Microtubule-associated Protein 1S, a Short and Ubiquitously
Expressed Member of the Microtubule-associated Protein 1 Family*

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Received for publication, August 5, 2004, and in revised form, October 27, 2004
Published, JBC Papers in Press, November 4, 2004, DOI 10.1074/jbc.M408984200

The classical microtubule-associated proteins (MAPs) MAP1A and MAP1B are predominantly expressed in the nervous system and are involved in axon guidance and synaptic function. MAP1B is implicated in fragile X mental retardation, giant axonal neuropathy, and ataxia type 1. We report the functional characterization of a novel member of the microtubule-associated protein 1 family, which we termed MAP1S (corresponding to sequence data bank entries for VCY2P1 and C19orf55). MAP1S contains the three hallmark domains of the microtubule-associated protein 1 family but hardly any additional sequences. It decorates neuronal microtubules and copurifies with tubulin from brain. MAP1S is synthesized as a precursor protein that is partially cleaved into heavy and light chains in a tissue-specific manner. Heavy and light chains interact to form the MAP1S complex. The light chain binds, bundles, and stabilizes microtubules and binds to actin. The heavy chain appears to regulate light chain activity. In contrast to MAP1A and MAP1B, MAP1S is expressed in a wide range of tissues in addition to neurons and represents the non-neuronal counterpart of this cytolinker family.

The related high molecular mass microtubule-associated proteins (MAPs) MAP1A and MAP1B are predominantly expressed in the nervous system and are involved in axon guidance and synaptic function. MAP1B is implicated in fragile X mental retardation, giant axonal neuropathy, and ataxia type 1. We report the functional characterization of a novel member of the microtubule-associated protein 1 family, which we termed MAP1S (corresponding to sequence data bank entries for VCY2P1 and C19orf55). MAP1S contains the three hallmark domains of the microtubule-associated protein 1 family but hardly any additional sequences. It decorates neuronal microtubules and copurifies with tubulin from brain. MAP1S is synthesized as a precursor protein that is partially cleaved into heavy and light chains in a tissue-specific manner. Heavy and light chains interact to form the MAP1S complex. The light chain binds, bundles, and stabilizes microtubules and binds to actin. The heavy chain appears to regulate light chain activity. In contrast to MAP1A and MAP1B, MAP1S is expressed in a wide range of tissues in addition to neurons and represents the non-neuronal counterpart of this cytolinker family.

The MAP1 family has two members: MAP1A and MAP1B. Both proteins are of high molecular mass (~300 kDa, 2500 aa), are expressed predominantly in the nervous system, and consist of several subunits, one heavy chain (HC) and at least one light chain (LC) (1). In each case, heavy and light chains are the products of proteolytic cleavage of a common polyprotein precursor. MAP1A and MAP1B share three substantial regions of sequence homology (2), one in the NH2 terminus of the heavy chains, one in the COOH terminus of the heavy chains, and one in the COOH-terminal half of the light chains. We termed these homologous hallmark domains of the MAP1 family MH1, MH2, and MH3, respectively. In MAP1B, the MH1 and MH3 domains mediate the interaction between heavy and light chains (3), and the MH3 domain of both proteins contains an actin binding site (4). MAP1A and MAP1B are conserved in vertebrates. A MAP1 ortholog termed Futsch has been identified in Drosophila (5).

MAP1B function has been investigated by gene targeting in the mouse, and the original contention that it is important for neuronal differentiation and development of the nervous system has been confirmed (6–9). Mice homozygous for hypomorphic or null alleles of MAP1B display defects in axonal guidance, neuronal migration, axon diameter, and myelination. Work on cultured neurons from MAP1B mutant mice indicated that MAP1B contributes to neuronal differentiation and axon extension and guidance by regulating microtubule and actin dynamics in the growth cone (10–12). Together, these observations suggest that MAP1B and perhaps MAP1A regulate the cytoskeleton in response to extracellular guidance cues to permit axon extension and growth cone turning. This view is supported by the finding that changes in the activity of serine-threonine kinases casein kinase II, glycogen synthase kinase-3β, and cyclin-dependent kinase 5 lead to altered MAP1B phosphorylation (13–15) and by the fact that local inactivation of MAP1B on one side of the growth cone induces growth cone turning (16). On the other hand, there is evidence that the function of MAP1B and perhaps MAP1A goes beyond regulation of the neuronal cytoskeleton. MAP1B interacts with and changes the ligand affinity of specific γ-aminobutyric acid receptor subunits (17, 18). There is also evidence that a fraction of MAP1B is inserted in the axonal plasma membrane, with its extracellular domains binding to myelin-associated glycoprotein expressed on the surface of glial cells (19).

Here we report the discovery and functional characterization of a third member of the MAP1 family encoded by the genomes of mouse, rat, and human that has thus far escaped detection. Because the novel MAP1 protein is unusually short compared with high molecular mass MAP1A and MAP1B, we propose to term it MAP1S.

EXPERIMENTAL PROCEDURES

cDNA Constructs

All amino acid numbering refers to the murine MAP1 protein sequence denoted in GenBank accession number AK032300. The full-length MAP1S cDNA encoding aa 1–973 was obtained by replacing a 689-base pair BstEI fragment of RIKEN clone ID 6430517J16.
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RNase extraction and cDNA synthesis were carried out using high-purity reagents and protocols to avoid contamination of the samples. The resulting cDNA was subjected to PCR amplification using specific primers that were designed to amplify the target regions of interest. The amplified products were then purified and cloned into appropriate expression vectors for subsequent analysis.

Purification of recombinant proteins was performed using a combination of affinity chromatography and size-exclusion chromatography. The purified proteins were then subjected to various functional assays to characterize their properties.

Results and Discussion

Our results indicate that recombinant MAP1S protein is capable of forming stable microtubule-binding complexes in vitro. These complexes exhibit a number of properties that are consistent with those of endogenous MAP1S, including a high degree of processivity and stability under a variety of conditions.

Future directions include the analysis of the role of MAP1S in the regulation of microtubule dynamics and its potential as a therapeutic target for neurodegenerative diseases.
1. Using the amino acid sequence of MH3 in a BLAST search (23) through available nucleic acid sequence databases, we identified numerous human, mouse, and rat cDNAs and expressed sequence tags. The majority of these sequences encoded either MAP1A or MAP1B MH3 domains. A third group of sequences showed consistent differences from either of the two known MAP1 proteins. Using these sequences in a renewed search on the nucleotide level, we identified full-length human and mouse cDNAs (representative GenBank™ accession numbers, for example, AJ440784 and AK033200, respectively) encoding a novel protein related to MAP1A and MAP1B that we termed MAP1S for reasons mentioned under “Introduction.” Analysis of human and mouse genomic sequences revealed that the MAP1S gene, like the genes for MAP1A and MAP1B, consists of seven exons and that exon-intron boundaries are conserved in MAP1A, MAP1B, and MAP1S. The considerable difference in size among the three proteins is due to differences in the length of internal sequences in exon 5, whereas the respective length of the other six exons is very similar or identical in all three genes. The MAP1S gene is located on human chromosome 19p13.12 (LocusID 55201) and on mouse chromosome 8 (LocusID 270058; MGI 2443304). No other MAP1-related genes or sequences were found, indicating that MAP1S is the only other member of the MAP1 family. A cDNA fragment encoding part of MAP1S has been identified previously in a yeast two-hybrid screen for potential interaction partners of the fibroblast growth factor-associated protein LRPPRC and was termed C19ORF5 (GenBank™ accession number XP_038600; Ref. 24). In a similar search for potential interaction partners of a testicular protein of unknown function termed VCY2, the light chain of MAP1B and MAP1S (86% and 81% identity, respectively) are indicated by hatched boxes. The vertical arrow shows the position of the proteolytic cleavage site in mammalian MAP1 proteins. The antibodies against the heavy chain (anti-HC) and the light chain (anti-LC) were generated against sequences unique for MAP1S.

**FIG. 1.** MAP1S contains all three hallmark domains of the MAP1 family of proteins. The MAP1 homology domains MH1, MH2, and MH3 are indicated for MAP1B. The numbers in the corresponding domains of rat MAP1A, murine MAP1S, and *Drosophila* Futsch indicate the percentage of amino acid sequence identity with murine MAP1B. Light and dark grey shading indicate regions of MH1 with a lesser or higher degree of conservation, respectively, between rodent MAP1A and MAP1B and *Drosophila* Futsch. Two shorter stretches of homology in the heavy chains of MAP1B and MAP1S (86% and 81% identity, respectively) are indicated by hatched boxes. The vertical arrow shows the position of the proteolytic cleavage site in mammalian MAP1 proteins. The antibodies against the heavy chain (anti-HC) and the light chain (anti-LC) were generated against sequences unique for MAP1S.
antibodies directed against unique amino acid sequences located in the presumptive heavy and light chains of MAP1S (Fig. 1). To demonstrate the specificity of these antibodies, we first conducted an immunoblot analysis of total brain homogenates (Fig. 3A). Anti-HC detected bands at 100 and 120 kDa, and anti-LC detected one band at 26 kDa. The 100-kDa band corresponds to the MAP1S heavy chain (calculated molecular mass, 80 kDa), and the 26-kDa band corresponds to the light chain (calculated molecular mass, 23 kDa). The identity of the remaining 120-kDa band became clear after copurification of MAP1S with microtubules from brain by temperature-dependent microtubule polymerization/depolymerization. After two cycles of polymerization, microtubule pellets contained MAP1S as revealed by immunoblot analysis (Fig. 3B). Treatment of the polymerized microtubules with a high concentration of salt (350 mM) led to the release of MAP1S from microtubules (data not shown), another feature reminiscent of the behavior of classical MAPs. In the immunoblot analysis, anti-HC again detected the band at 120 kDa and the heavy chain at 100 kDa, whereas anti-LC detected the light chain at 26 kDa and an additional band comigrating with the 120-kDa band detected by the heavy chain-specific antibody. This analysis identified the 120-kDa band as the uncleaved MAP1S polyprotein precursor (calculated molecular mass, 103 kDa) and showed that the MAP1S precursor is partially cleaved into heavy and light chains. It further demonstrated the specificity of the antibodies used and showed that MAP1S behaved like a classical MAP in temperature-dependent copurification with microtubules from brain. The failure of anti-LC to detect the precursor in total homogenates (Fig. 3A) is due to the lesser abundance of this protein and the weaker affinity of anti-LC compared with anti-HC. The discrepancies in observed and calculated molecular mass of precursor, heavy chain, and light chain might be due to slightly aberrant migration during electrophoresis and/or as yet unidentified posttranslational modifications.

The MAP1S Light Chain Binds to Microtubules and Actin Filaments in Vitro—Previous studies have shown that the light chains of MAP1A and MAP1B contain binding sites for microtubules and actin filaments (3, 4). To investigate whether association of MAP1S with microtubules might be due to binding sites in the light chain, we tested the microtubule binding properties of MAP1S in vitro. A recombinant protein consisting of the light chain fused to six histidines was synthesized in and purified from E. coli. Purified MAP-free tubulin was polymerized in vitro in the presence of purified MAP1S light chain. The MAP1S light chain bound to microtubules and was pelleted after centrifugation (Fig. 4A). In the absence of tubulin or in the presence of a control protein (BSA), the light chain remained in the supernatant, demonstrating that its interaction with microtubules was specific. In an additional control, we ruled out that this interaction was due to the His tag fused to the light chain. Thus, a His-tagged fragment of the protein plectin, which does not contain microtubule or actin binding sites, did not bind to microtubules, and only a trace amount was found in the pellet (Fig. 4A, right panel).

To test for a potential actin binding activity in the light chain, a similar analysis was carried out with actin (Fig. 4B). Again, the MAP1S light chain bound specifically to actin and remained in the supernatant in the absence of actin, and the interaction with actin was not due to the His tag.

The MAP1S Heavy and Light Chains Associate in Vivo—To determine whether heavy and light chains of MAP1S can interact with each other in vivo, we carried out immunoprecipitation experiments using either the MAP1S heavy or light chain antibody and analyzed the resulting precipitates by im-
FIG. 3. MAP1S copurifies with microtubules and is partially cleaved into heavy and light chains. A, SDS-PAGE and immunoblotting analysis of total brain protein lysates (120 µg) demonstrating the specificity of anti-LC and anti-HC antibodies. In total lysates, anti-LC only detects the light chain at 26 kDa and does not detect the less abundant, uncleaved, full-length precursor. Anti-HC detects the heavy chain at 100 kDa as well as the precursor at 120 kDa. B, microtubules and associated proteins were purified and enriched from brain by two cycles of temperature-induced polymerization and depolymerization. Approximately 70 µg of polymerized tubulin and associated proteins from the second cycle of polymerization were fractionated by SDS-PAGE and analyzed by immunoblot using light chain-specific (anti-LC) or heavy chain-specific (anti-HC) antibodies. The MAP1S light chain (MAP1S-LC, 26 kDa), heavy chain (MAP1S-HC, 100 kDa), and the uncleaved polyprotein precursor reacting with both antibodies (MAP1S-FL, 120 kDa) are indicated.

munoblot. When whole cell lysates of brain were precipitated with anti-LC, the precipitates contained not only the light chain but also the heavy chain (Fig. 5). Vice versa, precipitation with anti-HC led to precipitation of the heavy chain and coprecipitation of the light chain. In the absence of any antibody, neither the light chain nor the heavy chain was precipitated (data not shown). Because the heavy chain does not contain its own microtubule binding site (Fig. 7), this result suggested that the heavy chain copurified with microtubules from brain (Fig. 3) through binding to the microtubule-bound light chain. A potential caveat of this experiment is that anti-LC and anti-HC also precipitate the uncleaved full-length MAP1S. Subsequent proteolytic cleavage of full-length MAP1S at the correct position would mimic non-covalent association of heavy and light chains. However, this is highly unlikely because this proteolytic cleavage would have to occur during or after elution of the immunoprecipitate from the protein A-Sepharose matrix by incubation with a strong denaturing buffer containing 4% SDS and 5% β-mercaptoethanol. Moreover, we found that immunoprecipitation of a myc-tagged light chain ectopically expressed in N2a cells from a cDNA construct encoding only the light chain coprecipitates endogenous heavy chain (data not shown).

The Light Chain of MAP1S Contains an NH$_2$-Terminal Microtubule-binding Domain and Binds, Bundles, and Stabilizes Microtubules in Vivo—To investigate what effects binding of MAP1S might have on microtubules, we ectopically expressed MAP1S in epithelioid PtK2 cells in which we did not detect endogenous MAP1S expression. Ectopic expression of full-length myc-tagged MAP1S showed that the protein was able to bind to cellular microtubules without inducing recognizable changes in microtubule organization (Fig. 6, A–C). Treatment of cells with the microtubule depolymerizing drug colchicine led to destruction of microtubules and diffuse localization of tubulin and MAP1S (Fig. 6, D–F). In contrast, when the MAP1S light chain was expressed, it not only decorated microtubules but also induced the formation of microtubule bundles (Fig. 6, G–I). Thus, interaction of the light chain with actin was specific and was not due to the His tag. The positions on the gel of BSA, tubulin (tub), the MAP1S light chain (MAP1S-LC), the plectin fragment (contr), and insufficiently denatured MAP1S light chain dimers (asterisk) are indicated. B, purified actin was polymerized, followed by centrifugation and fractionation of equal amounts of supernatant (S) and pellet (P) fractions by SDS-PAGE and Coomassie Blue staining. The MAP1S light chain (MAP1S-LC) was pelleted in the presence (+tub), but not in the absence (–tub) of microtubules, nor did it pellet in the presence of the same molar concentration of BSA (+BSA). Only trace amounts of a His-tagged control protein (contr; a fragment of plectin) were found in the pellet fraction (right panel). Thus, interaction of the light chain with microtubules was specific and was not due to the His tag. The positions on the gel of BSA, actin, the MAP1S light chain (MAP1S-LC), the plectin fragment (contr), and insufficiently denatured MAP1S light chain dimers and trimers (asterisks) are indicated.
The COOH Terminus of the Light Chain Can Interact with Cellular Actin Fibers—The in vitro analysis presented in Fig. 4 revealed that the light chain can bind to actin filaments as well as to microtubules. Because the NH2 terminus of the light chain was shown to contain the microtubule-binding domain, we tested whether the MH3 domain comprising the COOH-terminal half of the light chain has actin binding activity. Indeed, when the MH3 domain was ectopically expressed in PtK2 cells, it was found to decorate cellular stress fibers (Fig. 7, D–F) and not microtubules. The results shown in Fig. 7, D–F, were obtained with the human MAP1S MH3 domain. Similar results were obtained with the corresponding mouse MAP1S MH3 domain (data not shown). These results showed that the COOH-terminal MH3 domain has actin binding activity and confirmed that the microtubule-binding domain of the light chain is located in the NH2 terminus.

Endogenous MAP1S Decorates Microtubules in N2a Cells and Is Found in the Soma and Dendrites of Cerebellar Purkinje Cells—A crucial requirement to establish MAP1S as a bona fide microtubule-associated protein is to demonstrate that endogenous MAP1S is indeed found on microtubules. We chose N2a mouse neuroblastoma cells for this experiment because they can be induced to differentiate in culture and immunoblot analysis revealed that these cells express considerable levels of MAP1S (data not shown). Confocal double immunofluorescence microscopy clearly showed that the microtubules in these cells are decorated with MAP1S (Fig. 8, A–C). To confirm that MAP1S is also expressed in neurons of the brain, we stained sections of the cerebellum. MAP1S was found to be expressed in dentrites and somata of Purkinje cells (Fig. 8, D and E). Staining of Purkinje cells was not observed when sections were incubated with secondary antibody alone (Fig. 8E). In addition, staining of Purkinje cells by the anti-HC antibody was blocked by preincubation of the antibody with excess antigen, but not by preincubation with an unrelated control antigen (data not shown). These results demonstrated that endogenous MAP1S binds to microtubules in cell bodies and neurites of cultured neuroblastoma cells and is expressed in neurons of the brain.

DISCUSSION

Here we report the discovery and functional characterization of the third and final member of the MAP1 family of proteins, MAP1S. It is somewhat surprising that this protein was not discovered along with other prominent MAPs about three decades ago and has escaped detection despite its structural relatedness to MAP1A and MAP1B, its expression in the brain, and its behavior as a MAP in the classical purification protocol. The main reason for MAP1S having been missed is probably its relatively low level of expression compared with MAP1A, MAP1B, MAP2, and tau.

What makes MAP1S unique among the members of the MAP1 family is its small size. In contrast to the other members of the family, MAP1S hardly contains any extra sequences in addition to the conserved hallmark domains MH1, MH2, and MH3. Most notably, MAP1S does not contain heavy chain domains that were implicated in microtubule binding of MAP1A (27, 28) and MAP1B (29). Consistent with this observation, we found only one microtubule-binding domain in MAP1S that is located in the NH2 terminus of the light chain (Fig. 6), corresponding in position but not in sequence to the microtubule-binding domains of the light chains of MAP1A and MAP1B (3, 4). Thus, the light chain microtubule-binding domains might represent the main microtubule-binding domains of MAP1 proteins, with the additional domains found in the heavy chains of MAP1A and MAP1B serving accessory functions. The comparison of the three MAP1 genes further showed that exon-intron boundaries and exon sizes are conserved, with the exception of exon 5, suggesting that all three genes were derived from a common MAP1 ancestor.

Another feature of MAP1 proteins highlighted by the characterization of MAP1S is that the hallmark domains are conserved not only in sequence but also in their position at either end of the heavy chains (MH1 and MH2) and at the COOH terminus of the light chains (MH3). This positional conservation might be necessary for the formation of a basic structural module common to all MAP1 proteins, in which the hallmark domains occupy pivotal areas or interact with each other. For example, in all MAP1 proteins, the light and heavy chains form a complex (Fig. 5) (1), in which the light chains are bound to the NH2 terminus of the heavy chains through interaction of the MH1 and MH3 domains (3). The sequences unique in each of the three MAP1 proteins might form additional structures embedded in the basic module and might confer specific individual properties.

Our analysis of endogenous MAP1S protein expression is based on two affinity-purified antibodies, the epitopes of which...
were predicted from the cDNA. We were able to show that MAP1S expression is widespread in murine tissues. In addition, we found that the full-length polyprotein precursor is expressed together with heavy and light chains. The latter are most likely proteolytic cleavage products of the polyprotein precursor because both heavy and light chains are encoded by a single contiguous reading frame in the cDNA. Alternative explanations, such as internal translation initiation on the full-length or truncated MAP1S mRNA to translate only the light chain, are not supported by our findings. We observed only one species of MAP1S mRNA, and in transfection studies, no evidence of internal translation initiation was obtained (data not shown). MAP1S shares this peculiar biosynthetic pathway with MAP1A (2) and MAP1B (30), and the proteolytic cleavage site that was identified for MAP1A and MAP1B (31) is conserved in MAP1S (data not shown). However, in contrast to MAP1B, which has not been detected in its uncleaved form, the MAP1S precursor is only partially cleaved into heavy and light chains, and the percentage of cleaved versus full-length precursor varied between tissues. This raises the possibility that proteolytic cleavage of the MAP1S precursor is regulated in a tissue-specific manner and perhaps represents a form of irreversible activation or maturation of the protein. Our finding of partial cleavage provides an opportunity to investigate the regulation and functional significance of precursor cleavage for MAP1S and the other members of the MAP1 family.

**FIG. 6.** MAP1S full-length and light chain proteins bind to microtubules in vivo and show different effects on microtubule stability in cells treated with colchicine. The top panel shows a schematic of the cDNA constructs used in this study. With the exception of MH3, all expression constructs were derived from mouse cDNA. FL, full-length MAP1S (aa 1–973); LC, light chain (aa 755–973); MH3, MH3 domain (aa 935–1059 in human, corresponding to aa 852–973 in mouse); Δ 645–875, full-length MAP1S lacking aa 645–875. All proteins contained either an NH2-terminal or a COOH-terminal myc tag. Bottom panels, PtK2 cells were transiently transfected with the indicated constructs, incubated for 48 h to allow for protein expression, incubated for an additional 1.5 h in the presence or absence of 10 μM colchicine, and subsequently analyzed by confocal double immunofluorescence microscopy using the indicated antibodies shown separately and merged. Full-length (A–F) and light chain (G–L) proteins colocalized with microtubules, but only the light chain in the absence of the heavy chain (G–L) induced formation of stable microtubule bundles (arrowheads). Scale bar, 10 μm.
Ectopic expression of MAP1S in PtK2 cells demonstrates that the light chain per se can have dramatic effects on microtubules. It transforms the cellular microtubule network; induces the formation of long, wavy microtubule bundles; and stabilizes microtubules against the effects of colchicine (Fig. 6) and nocodazole (data not shown). In contrast, when the light chain is expressed together with the heavy chain, microtubule binding is still observed, but microtubule bundling and stabilization are absent. For one, these results demonstrate another difference between MAP1S and MAP1B. The light chain of the latter is prevented even from microtubule binding in the presence of the heavy chain (3). On the other hand, these results suggest that the heavy chain has a regulatory function in the heavy chain/light chain complex. Conformational changes of the heavy chain perhaps triggered by phosphorylation or other posttranslational modifications or binding of additional regulatory proteins to either the heavy or the light chain might change light chain activity. A potential candidate for such a regulatory protein is the tumor suppressor protein RASSF1A, which has been reported to interact with MAP1S (24, 32). Moreover, overexpression of RASSF1A can induce bundling and stabilization of microtubules reminiscent of the effects of the MAP1S light chain. Thus, it is conceivable that RASSF1A, by binding to endogenous MAP1S, triggers conformational changes necessary for light chain activation.

One feature that MAP1S shares with the other members of the MAP1 family is the potential of the light chain to act as a cytolinker, cross-linking microtubules and actin. Like MAP1A and MAP1B (4), the MAP1S light chain contains a microtubule-binding domain in its NH2 terminus (which is not related in sequence to either MAP1A or MAP1B) and an actin-binding domain in the conserved MH3 domain in the COOH-terminal half. In vitro, the light chain can bind to both microtubules and microfilaments. In vivo, the MH3 domain displays actin-binding activity, but the entire light chain (containing microtubule-binding domain and MH3) binds to microtubules. This paradox was observed previously with MAP1A and MAP1B as well and attributed to posttranslational modification in mammalian cells (but not in E. coli-produced recombinant light chain used for in vitro assays). This hypothesis is supported by findings that actin binding of the native MAP1B complex is inhibited by phosphorylation (33).

Perhaps the most significant difference of MAP1S compared with the other members of the MAP1 family is that MAP1S protein expression is readily detected not only in neurons of the brain but also in a wide range of other tissues. Thus, whereas MAP1S is still expressed in neurons, it also qualifies as the non-neuronal and hence generic member of this MAP and cytolinker family, whereas MAP1A and MAP1B are expressed predominantly in neurons. This finding has implications for
the neuronal MAP hypothesis formulated many years ago. According to this hypothesis, neuronal MAPs confer special properties to an otherwise generic microtubule system to enable it to meet the special neuron-specific demands. From our characterization of MAP1S, it would appear that neither microtubule binding, bundling, stabilization, nor the putative cytolinker function of the MAP1 family of proteins is exclusively expressed in neurons. In a refinement of the above-mentioned hypothesis, we therefore propose that, not these functions, but perhaps the regulation of these activities by increased neuron-specific heavy chains of MAP1A and MAP1B is the crucial difference.

Acknowledgments—We are grateful to I. Fischer, W. Kutscher, and H. Stroissing for sharing essential experimental expertise. We thank the Resource Center of the German Human Genome Project, the UK Human Genome Mapping Project Resource Centre, and Dr. Yoshihide Hayashizaki (Genomic Exploration Research Group, Genomic Sciences Center, RIKEN, Kanagawa, Japan) for providing cDNA clones.

REFERENCES
1. Schoenfeld, T. A., and Obar, R. A. (1994) Int. Rev. Cytol. 151, 67–137
2. Langkopf, A., Hammarback, J. A., Müller, R., Vallee, R. B., and Garner, C. C. (1992) J. Biol. Chem. 267, 16961–16966
3. Tegel, W., Wiche, G., and Propst, F. (1998) J. Cell Biol. 143, 695–707
4. Noiges, R., Eichinger, R., Kutscher, W., Fischer, I., Németh, Z., Wiche, G., and Propst, F. (2002) J. Neurosci. 22, 2106–2114
5. Hummel, T., Krukkert, K., Ross, J., Davis, G., and Klambt, C. (2000) Neuron 28, 357–370
6. Edelmann, W., Zervas, M., Costello, P., Robbark, L., Fischer, I., Hammarback, J. A., Cowan, N., Davies, P., Wainer, B., and Kucherlapati, R. (1996) Proc. Natl. Acad. Sci. U. S. A. 93, 1270–1275
7. Takei, Y., Kondo, S., Harada, A., Inomata, S., Noda, T., and Hirokawa, N. (1997) J. Cell Biol. 137, 1615–1628
8. Mesner, A., Haverkamp, S., Wäsle, H., Führer, S., Thalhammer, J., Kropf, N., Bittner, R. E., Lassmann, H., Wiche, G., and Propst, F. (2000) J. Cell Biol. 151, 1169–1178
9. Gonzalez-Billault, C., Demandt, E., Wandoz, F., Torres, M., Bonaldo, P., Stoykova, A., Chowdhury, K., Gruss, P., Avila, J., and Sánchez, M. P. (2000) Mol. Cell. Neurosci. 16, 408–421
10. Takei, Y., Teng, J., Harada, A., and Hirokawa, N. (2000) J. Cell Biol. 150, 989–1000
11. Gonzalez-Billault, C., Avila, J., and Caceres, A. (2001) Mol. Biol. Cell 12, 2087–2098
12. Gonzalez-Billault, C., Owen, R., Gordon-Weeks, P. R., and Avila, J. (2002) Brain Res. 943, 56–67
13. Ulloa, L., Díaz-Nido, J., and Avila, J. (1993) EMBO J. 12, 1633–1640
14. Pigino, G., Paglioni, G., Ulloa, L., Avila, J., and Cáceres, A. (1997) J. Cell Sci. 110, 257–270
15. Lucas, F. R., Grodd, R. G., Gordon-Weeks, P. R., and Salinas, P. C. (1998) J. Cell Sci. 111, 1351–1361
16. Mack, T. G., Koester, M. P., and Pollerberg, G. E. (2000) Mol. Cell. Neurosci. 15, 51–65
17. Hanley, J. G., Kaulen, P., Bedford, F., Gordon-Weeks, P. R., and Moss, S. J. (1999) Nature 397, 66–69
18. Billups, D., Hanley, J. G., Orme, M., Attwell, D., and Moss, S. J. (2000) J. Neurosci. 20, 8643–8650
19. Franzén, R., Tanner, S. L., Dashiel, S. M., Rottkamp, C. A., Hammar, J. A., and Quares, R. H. (2001) J. Cell Biol. 155, 893–898
20. Gossen, M., and Bujard, H. (1992) Proc. Natl. Acad. Sci. U. S. A. 89, 5547–5551
21. Sambrook, J., Fritsch, E. F., and Maniatis, T. (1989) Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratory, Cold Spring Harbor, NY
22. Shelanski, M. L., Gaskin, F., and Cantor, C. R. (1973) Proc. Natl. Acad. Sci. U. S. A. 70, 765–768
23. Altschul, S. F., Madden, T. L., Schaffer, A. A., Zhang, J., Zhang, Z., Miller, W., and Lipman, D. J. (1997) Nucleic Acids Res. 25, 3389–3402
24. Liu, L., Amy, V., Liu, G., and McKeehan, W. L. (2002) In Vitro Cell. Dev. Biol. Anim. 38, 582–594
25. Wong, E. Y., Tse, J. Y., Yao, K. M., Lui, V. C., Tam, P. C., and Yeung, W. S. (2004) Biol. Reprod. 70, 775–784
26. Andreu, J. M., and Timasheff, S. N. (1982) Proc. Natl. Acad. Sci. U. S. A. 79, 6753–6756
27. Cravchik, A., Reddy, D., and Mattus, A. (1994) J. Cell Sci. 107, 661–672
28. Vaillant, A. R., Müller, R., Langkopf, A., and Brown, D. L. (1998) J. Biol. Chem. 273, 13973–13981
29. Noble, M., Lewis, S. A., and Cowan, N. J. (1989) J. Cell Biol. 109, 3367–3376
30. Hammarback, J. A., Obar, R. A., Hughes, S. M., and Vallee, R. B. (1991) Neuron 7, 129–139
31. Tegel, W., Eichinger, R., Wiche, G., and Propst, F. (1999) FEBS Lett. 451, 15–18
32. Dallol, A., Agathangelou, A., Fenton, S. L., Ahmed-Choudhury, J., Hesson, L., Vos, M. D., Clark, G. J., Downward, J., Maher, E. R., and Latif, F. (2004) Cancer Res. 64, 4112–4116
33. Pedrotti, B., and Islam, K. (1996) FEBS Lett. 388, 131–133

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J. Biol. Chem. 2005, 280:2257-2265.
doi: 10.1074/jbc.M408984200 originally published online November 4, 2004

Access the most updated version of this article at doi: 10.1074/jbc.M408984200

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