus on MAP1B, a developmentally regulated protein that is able to interact with both microtubules and actin microfilaments (Gonzalez-Billault et al., 2004). We will discuss its expression pattern and function in nascent and adult neurons, the molecular mechanisms regulating its expression and will explore novel functions either described or inferred from MAP1B interactomic analysis.

MAP1B STRUCTURE, EXPRESSION PATTERNS IN THE BRAIN AND OTHER CELL TYPES, AND CANONICAL FUNCTIONS

Structure

MAP1B was discovered in the mid-1980s by different groups, which named it MAP1.2, MAP1(x),

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MAP5, and MAP1B (Asai et al., 1985; Bloom et al., 1985; Calvert and Anderton, 1985; Riederer et al., 1986); eventually the last name prevailed. MAP1B consists of 2459 amino acids (according to the rat sequence), with a predicted molecular mass of 255.534 kDa but with an apparent size of 320 kDa in SDS-polyacrylamide gels (Noble et al., 1989). It exists in a nonstructured filamentous shape, with an average length of 186 ± 38 nm and a spherical portion at one end (Sato-Yoshitake et al., 1989). It is first synthesized and then is proteolytically cleaved to generate a heavy chain (HC) from the N-terminal end until about residue 2210 and a light chain (LC1), which begins at the cleavage site and includes the C-terminal end of the original protein (Hammarback et al., 1991), similarly, MAP1A is processed to give rise to MAP1A-LC2 (Langkopf et al., 1992). Although the exact MAP1B-LC1 cleavage site has not been mapped yet, studies on *Drosophila melanogaster* Futsch, the fly homolog of MAP1 (Hummel et al., 2000; Roos et al., 2000), show a conserved proteolytic site, which corresponds to the peptide bond after rat Gln2197 (Zou et al., 2008). Additionally, the sequence from amino acids 508 to 1022 enhances processing efficiency (Togel et al., 1999). MAP1B-HC can bind both LC1 and LC2 (Schoenfeld et al., 1989) and also LC3, another LC that copurifies with MAPs (Kuznetsov and Gelfand, 1987) but is expressed from a different gene (Mann and Hammarback, 1994). LC1/LC2 heterodimers have also been detected (Noiges et al., 2006) and may regulate MAP1B features during the transition between developing and mature neurons.

MAP1B has a microtubule-binding domain (MBD) and an actin-binding domain (ABD), both of which are in the HC (Noble et al., 1989; Cueille et al., 2007a) and in LC1 (Zauner et al., 1992; Togel et al., 1998), indicating that MAP1B might act as a linker between microtubules and microfilaments, as has been described for microtubule cross bridges (Sato-Yoshitake et al., 1989). Other MAP1B functional domains have been proposed, including a putative microtubule assembly helping domain, which could increase the microtubule assembly rate of the MBD (Bondallaz et al., 2006); a sequence showing homology with the MAP1S mitochondrial aggregation and genome destruction (MAGD) domain in the LC1 (Liu et al., 2005); a putative third MBD between the first 126 amino acids, which may subtly interact with microtubules (Gomi and Uchida, 2012) and a noncanonical transmembrane α-helix domain (Muramoto et al., 1994; Tanner et al., 2000). The MAP1B structural features are depicted in Figure 1(B).

Expression Patterns

MAP1B expression is developmentally regulated, being the first MAP expressed in the nervous system (Tucker and Matus, 1988). Its expression has been observed even in neuronal progenitor cells before the last mitotic division (Cheng et al., 1999). MAP1B is expressed at high levels during development and at low levels during adulthood. The decrease in the amount of MAP1B starts at 2 weeks postnatally in rodents (Calvert and Anderton, 1985; Safaei and Fischer, 1989; Schoenfeld et al., 1989; Garner et al., 1990). Its expression does, however, remain high in areas of the adult brain that retain plasticity, such as the olfactory bulb, olfactory epithelium, and the hippocampus (Safaei and Fischer, 1989; Schoenfeld et al., 1989; Tucker et al., 1989). Indeed, MAP1B is expressed in areas with structural plasticity during adulthood (Nothias et al., 1996). MAP1B phosphorylation by proline-directed protein kinases (PDPKs), known as Mode I phosphorylation, also decreases with development (Fischer and Romano-Clarke, 1990), whereas the phosphorylation by Casein Kinase II, known as Mode II phosphorylation, remains unaltered (Ulloa et al., 1993a).

MAP1B is mainly expressed in neurons, although it has also been detected in oligodendrocytes, astrocytes, and their progenitor cells (Fischer and Romano-Clarke, 1990; Ulloa et al., 1994b). It is not phosphorylated in astrocytes, whereas oligodendrocytes express MAP1B with Mode II phosphorylation. In the peripheral nervous system, MAP1B is highly expressed in sensory and motor neurons, as well as in the somatic compartment of neurons of the dorsal root ganglion (Ma et al., 1997).

At the subcellular level, MAP1B is localized in neuronal soma, dendrites, and axons; however, both total and Mode I-phosphorylated MAP1B are enriched toward the distal part of the axon (Fischer and Romano-Clarke, 1991; Black et al., 1994) and the axonal growth cone (Mansfield et al., 1991; Garcia Rocha and Avila, 1995). Mode II-phosphorylated MAP1B can be found both in the somatodendritic and axonal compartments during development (Ulloa et al., 1994a) and is enriched in the former domain during adulthood (Moreno et al., 1999). MAP1B is present in postsynaptic terminals and is commonly retrieved in proteomics analyses of postsynaptic densities (Kawakami et al., 2003).

Canonical Functions

The prevailing view regarding MAP1B functions is associated with the fact that it copurifies with

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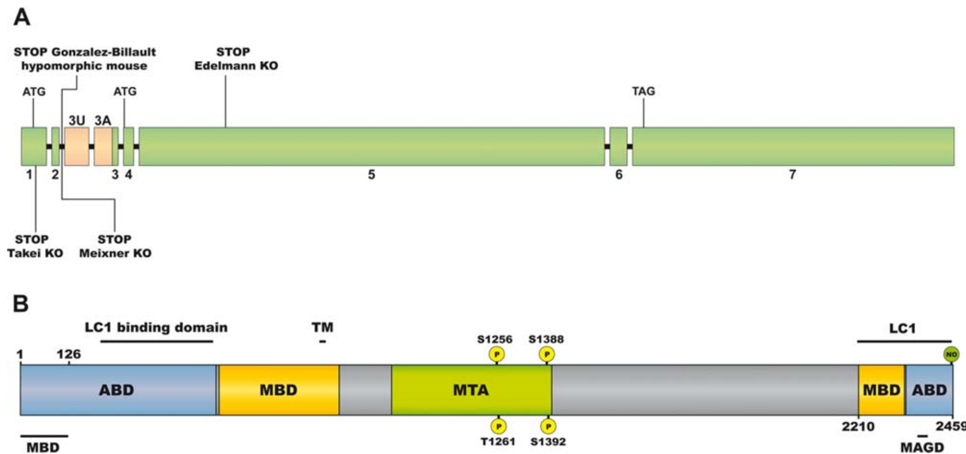

Figure 1 Rat MAP1B genomic and structural organization. MAP1B gene is depicted in (A), with codifying exons in green and alternative exons in orange (introns are not to scale). The first ATG codon represents translation start of the canonical protein, whereas the second ATG defines the initiation of alternative spliced transcripts if they were translated. The figure also indicates the sites in which each MAP1B mutant mice exhibit a stop codon. Rat MAP1B protein features are described in (B), showing a microtubule-binding domain (MBD) in the HC (523–843) and other in the LC1 (2210–2331). There are two actin-binding domains (ABD) in HC and LC1. The LC1 binding domain (211–508) in the HC is also represented. A putative microtubule assembly helping site or MTA (976–1401) and a transmembrane domain (789–805) have been proposed in the HC. New evidence suggests the existence of another MBD in the first 126 aminoacids of the HC, and a sequence inside LC1 related to mitochondrial aggregation and genome destruction (MAGD), between aminoacids 2367–2391. Finally, phosphorylation sites with known kinases and the S-nitrosylation site are presented. The numeration of MAP1B aminoacids depicted here has been adapted to the rat sequence. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

microtubules and, similar to other MAPs, promotes their polymerization. Its biological properties have also been extensively studied both *in vitro* and in genetic mouse models in which MAP1B is inactivated (Gonzalez-Billault and Avila, 2000). MAP1B polymerizes tubulin *in vitro* and *in vivo*, being more efficient than MAP2 in microtubule elongation (Takemura et al., 1992; Pedrotti and Islam, 1995). However, MAP1B is less efficient than other MAPs in the reduction of the critical concentration for tubulin polymerization and in the decrease of the microtubule disassembly rate, and is unable to suppress microtubule-dynamic instability (Vandecandelaere et al., 1996). Indeed, other MAPs such as MAP2 and tau are more efficient microtubule-polymerizing factors than MAP1B (Takemura et al., 1992; Pedrotti and Islam, 1995).

It has been shown that MAP1B overexpression does not induce microtubule bundles in COS cells, as tau and MAP2 does (Takemura et al., 1992). However, LC1 overexpression in PtK2 cells generates wavy bundles, similar to those observed in neuronal growth cones (Noiges et al., 2002), suggesting that the MBD present in the LC1 subunit could have different properties compared to the MBD present in MAP1B HC. Furthermore, JNK1 or MAP1B knockdown in neuroblastoma cells interfere with microtubules bundle formation during neuritogenesis (Feltrin et al., 2012). However, JNK1 can also modify MAP2, a MAP linked to microtubule bundles formation (Feltrin et al., 2012). Therefore, it is not completely clear whether MAP1B roles on microtubule bundles formation could be a cell specific phenotype. Further research is needed to clarify this point.

Recent evidence suggests that MAP1B preferably associates to tyrosinated/dynamic microtubules, rather than detyrosinated/stable microtubules (Tymanskyj et al., 2012), helping to maintain a pool of dynamic microtubules (Utreras et al., 2008; Tortosa et al., 2013). This is also reinforced by the fact that in a MAP1B loss-of-function model, levels of tyrosinated microtubules are decreased (Gonzalez-Billault et al., 2001). This apparent inefficiency to stabilize microtubules and the novel proposed roles as microtubule-dynamizing protein, may suggest that MAP1B function differs from other MAPs (Tymanskyj et al., 2012). Such behavior could be of great relevance for several biological processes, such as growth cone

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pathfinding and axon elongation (Lowery and Van Vactor, 2009).

Four MAP1B knockout (KO) mice have been generated [Fig. 1(A)], with notorious differences in their phenotypes. The first mouse model, which lacks full-length MAP1B, was generated by inserting a stop codon at amino acid 571. Homozygous mice die at embryonic day 8.5, and heterozygous mice have severe body weight loss, reduction in the size of the retina and the cerebellum, ataxia, and spastic tremors in the posterior limbs (Edelmann et al., 1996). These abnormalities were hypothetically attributed to a dominant-negative effect of the N-terminal 64-kDa fragment. The second mutant mouse model was generated with a stop codon inserted after amino acid 11 and showed just a mild reduction in the axonal myelination rate (Takei et al., 1997). This subtle phenotype was explained by the fact that the mutant mice expressed MAP1B splicing variants, which could rescue some of the alterations related to the absence of full-length MAP1B. The third mutant mouse model was generated using the gene trapping strategy, which was used to introduce a stop codon after amino acid 95. Those animals express approximately 5% of the normal protein levels, as some alternative splicing can still occur; they, therefore, represent a hypomorph model. These mutant mice present postnatal lethality; enlargement of the brain ventricles; absence of the corpus callosum; malformations of commissures; and abnormalities in the laminated structure of the cortex, cerebellum, and hippocampus (Gonzalez-Billault et al., 2000). The last KO mouse carries a stop codon after amino acid 96, and the most striking phenotype found in this mouse line showed agenesis of the corpus callosum, delocalized myelination of axons, reduced diameter in peripheral axons, reduced thickness of myelin sheaths, and a decrease in the nerve conduction velocity of some motor neurons (Meixner et al., 2000; Table 1).

MAP1B was implicated early on in the molecular mechanism involved in axonal elongation, as its knockdown reduces neurite and axonal length in cultured PC12 cells and neurons, respectively (Brugg et al., 1993; DiTella et al., 1996). Additionally, MAP1B deficiency reduces DRG axonogenesis (Gonzalez-Billault et al., 2002b). The axon elongation defects observed in MAP1B KO mice are even more severe when MAP2 or tau expression levels are knocked down (Gonzalez-Billault et al., 2002a). Along with decreased axonal elongation, MAP1B KO mice also exhibit lower levels of tyrosinated tubulin and an increase in detyrosinated microtubules (Gonzalez-Billault et al., 2001), decreased acetylated tubulin in the axonal shaft and increased axonal branching (Bouquet et al., 2004). Growth cone turning is also regulated by MAP1B, as Mode I-phosphorylated MAP1B depletion by microCALI in one side of the growth cone induces retraction of the lamellipodia in the affected region, with the consequent turning of the structure in the opposite direction (Mack et al., 2000). Another function associated with MAP1B is the coupling between the collapse of microfilaments and microtubules in the axonal growth cone, which is induced by repulsion cues (Bouquet et al., 2007) and the negative regulation of mitochondrial retrograde transport in the axon (Jimenez-Mateos et al., 2006). Finally, alterations in neuronal migration and axonal guidance have been reported, linking the signaling of Netrin-1 and Reelin upstream to MAP1B by way of Mode I phosphorylation (Del Rio et al., 2004; Gonzalez-Billault et al., 2005).

NEW CONCEPTS IN MAP1B EXPRESSION, REGULATION, AND FUNCTION

Regulation of Transcriptional Control

map1b includes two promoters, which confer its neuronal specificity (Liu and Fischer, 1989). MAP1B is highly expressed under the control of its upstream promoter during development, whereas the second promoter accounts for MAP1B expression in the adult brain. The homeoprotein transcription factors Engrailed and Hoxa5 regulate MAP1B expression (Montesinos et al., 2001), with the former inhibiting MAP1B expression in cerebellar neurons and in the neuronal tube of chick embryos and activating *map1b* transcription in CHP-100 human neuroblastoma cells (Montesinos et al., 2001). Hoxa5 also promotes MAP1B expression in neuroblastoma cells, although its role in neurons has not been determined. The activity of homeoprotein transcription factors is regulated by their expression levels, their combinatorial functions and by the presence of cofactors that bind them. For example, the transcriptional factor Foxa2 both binds Engrailed and competes with it, so in a model in which high amounts of Engrailed promotes MAP1B expression, as in the N2a neuroblastoma cell line (Foucher et al., 2003), Foxa2 represses Engrailed-driven MAP1B expression. In contrast, Foxa2 expression in the absence of Engrailed activates *map1b* transcription in the same model (Foucher et al., 2003).

The KO mice for the transcriptional factor COUP TFI have reduced MAP1B and MAP2 expression levels and also altered commissural axons, as well as abnormal axonal branching (Armentano et al., 2006),

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Table 1 MAP1B/Futsch Animal Models

Animal Model	MAPlB/Futsch Expression	Phenotype	References
Edelmann KO mice	Absent	Embryonic lethality at E8,5, heterozygous mice present severe body weight loss, smaller retina size and motor system abnormalities	Edelmann et al., 1996
Takei KO mice	Splicing variants are still present	Slight reduction in the axonal myelination rate	Takei et al., 1997
Gonzalez-Billault hypomorphic mice	About 5% of WT expression levels are still retained	Postnatal lethality, enlargement of brain ventricles, agenesis of the corpus callosum, abnormalities in commisures and in laminated structures of the brain, due to neuronal migration alterations	Gonzalez-Billault et al., 2000
Meixner KO mice	Absent	Agenesis of the corpus callosum, delocalized myelinated fibers due to misguided axons, decreased number of large myelinated axons in peripheral nerves and reduced thickness of some myelin sheaths	Meixner et al., 2000
Futsch^{P158} fly	Undetectable	Lethal mutation, dendrites and axons development is severely affected in embryos, as well as the motoneuron innervations pattern	Hummel et al., 2000
Futsch ^{K68} fly	Undetectable	Fewer and larger synaptic boutons in *Drosophila* NMJ, microtubule loop formation in boutons is lost, showing a diffuse tubulin staining	Hummel et al., 2000, Roos et al., 2000
Futsch^{N94} fly	About 20% of WT expression is still detected	Phenotype similar to futsch^{K68}, however the remaining expressed futsch is misslocalized within the nerve terminals	Hummel et al., 2000, Roos et al., 2000

Genetic models to inactivate MAP1B function in mice and fruit fly and their phenotypes. In addition to futsch^{P158}, futsch^{K68}, and futsch^{N94}, it also exist futsch^{M455} and futsch^{P28}, with futsch expression levels similar to futsch^{N94}. For a comprehensive description on futsch loss-of-function models, please see Hummel et al., 2000.

suggesting that COUP TFI could promote MAP1B expression. In mice, the knockdown of Bcl11A/CTIP1, a transcriptional factor that is functionally coupled to COUP TFI, also results in lower levels of MAP1B expression, in conjunction with increased axonal branching and a higher proportion of multiaxonic neurons (Kuo et al., 2009). It is likely that both transcription factors promote MAP1B expression, although it is not yet known if they act directly or indirectly on the *map1b* promoter. In the case of either mechanism, this regulation is downstream of NMDA receptor activation, as glutamate treatment reduces the amount of Bcl11A and MAP1B in culture (Kuo et al., 2010).

Post-Transcriptional Regulation of MAP1B

MAP1B has two exons that can be alternatively spliced, which are depicted in Figure 1(A). They are located between exons 2 and 3 and are called 3U and 3A. Exon 3U is upstream of 3A, and the latter is contiguous with exon 3. About 10% of MAP1B transcripts correspond to alternatively spliced variants that lack the first two exons and start at either 3U or 3A. However, the first start codon downstream of the alternative exons is located in exon 4, implying that if the alternatively spliced mRNA was translated, it would produce a protein that starts at amino acid 127 (Kutschera et al., 1998). Although it is tempting to speculate that some of the differences among genetic models in which MAP1B has been inactivated could be linked to the presence of uneven levels of shorter transcripts, the fact that MAP1B N-terminal truncated forms still could not be detected suggests that shorter alternatively spliced variants of MAP1B may not have physiological roles.

MAP1B protein expression is controlled by several RNA-binding proteins that associate with MAP1B mRNA and regulate its translation. QKI binds the 3′

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UTR of MAP1B mRNA in oligodendrocytes, which promotes MAP1B translation (Zhao et al., 2006). Staufen2 regulates MAP1B expression in neurons during metabotropic glutamate receptor (mGluR)-dependent long-term depression (LTD). Staufen2 knockdown reduces MAP1B levels in dendrites, releasing MAP1B mRNA from the RNA granules where it is translated (Lebeau et al., 2011). Fragile X mental retardation protein (FMRP) associates with the 5′ UTR of MAP1B mRNA and regulates its transport and expression (Darnell et al., 2001); this topic will be discussed more extensively below. Finally, Caprin1 is a FMRP-interacting protein that binds MAP1B mRNA independently from FMRP and exhibits a translation-repressing activity (El Fatimy et al., 2012).

MAP1B can also be regulated by microRNAs, either in the axon or dendrites. Interestingly, two different microRNAs exert subcellular-specific regulation of MAP1B. miR-9 loss-of-function increases axonal branching and reduces axonal length. This microRNA interferes with MAP1B translation in the axon and shows a biphasic behavior in response to Brain-derived neurotrophic factor (BDNF). Whereas acute doses of BDNF downregulate miR-9 levels, leading to an increase in MAP1B expression and axonal outgrowth, long-term BDNF administration increases miR-9 expression, with a subsequent decrease in MAP1B expression and induction of axonal branching (Dajas-Bailador et al., 2012). In dendrites, miR-146a-5p represses MAP1B mRNA translation, leading to reduced MAP1B-mediated α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) endocytosis (Chen and Shen, 2013). On group I mGluR (mGluR1 and mGluR5) activation by (S)-3,5-Dihydroxyphenylglycine (DHPG), miR146a-5p is reduced, and the levels of MAP1B are thus increased, allowing the induction of LTD. The local microRNA expression control on MAP1B, both in axon and dendrites, is depicted in Figure 2(C).

Post-Translational Modifications

MAP1B protein can be post-translationally modified at different sites. Some lines of evidence suggest that MAP1B may associate with membranes directly or through either transmembrane proteins or the cortical actin cytoskeleton. In this regard, MAP1B associates with vesicles formed by acidic phospholipids, such as phosphatidylserine, phosphatidylinositol, and phosphatidic acid, and also with vesicles formed by phosphatidylcholine and phosphatidylserine in a ratio that emulates biological membranes (Yamauchi et al., 1997). This interaction decreases the association of MAP1B with microtubules, as the domain involved is located within the C-terminal part of the MBD (rat sequence, 738–786). This suggests a competition between microtubules and phospholipids for binding to MAP1B.

Another post-translational modification of MAP1B is S-nitrosylation. The LC1 C-terminal domain interacts with the PDZ domain of neuronal nitric oxide synthase, and this mediates LC1 S-nitrosylation at Cys2455, preventing an autoinhibitory interaction between the N- and C-terminal domains of LC1 (Stroissnigg et al., 2007) and potentiating LC1 binding to microtubules. At the cellular level, the calcium ionophore calcimycin induces S-nitrosylation of LC1, which leads to retraction of neurites; however, dorsal root ganglia cultures from MAP1B KO mice do not show this neuritic collapse, which suggests that MAP1B is necessary for axonal retraction induced by nitric oxide, through LC1 S-nitrosylation and increased MAP1B-LC1/microtubule interactions (Stroissnigg et al., 2007). The mitochondrial E3-ubiquitin ligase MITOL specifically ubiquitinates mitochondria-associated S-nitrosylated LC1, avoiding LC1-induced mitochondrial aggregation (Yonashiro et al., 2012).

Phosphorylation is the main post-translational modification of MAP1B and has been, by far, the most widely studied modification of this protein. MAP1B was initially described as being phosphorylated in differentiated N2a cells. This phosphorylation was inhibited by heparin, a casein kinase II inhibitor (Diaz-Nido et al., 1988). This type of MAP1B phosphorylation is referred to as Mode II phosphorylation and induces a twofold increase in the binding of MAP1B to microtubules or tubulin oligomers (Diaz-Nido et al., 1988). If casein kinase II phosphorylation is abolished, MAP1B is released from the microtubules (Ulloa et al., 1993b), suggesting that this phosphorylation event is important for maintaining a pool of MAP1B-stabilized microtubules. The site(s) of casein kinase II-dependent phosphorylation on MAP1B are unknown; however, antibody Ab125 recognizes epitopes located in the N-terminal half of MAP1B.

In addition to Mode II phosphorylation, MAP1B can be phosphorylated in a PDPK-dependent manner (Mode I phosphorylation; Ulloa et al., 1993a). Studies in differentiated SH-SY5Y cells showed that Mode I phosphorylation is more efficiently inhibited by Li^{+}, which targets GSK3, whereas in proliferating neuroblastoma cells, it may be more dependent on cyclin-dependent kinases (CDKs; Garcia-Perez et al., 1998). Mode I-phosphorylated MAP1B is detected

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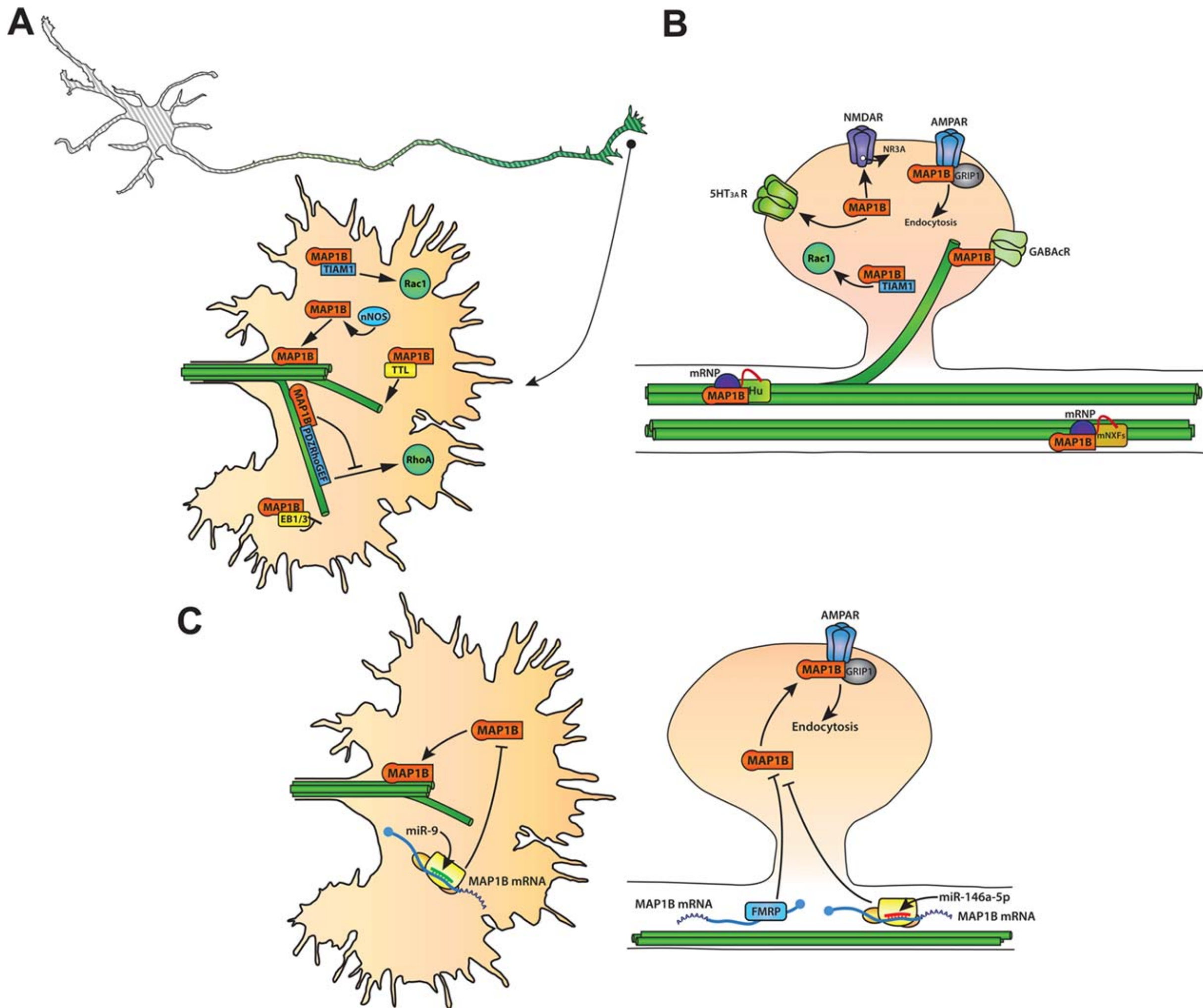

Figure 2 MAP1B functions according to its subcellular localization. Mode I phosphorylation in the developing neuron in (A) is represented by the green gradient toward the distal part of the axon, whereas Mode II phosphorylation is depicted as gray dashed lines. The inset at the growth cone shows some MAP1B functions related to axonal elongation, as the control of microtubule dynamics and GTPase activities (extended in Table 2). Some MAP1B roles during adulthood are presented in (B), mainly the regulation of the activity or distribution of neurotransmitter receptors, spine structure, and the transport of mRNP. The regulation of MAP1B translation in axon and dendrites is depicted in (C), showing MAP1B translation inhibition by microRNAs and by FMRP. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

with the antibody SMI-31, which recognizes phosphor-epitopes between amino acids 1244 and 1264 and in a region located between amino acids 1836 and 2076 (Johnstone et al., 1997).

GSK3β phosphorylates MAP1B both *in vitro* and *in vivo* at Ser1260 and Ser1265 (Lucas et al., 1998; Trivedi et al., 2005). MAP1B phosphorylated at these sites binds to tyrosinated microtubules and maintains a pool of dynamically unstable microtubules (Goold et al., 1999). Wnt7a inhibits GSK3β phosphorylation on MAP1B, increasing stable microtubules, growth cone surface area, and axonal branching (Lucas et al., 1998). Conversely, NGF promotes GSK3β phosphorylation on MAP1B, through the TrkA receptor (Goold and Gordon-Weeks, 2003) and the ERK1/2 pathway (Goold and Gordon-Weeks, 2005), although this regulation seems to be indirect, as ERK1/2 does not phosphorylate GSK3β. Ser1388 can also be phosphorylated by GSK3β, but this site requires the phosphorylation of a priming site by DYRK1A at Ser1392 (Scales et al., 2009). Similarly to Ser1260 and Ser1265, Ser 1388 phosphorylation also maintains a

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Table 2 MAP1B Interactome in Neurons and Nervous System Derived Cells Lines

Interactor	Physiological Effect	References
Channels, receptors and related proteins		
GABAcR ρ1 and ρ2	MAP1B reduces GABAcR sensitivity.	Hanley et al., 1999, Billups et al., 2000
GRIP1	GRIP1 participates in MAPlB-dependent AMPAR endocytosis.	Seog, 2004, Davidkova and Carroll 2007
Stargazin	Not determined, however LC2 may regulate GluR2/Stargazin traffic.	Ives et al., 2004
5-HT_{3A} receptor	LC1 reduces 5-HT_{3A} surface expression, promoting its desensitization.	Sun et al., 2008
5-HT_6 receptor	LC1 increases 5-HT_6 surface expression and reduces its endocytosis.	Kim et al., 2014
mGluR 4, 6, 7a, 7b, 8a, 8b	Not determinted.	Moritz et al., 2009
NR3A	MAP1B KO mice present an increased NR3A/NR1 ratio in NMDAR.	Eriksson et al., 2010
ee3	ee3 is not detected at the protein level in MAP1B KO mice.	Maurer et al., 2004
Cav2.2 channel	LC1 promotes Cav2.2 proteasomal degradation.	Gandini et al., in press
Nav 1.6	MAP1B increases Nav 1.6 current density in about 50%.	O'Brien et al., 2012
Apoptosis/Autophagy		
MITOL	MITOL induces mitochondria-associated LC1 ubiquitination.	Yonashiro et al., 2012
DJ-1	Dj-1 inhibits ER stress-induced apoptosis by LC1 overexpression.	Wang et al., 2011
p53	MAP1B inhibits p53 transcriptional activity.	Lee et al., 2008
Nbr1	LC1 links Nbrl positive vesicles to MT cytoskeleton.	Marchbank et al., 2012
Neurodegeneration linked proteins		
Aβ 1–42	Not determined	Gevorkian et al., 2008
α-synuclein	MAP1B is found in Lewy bodies.	Jensen et al., 2000
Gigaxonin	Gigaxonin induces LC1 degradation, allowing cell survival.	Ding et al., 2002, Allen et al., 2005
LANP	LANP enhances neurite growth in cells overexpressing FL-MAP1B.	Opal et al., 2003
RNA-binding proteins		
mNXFs	mNXF/MAPlB complex participates in mRNA transport.	Tretyakova et al., 2005
HuB, HuC, HuD	LCl/Hu targets mRNA granules toward MT cytoskeleton.	Fujiwara et al., 2011
Transmembrane proteins		
MAG	Not determined.	Franzen et al., 2001
Kidins220/ARMS	Kidins220 knock-downreduces MAP1B Mode I phophorylation.	Higuero et al., 2010
Cytoskeleton related proteins		
Dystonin-a2	Regulation of Golgi organization and MT dynamics.	Bhanot et al., 2011, Ryan et al., 2012
TTL	MAP1B enhances TTL activity and tyrosinated MT.	Utreras et al., 2008
LIS1	MAP1B regulates LIS1 affinity for MT and dynein.	Jiménez-Mateos et al., 2005b
EB1/3	EB1/3 is sequestered in the cytoplasm by MAP1B HC.	Tortosa et al., 2013
Signaling proteins		
EPAC1	LC1 Increases EPAC1 activity on Raplb.	Borland et al., 2006

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Table 2 ***Continued***

Interactor	Physiological Effect	References
PDZRhoGEF	Anchoring of PDZRhoGEF to MT by LC1 inhibits RhoA activity.	Longhurst et al., 2006
STEF	Not determined.	Takefuji et al., 2007
TIAM1	Enhanced TIAM1 activity on Racl, by LC1.	Montenegro-Venegas et al., 2010
GEF-H1	Not determined.	Tortosa et al., 2011
Osteopontin	Not determined.	Long et al., 2012
GAPDH	Not determined.	Cueille et al., 2007b
nNOS	LC1 S-nitrosylation.	Stroissnigg et al., 2007
αl-syntrophin	Not determined.	Fuhrmann-Stroissnigg et al., 2012

MAP1B interactors are presented. A short description above the relevance of the interaction was added. Some proteins described like MAP1B interactors in non-neuronal models were not included (Pes1, DAPK-1, and RASSF1A).

pool of dynamic microtubules, despite the fact that MAP1B phosphorylated at Ser1260 and S1265 is concentrated toward the distal part of the axon and Ser1388-phosphorylated MAP1B is evenly distributed.

As noted earlier, MAP1B can also be phosphorylated by CDKs. Knockdown of either Cdk5 or p35 reduces axonal length and laminin-induced MAP1B Mode I phosphorylation, as well as its binding to microtubules (Pigino et al., 1997; Paglini et al., 1998); however, the Cdk5 inhibitor roscovitine was not able to modify the phosphorylation recognized by SMI-31 (Kawauchi et al., 2005). It is interesting that this type of phosphorylation was also unchanged in cells overexpressing Cdk5/p35, however, Cdk5/p25 did lead to an increase in Mode I-phosphorylated MAP1B (Kawauchi et al., 2005). A potential explanation could be that Cdk5 phosphorylates MAP1B only in a pathological context, when the kinase is activated by p25, the proteolytic fragment of p35.

Mitogen-activated protein kinases (MAPKs) have also been linked to MAP1B phosphorylation; in fact, pharmacological inhibition of the MAPK JNK reduces the amount of Mode I-phosphorylated MAP1B in cultured cortical neurons, as recognized by SMI-31 (Kawauchi et al., 2003). Consistently, KO of JNK1 and JNK2 leads to a decrease in the amount of phosphorylated MAP1B (Chang et al., 2003; Barnat et al., 2010). Similarly, it has been proposed that JNK1/2 phosphorylation on MAP1B could be regulated by MKK7 (Feltrin et al., 2012).

NGF activates nemo-like kinase (NLK) in PC12 cells, inducing MAP1B phosphorylation in a bimodal manner. First, a peak in MAP1B phosphorylation (as detected with SMI-31) occurs 10–30 min after NGF addition, which is linked to NLK activation. In contrast, NGF also leads to long-term MAP1B phosphorylation (i.e., 3 days after NGF exposure) that is dependent on NLK and GSK3β (Ishitani et al., 2009).

Many different kinases are able to phosphorylate MAP1B in regions recognized by SMI-31, suggesting that these epitopes seem to be promiscuous and raising the question of how the regulation of these kinases could be coordinated to produce the classical proximo-distal SMI-31 axonal gradient that is present in cultured neurons. In addition, it is very likely that other kinases may phosphorylate MAP1B. Synaptic phosphoproteomic analysis and mass spectrum assays have identified several new MAP1B phosphorylation sites (33 and 28 new sites identified, respectively), showing that MAP1B is a highly phosphorylated protein (Collins et al., 2005; Scales et al., 2009). Based on bioinformatic analyses, these novel phosphorylation sites have been predicted to be linked to the activity of several protein kinases. It would not be

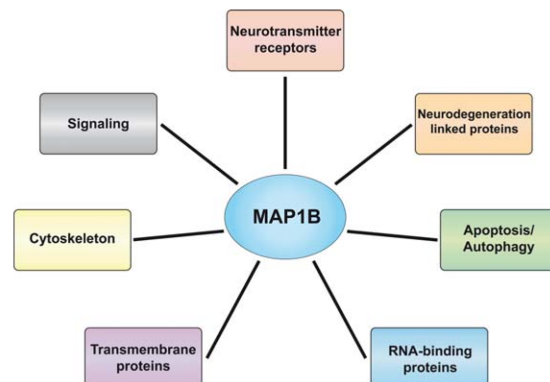

Figure 3 Classification of MAP1B interactomics. The different MAP1B interactors were grouped into seven different categories, according their cellular function. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

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surprising if novel modes of MAP1B phosphorylation were discovered in the future. We envision that these putative novel phosphorylation modes could be associated with different subcellular domains of MAP1B activity in neurons.

Novel Roles of MAP1B in the Adult Brain

MAP1B as a Regulator of the Actin Cytoskeleton and Dendritic Spine Morphology. MAP1B is able to bind F-actin through two ABDs, which (as noted above) are located in the HC and LC1. Initially, *in vitro* experiments indicated that MAP1B that was dephosphorylated at Mode I sites (i.e., purified MAP1B treated with alkaline phosphatase) associates with actin microfilaments, although with less efficiency than dephosphorylated MAP2 and MAP1A (Pedrotti and Islam, 1996). Purified MAP1B-HC binds actin independently of its phosphorylation state or developmental stage (Cueille et al., 2007a). These contradictory findings might be explained if the ABD involved in these functions is not exactly the same. The ability of MAP1B to associate with actin microfilaments becomes relevant to understanding its function in neurotransmission.

MAP1B is present in dendrites during synaptogenesis (Kitamura et al., 2007) and has also been detected in dendritic spines (Tortosa et al., 2011), although it is not clear if MAP1B protrudes into the spine in association with the actin cytoskeleton or with microtubules. MAP1B is present in 1–2% of dendritic spines, a proportion consistent with the fraction of spines that contain transient microtubules (Hu et al., 2008; Jaworski et al., 2009; Shirao and Gonzalez-Billault, 2013). Therefore, it is likely that MAP1B is not associated with actin microfilaments in spines. Further work is needed to precisely define which cytoskeleton polymer is the main binding partner for MAP1B in spines. In addition to its presence in dendritic spines, neurons lacking MAP1B display a decrease in the number of mature mushroom-type dendritic spines and have decreased miniature excitatory postsynaptic currents (mEPSC) amplitude (Tortosa et al., 2011). These changes in dendritic spine morphology and PSC are paralleled by a reduction in the activity of the small GTPase Rac1 and an increase in the levels of active RhoA. Abnormal activity of these GTPases modifies the dynamics of the actin cytoskeleton, a feature that is dependent on the interaction of MAP1B with TIAM1 and GEF-H1, which are guanine exchanging factors (GEFs) for Rac1 and RhoA, respectively (Tortosa et al., 2011). Additionally, in the brains of mice with heterozygous MAP1B expression, LTD induction is disrupted because of a reduction in AMPAR endocytosis, which can be rescued with TIAM1 overexpression, whereas the magnitude of long-term potentiation is enhanced (Davidkova and Carroll, 2007; Benoist et al., 2013).

Gain- and Loss-of-Function Models can Modify Dendritic Spine Morphology, the FMRP Case. Fragile X syndrome is the most frequently inherited form of mental retardation and is generated by transcriptional silencing of FMRP. This protein binds messenger ribonucleoproteins and mRNAs through G quartets present in the secondary structure of target RNAs (Darnell et al., 2001; Menon et al., 2008), repressing its translation (Zalfa et al., 2003). In addition to its function in translational repression, FMRP also regulates mRNA transport toward dendrites, in response to mGluR activation (Antar et al., 2005).

FMRP binds MAP1B mRNA and represses its expression (Brown et al., 2001; Zalfa et al., 2003). Consistent with this, FMRP KO mice show an abnormal increase in the levels of dendritic MAP1B and in stable microtubules (Lu et al., 2004); a similar condition occurs in MAP1B gain-of-function mice during synaptogenesis. The FMRP KO phenotype, that is, an increased number of filopodia spines and longer filopodia, can be compared with *D. melanogaster* that are null for dFRX, the FMRP ortholog in this species. This model has two interesting features: first, in the neuromuscular junction, dFRX that is either overexpressed or absent increases the synaptic area and the size of the synaptic bouton, which decreases neurotransmission, but in Drosophila eyes, either gain- or loss-of-function of dFRX increases neurotransmission; the second feature is that an absence of Futsch is sufficient to rescue the entire phenotype in the null dFRX synapses (Zhang et al., 2001), even though there are >400 other mRNAs associated with FMRP. Altogether, this evidence suggests that either gain- or loss-of-function of MAP1B is deleterious and that the level of this protein as well as its activity must be precisely regulated not only at the transcriptional level but also as originally proposed.

MAP1B AS A NONCANONICAL SIGNALING/ADAPTOR PROTEIN: LESSONS FROM THE MAP1B INTERACTOME

Interaction of MAP1B with Neurotransmitter Receptors

In the last part of this review, we will focus our attention on noncanonical functions of MAP1B, most of

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which are unrelated to its role as a microtubule-stabilizing factor. The majority of the studies discussed in this section derive from interactomics approaches, with MAP1B interacting partners listed in Table 2.

MAP1B interacts with several ligand-gated ion channels or transmembrane receptors and shows different physiological effects in each case. The $\rho 1$ and $\rho 2$ subunits of the ionotropic Cl^--permeable GABAcR interact with MAP1B HC, anchoring the channel subunits to microtubules, modifying channel activity and reducing its sensitivity (Hanley et al., 1999; Billups et al., 2000; Pattnaik et al., 2000).

LC1 and LC2 bind to Stargazin (Ives et al., 2004), a protein involved in AMPAR trafficking toward the synapses (Chen et al., 2000), which suggests a role for MAP1B in the regulation of AMPAR. Indeed, LC1 also interacts with GRIP1, an AMPAR-interacting protein, which anchors this receptor to the cytoskeleton (Seog, 2004). During DHPG-induced LTD, MAP1B levels are enriched in dendrites, increasing the interaction between MAP1B and GRIP1, ultimately enhancing AMPAR endocytosis (Davidkova and Carroll, 2007). This could be a mechanism for the maintenance of LTD as suggested by recent experiments using brain slices from MAP1B heterozygous mice (Benoist et al., 2013). Stargazin is not the only protein shown to interact both with LC2 and LC1 subunits. It has been shown that MAP1A and MAP1B LCs bind $Ca_v2.2$ channels in hippocampal neurons (Leenders et al., 2008; Gandini et al., in press). While binding of LC2 promotes the anchoring and stabilization of the calcium channel in presynaptic neurons (Leenders et al., 2008); LC1 is involved in $Ca_v2.2$ proteasomal degradation, mediated by the formation of a multiprotein complex with the ubiquitin-conjugating enzyme Ube2L3 (Gandini et al., in press).

Another MAP1B-interacting partner is the NMDAR subunit NR3A, which binds to LC1 at the N-terminal domain. This binding leads to an increase in the NR3A-containing NMDARs and reduces the conductance and permeability of the channel (Eriksson et al., 2010). LC1 is also able to interact with the glycine receptor $\alpha 1$ subunit and with the 5-HT_{3A} receptor (Sun et al., 2008), reducing the expression of the latter in the plasma membrane and promoting its desensitization. Conversely, LC1 interaction with 5-HT_6 receptor increases the receptor activity, as LC1 promotes the 5-HT_6 receptor surface expression, and reduces the receptor endocytosis (Kim et al., 2014). It is not clear if LC1 is able to bind other 5-HT receptors, and if this could increase or reduce its activity.

MAP1B is also implicated in the regulation of sodium channels, as suggested by studies showing that LC1 can bind the channel $Na_v1.6$, increasing its current density by 50% in a mechanism that enhances the density of these receptors at the cell surface (O'Brien et al., 2012).

LC1 also interacts with an erythropoietin-upregulated G protein-coupled receptor, called ee3, and, interestingly, MAP1B KO mice have reduced ee3 expression, indicating that ee3 expression or folding is regulated by MAP1B (Maurer et al., 2004).

Finally, MAP1B binds to mGluR 6, 7a, 7b, 8a, and 8b, which can be inhibited by Ca^{+2}/calmodulin; this interaction may regulate the function and/or trafficking of the receptors (Moritz et al., 2009). Altogether, these interactions with surface receptors support a role for MAP1B during adulthood with respect to either receptor subcellular localization or activity at synapses.

Interaction of MAP1B with Nonreceptor Proteins

There are several new MAP1B interactors that are not neurotransmitter receptors. In this section, we grouped them arbitrarily to emphasize novel roles for MAP1B based on these associations. The different classes of MAP1B interactors are depicted in Figure 3.

The first group encompasses proteins that are altered in neurodegenerative disorders or other pathological conditions. This "neurodegeneration-linked proteins" class includes α-synuclein, which is a component of the Lewy bodies that are present in Parkinson's disease. MAP1B binds α-synuclein fibers, and, as a consequence, MAP1B also becomes a component of Lewy bodies both in the brainstem and cortex (Jensen et al., 2000).

The accumulation of $A\beta$ peptide aggregates is a hallmark of Alzheimer's disease (AD), and an interaction between $A\beta$ 1–42 and the MBD in the HC of MAP1B has been described (Gevorkian et al., 2008). An AD-MAP1B link is also supported by the fact that phosphorylated MAP1B is present in neurofibrillary tangles (Hasegawa et al., 1990) and in semaphorin 3A–positive aggregates that are formed during the onset of AD (Good et al., 2004).

Giant axonal neuropathy is an autosomal recessive disease caused by a mutation in the gene codifying the protein gigaxonin, which is a MAP1B interactor (Ding et al., 2002). Gigaxonin also binds E1-ubiquitin ligase and induces MAP1B degradation; this is relevant as neurons derived from gigaxonin null mice degenerate after 6 days *in vitro*, a process that can be rescued by reducing the expression level of MAP1B (Allen et al., 2005). It follows that over-expression of MAP1B can be deleterious for neuronal survival or functions (Jimenez-Mateos et al., 2005a).

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Finally, the protein mutated in spinocerebellar ataxia type 1, known as LANP, binds LC1 and translocates to the cytoplasm from the nucleus, where it enhances neurite elongation in cells that overexpress MAP1B (Opal et al., 2003).

As we have already discussed, some evidence has suggested a toxic effect for gain-of-function MAP1B mutations; however, the mechanisms involved in this issue are not well defined. A group of MAP1B interactors form a class related to "Apoptosis/Autophagy." The outer mitochondrial membrane-associated E3-ubiquitin ligase MITOL induces the degradation of mitochondrial-associated S-nitrosylated LC1, avoiding the MAGD that results from LC1 overexpression (Yonashiro et al., 2012).

Apoptosis that results from endoplasmic reticulum-related stress has also been observed during LC1 overexpression, as high levels of LC1 expression generate protein aggregates. This effect can be inhibited by DJ-1, a Parkinson's disease-related protein that has been proposed to act like a chaperone for LC1 (Wang et al., 2011).

Another LC1-interacting partner is p53, a transcription factor that is typically associated with cell cycle arrest and apoptosis; however, MAP1B overexpression does not induce p53-related cell death (conversely to the pro-apoptotic effects associated with LC1 overexpression), but it does inhibit p53 transcriptional activity and reduces doxorubicin-induced apoptosis (Lee et al., 2008).

The role of MAP1B in autophagy emerges from its association with LC3, a MAP1 LC that is also an autophagosomal marker (Tanida et al., 2004), which suggests a function in either autophagosome formation or transport. There is still, however, no direct evidence of MAP1B direct or indirect participation in any of these roles. It is noteworthy that LC1 and LC3 interact with Nbr1, a cargo receptor that selectively binds ubiquitinated proteins for autophagosomal degradation (Kirkin et al., 2009). MAP1B is not necessary for the formation of Nbr1-positive vesicles, so it is believed that LC1 could regulate the movement of Nbr1 vesicles on microtubules (Marchbank et al., 2012). More research is required to shed light on MAP1B functions related to autophagy and on how these apoptotic effects are inhibited during development, when MAP1B expression levels are high. In addition, it may be interesting to compare the sensitivity to autophagy-promoting signals in cells that either express or lack MAP1B, as its presence may have an impact on LC3 availability for autophagosome formation.

Another group of MAP1B-associated proteins consists of the "mRNA-associated proteins," such as mNXF2, which participates in the export of mRNA from the nucleus, and mNXF7, which has a role in mRNA transport toward neurites in N2a cells, indicating a role for MAP1B in the transport of mNXF-containing ribonucleoproteins (Tretyakova et al., 2005). Other members in this class are the Hu proteins, among which all of the Hu protein expressed in neurons are able to interact with LC1 (HuB, HuC, and HuD) and, simultaneously, with mRNAs, indicating that Hu proteins can be involved in microtubule-dependent mRNA transport in neurons (Fujiwara et al., 2011). MAP1B interactions with these proteins suggest a role in mRNA transport, likely toward neuritic processes.

There is another MAP1B-interacting group of proteins composed of "membrane-associated proteins" that are not neurotransmitter receptors, such as the myelin-associated glycoprotein, the physiological consequences of which are still unknown (Franzen et al., 2001). The other integral membrane protein that binds LC1 is Kidins220/ARMS, a protein that inhibits neuronal development in cultured neurons (Higuero et al., 2010). The context and relevance of MAP1B interactions with transmembrane proteins remain unknown, but they could be related to the putative transmembrane domain that has been described in MAP1B HC (Tanner et al., 2000).

Additionally, another class of MAP1B-binding proteins contains "cytoskeleton-related proteins," such as the cytoskeletal linker dystonin-a2 (Bhanot et al., 2011). In the dystonin mutant mice, MAP1B maintains a population of acetylated microtubules in the perinuclear region, which prevent Golgi fragmentation and allow vesicle trafficking by the secretory pathway (Ryan et al., 2012).

MAP1B HC interacts with tubulin tyrosine ligase (TTL), enhancing its activity and promoting the formation of tyrosinated microtubules (Utreras et al., 2008). In neurons, MAP1B could, therefore, induce both acetylated and tyrosinated microtubules; differentiation between the two may be explained by compartmentalized MAP1B activity. A good candidate for such regulation could be MAP1B phosphorylation. Although the MAP1B-TTL interaction is independent of GSK3β-dependent phosphorylation, other post-translational modifications cannot be ruled out.

LIS1 is a MAP that can bind MAP1B, an interaction that is inhibited by Mode I phosphorylation. In MAP1B KO mice, LIS1 association with microtubules is reduced, whereas its interaction with dynein is enhanced, resulting in Golgi fragmentation (Jimenez-Mateos et al., 2005b).

MAP1B also interacts with the + TIPs EB1/3, sequesters the protein in the cytoplasm and restricts

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EB1/3 binding to microtubules. This is an alternate indirect mechanism for MAP1B to regulate microtubule dynamics, as in MAP1B KO mice there is an increase in the association of EB1/3 with the plus ends of microtubules, which leads to more stable and looped microtubules in the neuronal growth cones (Tortosa et al., 2013). This is in good agreement with recent reports showing that MAP1B associates with dynamic microtubules, enhancing their elongation rate (Tymanskyj et al., 2012). Altogether, these MAP1B interactor proteins suggest that MAP1B acts through multiple mechanisms to regulate microtubule dynamics.

The last class of MAP1B-binding proteins comprises "signaling proteins," molecules involved in signaling pathways or acting as molecular hubs. One such interactor is EPAC1, a cAMP-activated GEF for Rap1b, which seems to use MAP1B as a molecular chaperone that promotes the GEF activity of EPAC1 in *in vitro* assays (Borland et al., 2006).

LC1 and LC2 are able to interact with the PDZ domain of PDZRhoGEF, a GEF for RhoA, regulating its subcellular localization and reducing its activity, as the PDZRhoGEF mutant that is unable to interact with LC1/LC2 has increased RhoA and Cdc42 activity, which leads to altered cell morphology (Longhurst et al., 2006). PDZRhoGEF is not the only Rho GEF protein that interacts with MAP1B. MAP1B-GEF-H1 interaction is involved in the regulation of dendritic spines in long-term cultures of neurons (Tortosa et al., 2011).

LC1 binds to the GEFs for Rac1, STEF, and TIAM1 (Takefuji et al., 2007; Henriquez et al., 2012), enhancing TIAM1 GEF activity, which is relevant during axonal growth and synaptic plasticity, as TIAM1 overexpression can rescue MAP1B KO mice phenotypes during both processes (Montenegro-Venegas et al., 2010; Benoist et al., 2013).

There are other MAP1B interactors involved in signaling pathways that are not GEFs, such as osteopontin, a protein with pleiotropic effects that protect neurons during Parkinson's disease; however, the consequences of this interaction are still not determined (Long et al., 2012).

MAP1B is able to interact with GAPDH (Cueille et al., 2007b), a classical glycolytic enzyme with a wide spectrum of nonglycolytic functions, from microtubule bundling to nuclear RNA export, including apoptosis and others (Sirover, 1999). Similar to osteopontin, consequences of the MAP1B-GAPDH interaction have not yet been determined.

Finally, LC1 interacts with the adaptor protein α1-syntrophin, which reinforces the viewpoint that MAP1B is a protein involved not only just in cytoskeleton dynamics but also in the regulation of several molecular pathways (Fuhrmann-Stroissnigg et al., 2012). Figure 2(A,B) shows graphical models of some MAP1B interacting proteins in axon and dendrites, respectively.

FUTURE DIRECTIONS

Although MAP1B has been extensively studied since its discovery, there are some features that remain unknown, as well as new evidence arguing for novel functions that are not related to its role as a MAP. Regarding MAP1B structure, neither the protease that generates HC and LC1 nor the proteolytic site have been determined, although the site has been delimited and good predictions exist for Futsch in *D. melanogaster*. Phosphorylation sites also remain to be discovered, as phospho-proteomic assays have revealed more sites of phosphorylation in MAP1B than were previously known, which implies that novel kinases could phosphorylate MAP1B, modifying our conception of Mode I and Mode II phosphorylation.

MAP1B expression is developmentally regulated; however, the increasing evidence of its role in the adult brain suggests that its levels during adulthood are enough to regulate synaptic-related processes. It is not clear which functions are shared or overlap with MAP1A. This is an interesting area of study, as MAP1B has been linked to some neurodegenerative disorders, and now its role in the pathogenesis of those diseases has begun to be revealed.

Finally, MAP1B interactions with proteins not related to its role in stabilizing microtubules suggest that MAP1B may be considered a "signaling protein" that regulates molecular pathways through key elements, such as GEFs, adaptor proteins, and others. The analysis of the MAP1B interactome indicates that both HC and LC1 interact with other proteins, although LC1 interactors reported in the literature are more abundant and diverse. We have grouped MAP1B binding proteins to shed light on the processes in which these partners are involved, although we expect that new interactors will be found, consolidating our belief that MAP1B is a multitasking protein. In this regard, it will be interesting to consider whether the main function of MAP1B is to promote microtubule stabilization or whether this is just one of the many cellular functions of this protein.

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