Chapter 3
Microtubule Organization and Microtubule-Associated Proteins (MAPs)

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Abstract Dendrites have a unique microtubule organization. In vertebrates, dendritic microtubules are organized in antiparallel bundles, oriented with their plus ends either pointing away or toward the soma. The mixed microtubule arrays control intracellular trafficking and local signaling pathways, and are essential for dendrite development and function. The organization of microtubule arrays largely depends on the combined function of different microtubule regulatory factors or generally named microtubule-associated proteins (MAPs). Classical MAPs, also called structural MAPs, were identified more than 20 years ago based on their ability to bind to and copurify with microtubules. Most classical MAPs bind along the microtubule lattice and regulate microtubule polymerization, bundling, and stabilization. Recent evidences suggest that classical MAPs also guide motor protein transport, interact with the actin cytoskeleton, and act in various neuronal signaling networks. Here, we give an overview of microtubule organization in dendrites and the role of classical MAPs in dendrite development, dendritic spine formation, and synaptic plasticity.

3.1 Introduction

Microtubules (MTs) are cytoskeletal structures that play essential roles in all eukaryotic cells. MTs are important not only during cell division but also in non-dividing cells, where they are critical structures in numerous cellular processes such as cell motility, migration, differentiation, intracellular transport and organelle positioning. MTs are composed of two proteins, α- and β-tubulin, that form heterodimers and organize themselves in a head-to-tail manner. MTs are dynamic and they can rapidly switch between cycles of growth and shrinkage. This MT

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behavior is known as dynamic instability (Desai and Mitchison 1997; Howard and Hyman 2003; Mitchison and Kirschner 1984). Due to the head-to-tail polymerization, MTs are polar structures, designated by "plus" and "minus" ends, each with distinct characteristics. The two MT ends grow and depolymerize at very different rates; the "plus end" is the preferred site for MT assembly and disassembly, while the "minus end" is generally more stable in cells. Although MT minus ends can grow in vitro, minus ends are usually attached and stabilized at the centrosome or MT organizing center (MTOC) in cells (Jiang and Akhmanova 2011). The centrosome is also the primary site for MT nucleation in many cell types. Alternative sites for MT nucleation have been recently described (Bornens 2008). In addition to de novo MT nucleation, new MT ends can also be formed by breakage of preexisting MTs by severing proteins like spastin and katanin (Salinas et al. 2007).

The precise organization of MTs, including their composition, stability, orientation, and spacing, is essential for the correct development, morphology, and function of the neuron. The MT organization depends on several regulatory factors such as various tubulin isoforms, posttranslational modifications, and MT-associated proteins (MAPs). Largely based on their mode of action, the different MAPs can be roughly divided into five groups. The first group contains the MT-based motor proteins that are important for neuronal transport, such as kinesin and dynein motors (Hirokawa et al. 2010; Kardon and Vale 2009; Karki and Holzbaur 1999). The second set consists of regulators of MT dynamics, such as plus-end tracking proteins (+TIPs) and MT depolymerizers (Akhmanova and Steinmetz 2008; Brouhard and Rice 2014; Walczak et al. 2013). The third group contains proteins that modulate MT number, such as regulators of nucleation (Luders and Stearns 2007), enzymes that sever preexisting MTs (Roll-Mecak and McNally 2010; Sharp and Ross 2012), and minus-end targeting proteins (-TIPs), stabilizing minus ends (Akhmanova and Hoogenraad 2015). The fourth set comprises tubulin-modifying enzymes that, through posttranslational modifications, can generate distinct MT subtypes (Hammond et al. 2008; Janke and Bulinski 2011). The fifth group includes cross-linking proteins that align filaments and form MT bundles, such as classical MAPs and some kinesin motors that drive MT sliding (Bratman and Chang 2008; Dehmelt and Halpain 2005; Maccioni and Cambiazo 1995). The actions of many different MAPs together provide the mechanism to spatiotemporal control the architecture of the neuronal MT cytoskeleton during the different steps of development. It is therefore not surprising that, given the importance of these MT regulators, compensation mechanisms exist among different MAPs. This phenomenon is shown in the viability and the absence of strong phenotype in many MAP knockout mice (Table 3.1). However, more severe phenotypes have been observed in double knockouts for MAPs like MAP1B/MAP2 or MAP1B/tau. Double-knockout mice for MAP1B/tau or MAP1B/MAP2 show defects in brain layered structures and fiber track formation (Takei et al. 2000; Teng et al. 2001). Here, we give an overview of the MT organization in neurons and focus on the role of classical MAPs in dendrite development, dendritic spine formation, and synaptic plasticity.

Table 3.1 Animal models – phenotypes associated with classical MAPs

MAP	Knockout animal model phenotypes	References
MAP1A	Perturbation of learning processes Reduced LTP and LTD	Takei et al. (2015)
MAP1B/ MAP5	Body and brain weight loss	Takei et al. (2000), (1997), Edelmann et al. (1996), Gonzalez-Billault et al. (2000, 2005), Meixner et al. (2000), and Benoist et al. (2013)
	Delayed nervous system development	
	Reduced myelination	
	Corpus callosum absent	
	Impaired neuronal migration	
	Altered brain commissures and laminated structures	
	Smaller retina size	
	LTP enhanced and LTD disrupted	
	Motor system abnormalities and lack of exploring activity	
	Reduced motor nerve conduction velocity	
MAP8/ MAP1S	No major defect	Xie et al. (2011)
MAP2	No major defect	Harada et al. (2002), Teng et al. (2001), and Khuchua et al. (2003)
	Decrease in dendritic microtubule (MT) density	
	Disrupted dendritic morphology from CA1 neurons	
	Contextual memory altered	
MAP3/ MAP4	Not reported	
MAP6	Depleted synaptic vesicle pool	Andrieux et al. (2002), Brun et al. (2005), Bouvrais-Veret et al. (2007), (2008), Powell et al. (2007), Fradley et al. (2005), Fournet et al. (2010, (2012b), and Daoust et al. (2014)
	Impaired synaptic plasticity	
	Severe behavioral disorders	
	Abnormalities of glutamatergic, dopaminergic, acetylcholinergic/nicotinic, serotonergic, and noradrenergic neurotransmissions	
	Sensorimotor gating impairment	
	Defects in neuronal transport	
MAP7	Viable. Defects in spermatogenesis	Komada et al. (2000), Sung et al. (2008), Barlan et al. (2013), and Metzger et al. (2012)
	Reduced viability (in *Drosophila*)	
	Myonuclear positioning altered (in *Drosophila*)	
MAP9	Severe developmental defects and embryonic lethality (in zebra fish)	Fontenille et al. (2014)
Tau	Viable	Harada et al. (1994), Dawson et al. (2001), Ikegami et al. (2000), Lei et al. (2012), and Ma et al. (2014)
	Muscle weakness	
	Small caliber axons	
	Behavioral impairments and motor deficits	

3.2   Organization of Axonal and Dendritic Microtubules

The MT cytoskeleton in neurons differs from many other cell types. Even within a single neuron, different compartments have distinct MT properties and organization (Conde and Caceres 2009). For instance, MTs in axon and dendrites differ in their polarity orientations. In mammalian neurons, axons contain MTs with uniform orientation, directed away from the cell body (plus-end out), whereas in dendrites MT orientation is mixed, with about half plus-end out and half minus-end out MTs (Baas et al. 1988; Burton 1988) (Fig. 3.1). In *Drosophila* and *C. elegans* neurons, MTs in axons are arranged with their plus ends distal to the cell body, as in vertebrates. However, in dendrites most MTs are arranged with their minus ends distal to the cell body, although some mixed MTs have also been observed (Stone et al. 2008; Maniar et al. 2011). It is thought that differences in the MT cytoskeleton in axons and dendrites can facilitate polarized cargo trafficking (Kapitein and Hoogenraad 2011; Rolls 2011).

Three different techniques have been used to establish MT orientations in axons and dendrites: the hook-decoration method; fluorescently labeled plus-end tracking proteins, such as GFP-EB3; and second-harmonic generation (SHG) microscopy. In the hook method, exogenous tubulin is added to permeabilized cells and forms curved sheets ("hooks") on existing neuronal MTs. These hooks are visualized in cross section by electron microscopy and provide information about the orientation of axonal and dendritic MTs. This method provides sufficient resolution for counting individual MT orientations. However, the results are usually ambiguous because of the small sample size and the large fraction of non-marked MTs (Baas and Lin 2011). The use of fluorescently labeled plus-end tracking proteins as markers of growing MTs is a relatively easier technique (Stepanova et al. 2003). This method also has limitations because it only detects dynamic MTs and not the stable MT population. Recently, in vivo imaging of growing MTs has confirmed the presence of a mixed MT organization in mature dendrites (Kleele et al. 2014; Yau et al. 2016). SHG microscopy allows label-free imaging without the addition of exogenous probes, but is hard to interpret quantitatively. SHG was used in hippocampal slices to visualize the neuronal MT organization in axon and dendrites (Dombeck et al. 2003; Kwan et al. 2008).

How are the mixed MT arrays in dendrites generated and stabilized? It has been suggested that dendritic MTs are generated by (i) centrosomal nucleation and subsequent release from the centrosome, (ii) breakage of preexisting MTs by katanin or spastin, or (iii) nucleation at noncentrosomal sites, such as cortical γ-tubulin complexes, intracellular membranes, or preexisting MTs (Kuijpers and Hoogenraad 2011). Although the centrosome is the main nucleating point in non-polarized neurons, it loses its function as MTOC during early neuronal development, and only a few MTs emanate from the centrosome in mature neurons (Stiess et al. 2010). Consistently, it has been shown that noncentrosomal MTs are abundantly present in neurons (Yau et al. 2014). Recently, CAMSAP/Patronin/ Nezha family proteins have been characterized and found to specifically recognize
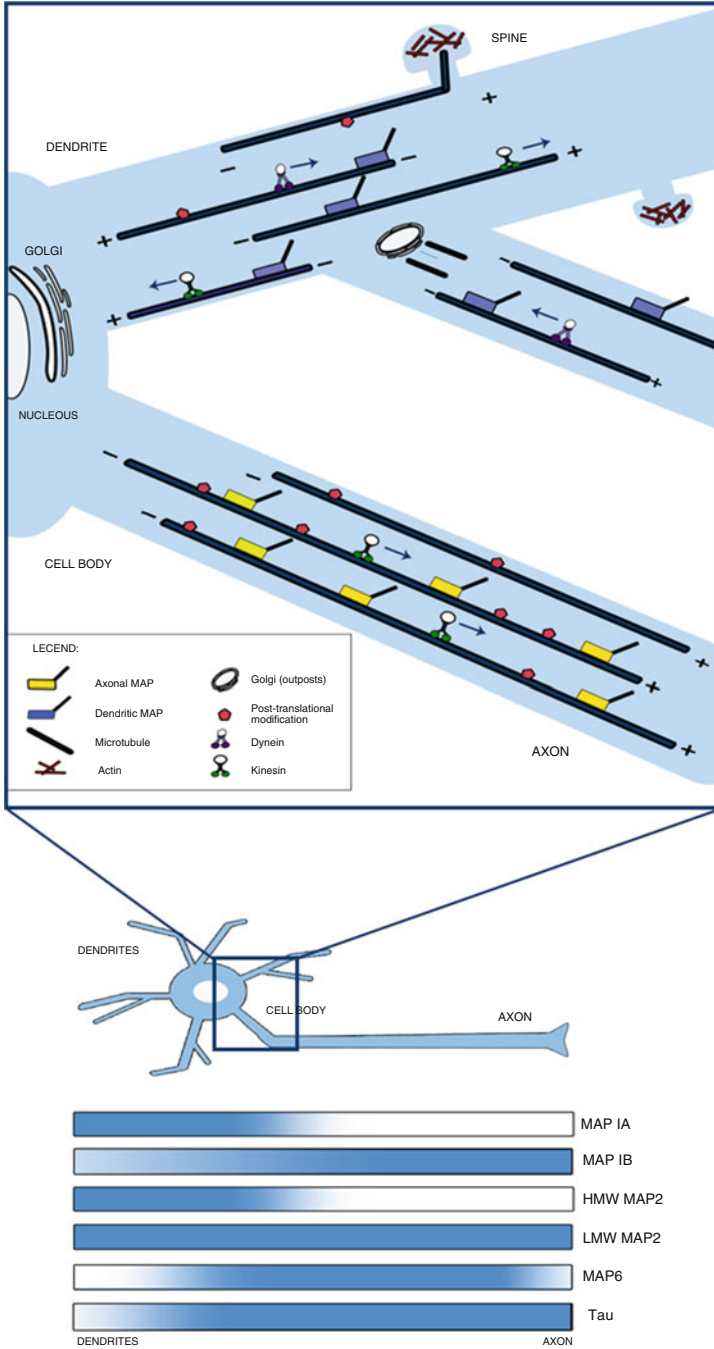
SPINE

DENDRITE

GOLGI

NUCLEOUS

CELL BODY

AXON

LEGEND:

Axonal MAP

Dendritic MAP

Microtubule

Actin

Golgi (outposts)

Post-translational modification

Dynein

Kinesin

DENDRITES

CELL BODY

AXON

MAP IA

MAP IB

HMW MAP2

LMW MAP2

MAP6

Tau

DENDRITES

AXON

Fig. 3.1 Cytoskeletal organization in neurons. Axons and dendrites present different MT polarity orientations. Axonal MTs are uniformly orientated, whereas MTs in dendrites have mixed orientations. Axonal and dendritic MTs also contain distinct MAPs and differ in their posttranslational modifications. Motor proteins carry out ATP-dependent movements along MTs and either

MT minus ends and stabilize free minus ends against depolymerization (Akhmanova and Hoogenraad 2015). By forming stable CAMSAP stretches at the MT minus ends, these short MT fragments may also serve as "seeds" for new MT regrowth. Indeed, repetitive MT plus-end growth was observed from CAMSAP2 stretches in neurons (Yau et al. 2014). CAMSAP2 is required for neuronal polarity, axon specification, and dendritic branch formation in vitro and in vivo (Yau et al. 2014). The Golgi has also been proposed as a potential site of noncentrosomal MT nucleation (Efimov et al. 2007). In neurons, Golgi outposts have been found in the dendrites and may not only provide local membrane delivery but also act as local MT nucleation points (Horton et al. 2005; Ori-McKenney et al. 2012; Ye et al. 2007). Several other factors are known to regulate MT bundle formation in nonneuronal cells and may play a role in setting up mixed MT organizations in dendrites. For instance, motor proteins, such as MKLP1 (kinesin-6), Eg5 (kinesin-5), and KIF15 (kinesin-12, also called HKLP2), are known to organize antiparallel MT organizations in other systems. Indeed, depletion of each of these factors has been shown to disturb dendrite morphology (Kahn et al. 2015; Lin et al. 2012). In *Drosophila* neurons, EB proteins and kinesin-2 motors are important factors in setting up the uniform minus-end out MT network in dendrites (Mattie et al. 2010). It has been suggested that the minus-end out MT organization in neurons is maintained by steering of polymerizing MTs along the stable MTs by kinesin-2 motors bound to growing MT plus ends (Chen et al. 2014; Doodhi et al. 2014). Other motor proteins, such as kinesin-1, might also be able to cross-link antiparalleled MTs and are critical in forming the characteristic minus-end out MT organization of *C. elegans* dendrites (Yan et al. 2013).

Axonal and dendritic MTs not only differ in their organization but also in their stability. It has been demonstrated that axonal MTs are more resistant to the MT depolymerizing drug nocodazole compared to the dendritic MT population (Baas et al. 1991; Witte et al. 2008). Recently, a new posttranslational modification of tubulin has been identified that directly confers stability to MTs (Song et al. 2013). Biochemical characterization of stable MT fractions demonstrated that polyamination of tubulin is directly involved in stabilizing neuronal MTs. The most commonly studied posttranslational modifications are either acidic (phosphorylation and glutamylation) or charge neutral (acetylation and detyrosination), and they do not directly confer stability to MTs but, rather, accumulate on long-lived MTs (Janke and Kneussel 2010). There is a clear correlation between MT acetylation/detyrosination and stable MTs, and MT tyrosination with dynamic MTs. The different MT posttranslational modifications show a polarized distribution in neurons (Hammond et al. 2010; Kollins et al. 2009; Witte et al. 2008). In growing axons, the ratios of acetylated and

Fig. 3.1 (continued) drive cargo transport toward the *minus end* (dynein) or toward the *plus end* (kinesin). Dynamic MTs can enter dendritic spines and may deliver specific cargos to individual spines. Golgi outposts are present along dendrites and may serve as sites of noncentrosomal MT nucleation. CAMSAP binds to MT *minus ends* and is required for the stabilization of noncentrosomal MTs

detyrosinated tubulin are higher than in the developing neurites, whereas the ratio of glutamylated tubulin does not show differences between these two compartments (Hammond et al. 2010). On the other hand, tyrosinated MTs are more abundant at the tip of the axon and in developing dendrites (Kollins et al. 2009). It has been suggested that the local diversity of posttranslational modifications is due to the specific local-ization or activity of the modifying enzymes (Hammond et al. 2010). Some posttrans-lational modifications seem to be essential for proper neuronal development. For example, lack of tyrosinated tubulin in tubulin-tyrosine ligase (TTL) null neurons caused extensive defects in neurite outgrowth and axon development (Erck et al. 2005). The MT posttranslational modifications may also regulate the interaction of other factors with MTs. For example, acetylation of MTs increases the severing activity of katanin (Sudo and Baas 2010). Moreover, posttranslational modifications have been implicated in the regulation of several motor proteins. For instance, kinesin-1 has been reported to prefer stable (acetylated/detyrosinated) MTs (Dunn et al. 2008; Konishi and Setou 2009; Liao and Gundersen 1998; Reed et al. 2006). Additional in vitro studies showed that kinesin-1 motility is increased by polyglutamylation and that detyrosination of α-tubulin promotes kinesin-2 motility (Sirajuddin et al. 2014). It has been hypothesized that posttranslational modifications, together with specific MAP patterns, form a "tubulin code" that can be "read" by factors that interact with MTs, such as motor proteins (Janke and Bulinski 2011; Tischfield and Engle 2010; Verhey and Gaertig 2007). In this way, distinct "tubulin codes" in axons and dendrites may drive polarized cargo sorting of various organelles and proteins into axons and dendrites (Kapitein and Hoogenraad 2011; Rolls 2011).

3.3   Functions of Axon and Dendritic Microtubules

MTs are essential structures in axons and dendrites because they serve as major tracks for long-distance transport and form the basis for stable neuronal morphol-ogy. However, MTs are not just passive elements, they also confer plasticity to the neuron and have an active role during different phases of neuronal development. MTs participate in the morphological changes during neuronal migration and differentiation, for instance, by regulating axonal outgrowth, organelle positioning, and dendritic spine dynamics (Hoogenraad and Bradke 2009). Recent studies have found that defects in many MT-related genes lead to a range of nervous system abnormalities and several neurological and neurodegenerative diseases (Gupta et al. 2002; Jaglin and Chelly 2009; Manzini and Walsh 2011; Tischfield et al. 2011). For instance, mutations in genes encoding α- and β-tubulin subunits alter MT dynamics and show defects in axon guidance, neuronal migration, and synaptic connectivity (Jaglin et al. 2009; Keays et al. 2007; Tischfield et al. 2010). In addition, recent studies highlight MTs as a potential target for therapeutic interventions for axon regeneration and neurodegenerative diseases (Baas and Ahmad 2013; Gerdes and Katsanis 2005). Therefore, control of MT organization is of key importance for proper neuronal development and function.

MTs have been extensively studied with respect to axon formation, axon growth, and axon guidance (Hoogenraad and Bradke 2009; Poulain and Sobel 2010). It is known that MTs are also required for dendritic development and dendritic tiling (Grueber and Sagasti 2010; Koleske 2013; Rolls 2011). In many different organisms, proper dendrite morphology depends on MAPs, which regulate MT stabilization, bundling, spacing, and dynamics. MAPs also regulate intracellular transport or link MTs to the actin cytoskeleton, which is another important player in dendrite development (Lansbergen and Akhmanova 2006; Poulain and Sobel 2010; Siegrist and Doe 2007). For instance, classical MAPs like MAP1A and MAP2 are important for dendrite morphogenesis, and upregulation of their expression is correlated with dendrite outgrowth (Harada et al. 2002; Szebenyi et al. 2005; Vaillant et al. 2002). MAP2 knockout mice show altered MT spacing and reduced dendrite arbor size (Harada et al. 2002; Teng et al. 2001). Other MT-related proteins, such as the plus-end binding proteins CLIP-170 and CLASP2, and the minus-end binding protein CAMSAP2, are also involved in dendrite development (Beffert et al. 2012; Swiech et al. 2011; Yau et al. 2014). Moreover, the MT-destabilizing proteins stathmin and SCLIP, or MT-severing proteins, like spastin and katanin p60-like 1, have been reported to regulate dendrite development (Jinushi-Nakao et al. 2007; Lee et al. 2009; Ohkawa et al. 2007; Poulain et al. 2008; Stewart et al. 2012; Ye et al. 2011). In addition, motors that drive dendritic transport are crucial for dendrite morphology (Kapitein et al. 2010; Satoh et al. 2008; Zheng et al. 2008). Therefore, many MT-related factors regulating MT organization, dynamics, and remodeling are critical for proper dendritic development.

In addition to the growth and development of dendrites, MTs are needed for spine morphology and various synaptic processes, including spine formation (Shirao and Gonzalez-Billault 2013), dendritic and synaptic pruning (Kage et al. 2005; Lee et al. 2009; Luo and O'Leary 2005), and synaptic plasticity (Conde and Caceres 2009; Hoogenraad and Bradke 2009). MTs are abundantly present in the dendritic shaft; however, dynamic MTs can also enter actin-rich dendritic spines and regulate synaptic processes (Gu and Zheng 2009; Hu et al. 2008; Jaworski et al. 2009). MT entries in spines may directly regulate spine morphology or provide a way to selectively transport organelles, receptors, and other regulatory factors necessary for synaptic function (Hoogenraad and Bradke 2009). In addition, some classical MAPs like MAP1B and MAP2 have been found in dendritic spines and may regulate their development (Caceres et al. 1983; Collins et al. 2005; Kawakami et al. 2003; Peng et al. 2004; Tortosa et al. 2011). Several other MT regulatory factors such as collapsin response mediator protein (CRMP) members, doublecortin family member DCLK1, and spinophilin/neurabin control dendritic spine maturation (Ryan et al. 2005; Shin et al. 2013; Terry-Lorenzo et al. 2005; Yamashita et al. 2007). Moreover, MAP1B, MAP6, CLASP2, and CRMP family proteins have been implicated to influence synaptic plasticity processes (Andrieux et al. 2002; Beffert et al. 2012; Benoist et al. 2013; Su et al. 2007; Yamashita et al. 2011).

3.4 Classical Maps

Classical MAPs, also called structural MAPs, were isolated more than 20 years ago from mammalian brains by copurification with MTs (Schoenfeld and Obar 1994). A general overview of domain structure of classical MAPs is given in Fig. 3.2. In vitro studies showed that most MAPs bind along the MT lattice and regulate MT polymerization and stabilization. However, the binding characteristics and effect on MTs are different among all MAPs. For instance, MAP2 only needs a single protofilament for MT binding, while other MAPs like MAP4 interact with adjacent protofilaments (Al-Bassam et al. 2002; Kawachi et al. 2003). Some of them, like tau or MAP2, induce MT bundling, whereas others like MAP4 do not have bundling activity (Burgin et al. 1994; Kanai et al. 1989, 1992; Nguyen et al. 1997; Olson et al. 1995). In addition, MAP1B has been shown to control MT dynamic, while MAP4 alters MT surface properties and affects motor protein activity (Bulinski et al. 1997; Samora et al. 2011; Semenova et al. 2014; Tokuraku et al. 2007; Tortosa et al. 2013; Utreras et al. 2008). Interestingly, many of these MAPs not only bind MTs but also interact with actin and participate in numerous signal pathways. Tables 3.2 and 3.3 give an overview of the various phenotypes observed in cultured cells caused by MAP downregulation or overexpression. Given the importance of MAPs for neuronal development and function, it is not surprising that many MAPs are associated with neurological and neurodegenerative diseases. For example, pathological aggregation of tau protein in the human brain leads to neurodegenerative diseases called tauopathies (Zempel and Mandelkow 2014). The best-known tauopathy is Alzheimer's disease, where tau protein is deposited within neurons in the form of neurofibrillary tangles (Avila et al. 2004). Moreover, the deletion of MAP6 in mice leads to severe phenotypes reminiscent of schizophrenia-like symptoms (Andrieux et al. 2002; Fournet et al. 2012b).

3.4.1 MAP1 Family of Microtubule-Associated Proteins

In mammals, MAP1 family proteins include three members: MAP1A, MAP1B, and MAP1S, which are all encoded by different genes. MAP1A and MAP1B are predominantly expressed in neurons and important for the formation and development of axons and dendrites. MAP1S is widespread in murine tissues, and little is known about its function. In *Drosophila*, the single MAP1 homolog is called Futsch, which has been shown to be important in dendritic and axonal development, and regulates synaptic growth. All MAP1 members are multiprotein complexes, formed by a heavy chain and one or two light chains. They are translated as polypeptides and processed by proteolytic cleavage, which leads to the generation of distinct heavy chains (MAP1A-HC, MAP1B-HC, and MAP1S-HC) and light chains (LC2 from MAP1A, LC1 from MAP1B, and MAP1S-LC). Later, HC and LC are assembled together with LC3, which is encoded by a separate gene. Both
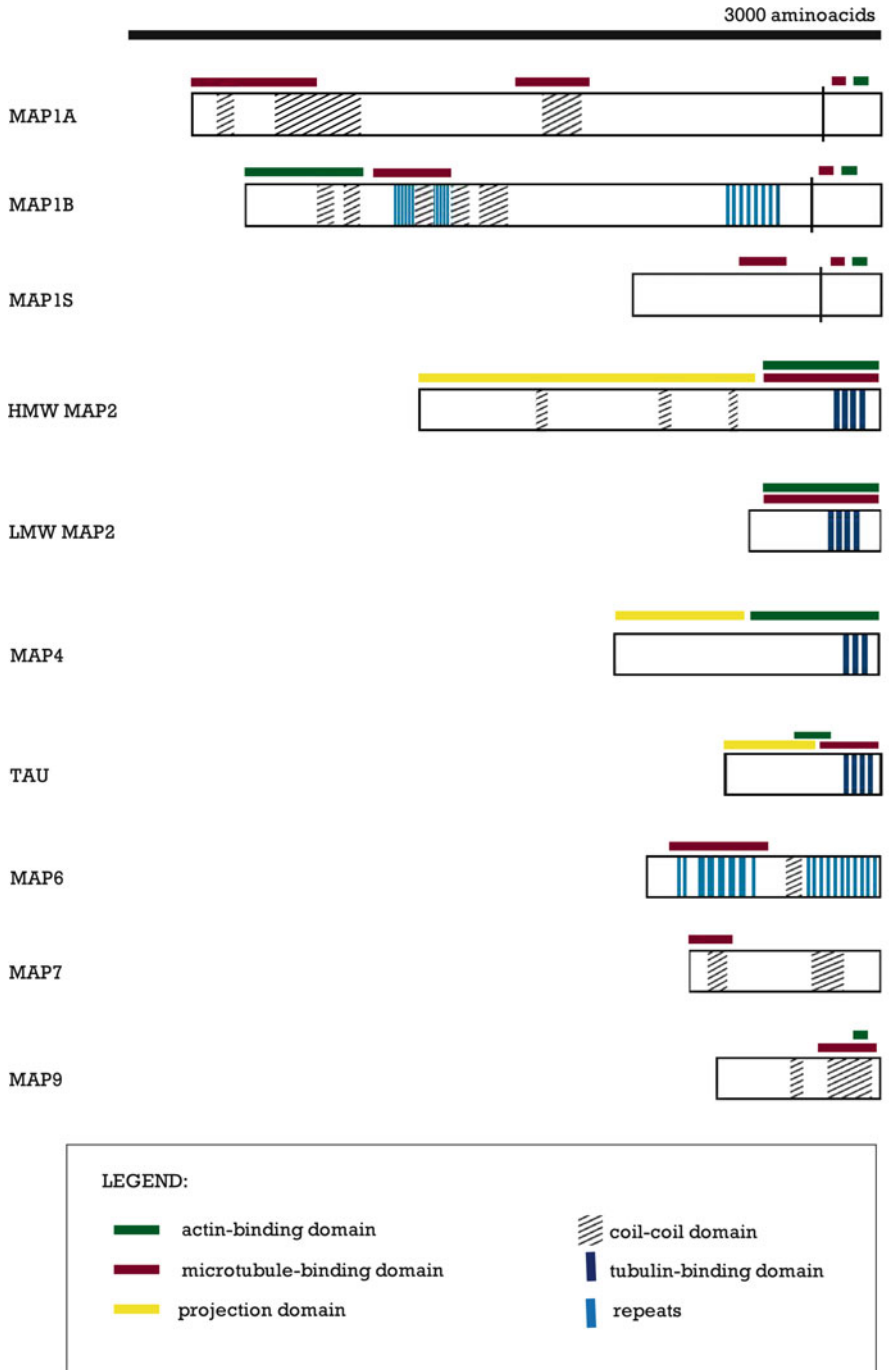
Fig. 3.2 Schematic diagram of classical microtubule-associated proteins (MAPs). The major structural motifs in classical MAPs are illustrated in the diagram. The MAP family proteins contain different MT-binding domains. In MAP2, MAP4, and tau, the MT-binding regions are

HC and LC can bind MTs, filamentous actin, and many other cellular components. Furthermore, their activity is controlled by upstream signaling mechanisms, such as the MAP kinase and glycogen synthase kinase-3 pathways (Halpain and Dehmelt 2006).

MAP1C was originally described as a MAP1 family member with ATPase activity, and further characterization revealed that it represents the microtubule-based motor protein cytoplasmic dynein (Johnson et al. 1984; Paschal et al. 1987; Paschal and Vallee 1987; Vale et al. 1985; Vallee et al. 1988). Dynein is involved in a variety of basic cellular functions, such as the movement of organelles; transport of vesicles, proteins, and mRNA; maintenance of the Golgi apparatus; endosome recycling; cytoskeletal reorientation; and the positioning of the mitotic spindle (McNally 2013; Vallee et al. 2004; Yadav and Linstedt 2011). In neurons, it has a role in neuronal migration, retrograde axonal transport, and polarized trafficking into dendrites (Chevalier-Larsen and Holzbaur 2006; Kapitein and Hoogenraad 2011; Vallee et al. 2009). Mutations in dynein have been directly linked to various neurological and neurodegenerative diseases (Lipka et al. 2013). Here, we will give a general overview of the other three MAP1 family members (MAP1A, MAP1B, and MAP1S) and briefly discuss their role in neuronal development.

3.4.1.1 MAP1 Family Member MAP1A

MAP1A is predominantly expressed in neurons, where it is enriched in dendrites (Schoenfeld et al. 1989) (Fig. 3.1). MAP1A expression increases between 4 and 7 days in hippocampal cultures in vitro and around the second week after birth in the developing mouse brain. During this time, dendrites elongate, branch, and start to make contact with other neurons (Schoenfeld et al. 1989; Szebenyi et al. 2005). MAP1A is a weak MT stabilizer and is important for the functional maintenance and plasticity in mature neurons (Faller and Brown 2009; Takei et al. 2015). MAP1A interacts with actin and postsynaptic components like PSD93/PSD95, and anchors NMDA receptors to the cytoskeleton, supporting their transport along the dendrites (Brenman et al. 1998; Pedrotti et al. 1994b; Reese et al. 2007; Takei et al. 2015). Loss of the MAP1A-PSD95 interaction has been associated with hearing loss, due to defects in synaptic function (Ikeda et al. 2002). MAP1A also

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Fig. 3.2 (continued) conserved and well defined (see tubulin-binding domain: pfam00418). Most of the MAPs also contain a coiled-coil region and binding sites for actin. The *light-blue boxes* in the MAP structure indicate repeat domains contributing in some cases to MT binding (amino terminal repeats in MAP1B or repeats in MAP6) or with unknown function in other cases (carboxyl terminal repeats in MAP1B or MAP6). The *yellow lines* indicate the projection domain of some MAPs (MAP2 projection domain: pfam08377). The following rat protein sequences were used for the drawings: MAP1A (NP_112257.1), MAP1B (NP_062090.1), MAP1S (NP_001099540.1), HMWMAP2 (P15146.1), LMWMAP2 (P15146.4), MAP4 (NP_001019449.1), tau (XP_008766496.1), MAP6 (NP_058900.1), MAP7 (NP_001099740.2), and MAP9 (NP_001129188.1)

Table 3.2 Cell culture – alterations caused by classical MAP downregulation

MAP	Inhibition in culture	References
MAP1A	Activity-induced remodeling of the dendritic arbor (dendritic length and branching) blocked	Szebenyi et al. (2005), Takei et al. (2015) and Leenders et al. (2008)
	Dendritic growth inhibited (in mature cultures)	
	Retraction of existing branches	
	Density of active synapses reduced	
	Synaptic surface density of Ca(V)2.2 decreased	
	Enhanced activity-dependent degradation of PSD-93	
	Reduced surface expression and transport of NR2A/2B	
MAP1B/ MAP5	Axon formation delayed	Gonzalez-Billault et al. (2001, 2002b), DiTella et al. (1996), Bouquet et al. (2004), Del Rio et al. (2004), Tortosa et al. (2011, 2013), and Benoist et al. (2013)
	Reduced neurite and axonal length	
	Increased axonal branching	
	Axon guidance altered	
	Formation and maturation of dendritic spines disrupted	
	AMPA receptor-mediated synaptic currents diminished	
	MT dynamics altered	
	Tyrosinated MTs decreased	
MAP8/ MAP1S	Accumulation of dysfunctional mitochondria and autophagosomes (in cardiomyocytes)	Xie et al. (2011)
MAP2	Neurite and axon outgrowth inhibited	Caceres et al. (1992), Gonzalez-Billault et al. (2002a), Sharma et al. (1994), Harada et al. (2002), Dehmelt et al. (2003), and Iriuchijima et al. (2005)
	Reduction in dendritic length	
	cAMP-dependent protein kinase reduced in the dendrites	
	KAP expression reduced	
MAP3/ MAP4	Transport altered (Xenopus melanophores)	Semenova et al. (2014), Samora et al. (2011), and Nguyen et al. (1999)
	Spindle misorientation (epithelia cells)	
	Decreased content of total tubulin (HeLa cells)	
MAP6	Neurite formation impaired (in PC12 cells)	Guillaud et al. (1998), and Andrieux et al. (2002)
	MT loss to cold or nocodazole	
MAP7	Transport altered (in *Drosophila* neurons)	Barlan et al. (2013) and Sung et al. (2008)
	Kinesin-1 recruitment to MTs and motility impaired (ovary extracts and S2 cells, in *Drosophila*)	
MAP9	Severe mitotic defects and cell death (U2OS cells)	Saffin et al. (2005)

(continued)

Table 3.2 (continued)

MAP	Inhibition in culture	References
Tau	Reduced neurite number and length	Liu et al. (1999), Yu et al. (2008), Caceres and Kosik (1990), Caceres et al. (1991), Dawson et al. (2001), and Zempel et al. (2013)
	Decreased axonal elongation and increased axonal branching	
	Neuronal migration inhibited	
	Delayed axonal extension	
	Dendritic length decreased	
	MTs and synapses resistant to Aβ toxicity	

Table 3.3 Cell culture – alterations caused by classical MAP overexpression

MAP	Overexpression in culture	References
MAP1A	MT dynamic altered	Faller and Brown (2009) and Gupta and Yarwood (2005)
	Enhances Rap1 activation by EPAC1	
MAP1B/ MAP5	Cell death	Allen et al. (2005), Tortosa et al. (2013), Tymanskyj et al. (2012), and Opal et al. (2003)
	Altered MT dynamics	
	Delayed neuritogenesis (in PC12 cells)	
MAP8/ MAP1S	Neurite degeneration and cell death	Ding et al. (2006a)
	MT alterations	
	Axonal transport disruptions	
MAP2	Increased axonal branching	Fukata et al. (2002) and Dehmelt et al. (2003)
	Neurite formation in N2A	
MAP3/ MAP4	Transport altered (Ltk cells and Xenopus melanophores)	Semenova et al. (2014) and Bulinski et al. (1997)
MAP6	Reduced dendritic arborization	Schwenk et al. (2014)
	Accelerated retrograde transport	
MAP7	Formation of noncentrosomal MTs (Vero cells)	Masson and Kreis (1993)
MAP9	Aberrant spindles in mitosis (HEK-293 cells)	Saffin et al. (2005)
Tau	Reduced axon elongation	Fukata et al. (2002), Dubey et al. (2008), Chee et al. (2006), Hoover et al. (2010), Stamer et al. (2002), and Zempel et al. (2013)
	Synaptic responses impaired (mutant tau)	
	Dendritic TTLL6 translocation	
	Decreased MT stability	
	Impaired axonal transport	
	Retraction of growing neurites (NB2 cells)	
	Defective synaptic transmission (in *Drosophila* neuromuscular junctions)	

has a presynaptic function. LC2 interacts with the voltage-dependent calcium channels Ca(V)2.2 and mediates its surface localization at presynaptic boutons (Leenders et al. 2008). In addition, MAP1A has been found to localize to clathrin-coated vesicles and to the cargo-adaptor protein AP2 complex (Murakami et al. 2012; Praefcke et al. 2004). Many MAP1A binding partners have been described as signaling factors, suggesting that MAP1A functions as an adaptor to link signaling molecules to MTs. For example, MAP1A can interact with proteins EPAC (exchange protein directly activated by cAMP) (Gupta and Yarwood 2005), the disrupted-in-schizophrenia 1 protein (DISC1) (Morris et al. 2003), the kinase CK1δ (Wolff et al. 2005), BKCa potassium channel (Park et al. 2004), tubby-like protein-1 (Tulp1) (Grossman et al. 2014), the small GTPases RhoB (Lajoie-Mazenc et al. 2008), and a component of the dystrophin-associated protein complex, α1-syntrophin (Fuhrmann-Stroissnigg et al. 2012). Interestingly, disruption of MAP1A could be a very early manifestation of amyloid β-mediated synaptic dysfunction since sublethal doses of soluble Aβ species induce degradation of MAP1A (Clemmensen et al. 2012).

3.4.1.2 MAP1 Family Member MAP1B

In the 1980s, different labs described MAP1B and named the protein MAP1.2, MAP1(x), and MAP5 (Asai et al. 1985; Bloom et al. 1985; Calvert and Anderton 1985; Riederer et al. 1986). MAP1B is strongly expressed in the nervous system during early embryonic development and downregulated during later developmental stages (Diaz-Nido et al. 1990; Garner et al. 1989; Schoenfeld et al. 1989; Tucker et al. 1988b; Tucker and Matus 1988; Viereck et al. 1989). In the mature brain, MAP1B is present in regions with high plasticity, such as the hippocampus (Schoenfeld et al. 1989; Tucker et al. 1989; Viereck et al. 1989). MAP1B is mainly expressed in neurons; however, it is also detected in neuronal progenitors, oligodendrocytes, and astrocytes (Cheng et al. 1999; Fischer and Romano-Clarke 1990; Ulloa et al. 1994a). In developing neurons, MAP1B is present at high levels in growing axons, whereas in mature neurons MAP1B is also present in dendrites and postsynaptic densities (Fig. 3.1) (Black et al. 1994; Collins et al. 2005; Kawakami et al. 2003; Peng et al. 2004; Tortosa et al. 2011). Posttranslational modifications can affect both MAP1B distribution and function. MAP1B can be phosphorylated by many kinases such as casein kinase II (Diaz-Nido et al. 1988; Ulloa et al. 1993), the serine/threonine protein kinase GSK3 (Garcia-Perez et al. 1998; Tymanskyj et al. 2012), the cyclin-dependent kinase 5 together with its regulatory subunit p35 (Kawauchi et al. 2005; Paglini et al. 1998; Pigino et al. 1997), the dual-specificity tyrosine phosphorylation-regulated kinase DYRK1 (Scales et al. 2009), cdc2 (Ulloa et al. 1994b), and members of the mitogen-activated protein kinase family like ERK1/ERK2 (Loeb et al. 1992) and JNK1 (Chang et al. 2003). MAP1B can bind both actin and MTs, and has been suggested to link the two cytoskeletal elements together (Garcia Rocha and Avila 1995; Mansfield et al. 1991; Pedrotti and Islam 1995; Pedrotti et al. 1996). MAP1B, compared with other MAPs, is a weak MT stabilizer (Takemura et al. 1992). Recent studies suggest that MAP1B preferably

associates to dynamic, tyrosinated MTs (Tortosa et al. 2013; Tymanskyj et al. 2012; Utreras et al. 2008). MAP1B also interacts with other MT-interacting proteins, including tubulin-tyrosine ligase and EB1/EB3, dynein regulators like LIS1, scaffolding proteins such as dystonin-α2, and motor protein KIF21A (Cheng et al. 2014; Villarroel-Campos and Gonzalez-Billault 2014).

The role of MAP1B in axon formation has been studied for many years (Gordon-Weeks and Fischer 2000). Suppression of MAP1B with antisense oligonucleotides inhibits laminin-enhanced axon growth (DiTella et al. 1996). In addition, hippocampal neurons from MAP1B-deficient mice show a significant delay in axon outgrowth and a decreased axonal elongation (Gonzalez-Billault et al. 2001; Takei et al. 2000). MAP1B is involved in dendritic spine formation and synaptic maturation by regulating the actin cytoskeleton, and has a role in AMPA receptors endocytosis and long-term depression (LTD) in mature neurons (Benoist et al. 2013; Davidkova and Carroll 2007; Lebeau et al. 2011; Tortosa et al. 2011). Moreover, MAP1B can interact with many neurotransmitter receptors such as GABAc receptor, NMDA receptor subunit NR3A, glycine receptor α1 subunit, mGluR receptors, serotonin receptors, and various channels, including the voltage-gated Ca2+ channel Ca(V)2.2 and the sodium channel Nav1.6. It can also interact with receptor regulatory proteins such as glutamate receptor-interacting protein GRIP1 and the AMPA receptors regulating protein stargazin (Villarroel-Campos and Gonzalez-Billault 2014). It is widely believed that MAP1B could act as a scaffold for many of the above mentioned factors by anchoring them to the MT cytoskeleton or controlling their activity and localization. MAP1B has been linked to various neurodegenerative disorders, including Parkinson's disease (Chan et al. 2014; Jensen et al. 2000), Alzheimer's disease (Gevorkian et al. 2008; Good et al. 2004; Hasegawa et al. 1990), giant axonal neuropathy (Allen et al. 2005; Ding et al. 2002), spinocerebellar ataxia type 1 (Opal et al. 2003), fragile X syndrome (Brown et al. 2001; Lu et al. 2004; Zalfa et al. 2003), and the eye-related muscular disorder congenital fibrosis of the extraocular muscles type 1 (CFEOM) (Cheng et al. 2014).

3.4.1.3 MAP1 Family Member MAP1S

MAP1S (also named MAP8, VCY2IP1, and C19ORF5) is the shortest MAP1 protein. MAP1S is expressed in various tissues, including the brain, where it is predominately present in neurons. Compared to other MAPs, this protein has relatively low expression levels (Ding et al. 2006b; Orban-Nemeth et al. 2005). The light chain of MAP1S not only binds and stabilizes MTs but also contains an actin-binding site, suggesting that it may act as a cross-linker between the MT and actin cytoskeletal networks (Ding et al. 2006b; Orban-Nemeth et al. 2005). Recent evidences suggest that MAP1S can also link mitochondria and autophagosomes to MTs (Xie et al. 2011). In the mammalian brain, interaction between NMDA receptor subunit NR3A and MAP1S has been described, and a role in the trafficking and localization of NR3A-containing NMDAR has been proposed (Eriksson et al. 2007). Another neuronal interactor for MAP1S is the WD40 repeat protein nemitin (Wang et al. 2012). No developmental or behavioral defects have been

observed in MAP1S-deficient mice (Xie et al. 2011). However, high levels of MAP1S cause excessive MT stabilization, disrupt axonal transport, and lead to neuronal death (Ding et al. 2006a).

3.4.2   MAP2 Family of Microtubule-Associated Proteins

MAP2 is the most abundant structural MAP in the brain (Matus 1988; Olmsted 1986; Wiche et al. 1991). MAP2 is mainly expressed in neurons, but it is also detected in nonneuronal cells such as oligodendrocytes and astrocytes (Papasozomenos and Binder 1986; Vouyiouklis and Brophy 1995). All MAP2 isoforms are transcribed from a single gene. MAP2 isoform has been classified into two groups: high molecular weight MAP2 (HMWMAP2), which includes MAP2A and MAP2B, and low molecular weight (LMWMAP2), with MAP2C and MAP2D. MAP2A is mainly present in the adult brain, whereas MAP2B is expressed all along the development of the nervous system (Binder et al. 1984; Burgoyne and Cumming 1984; Nunez 1988). MAP2C is mainly expressed at early developmental stages, but also present in adult brain areas where neuritogenesis occurs like the retina and olfactory bulb (Goedert et al. 1991; Hartel and Matus 1997; Nunez 1988; Przyborski and Cambray-Deakin 1995; Riederer and Matus 1985; Tucker and Matus 1988; Viereck et al. 1989). In contrast, MAP2D is detected in rat brain early after birth and is present at all developmental stages (Doll et al. 1993; Ferhat et al. 1998).

LMWMAP2 is widely distributed in all neuronal compartments (Albala et al. 1995; Meichsner et al. 1993; Tucker et al. 1988a). In contrast, HMWMAP2 is selectively localized in the cell body and dendrites of neurons (Bernhardt and Matus 1982; Caceres et al. 1984, 1986; Chung et al. 1996; Lev and White 1997; Scheetz and Dubin 1994; Shafit-Zagardo and Kalcheva 1998) (Fig. 3.1). MAP2 has also been found in dendritic spines and postsynaptic densities (Caceres et al. 1983; Fifkova and Morales 1992; Hayashi et al. 1996; Langnaese et al. 1996). The specific localization of MAP2 in dendrites is most likely due to a combination of several mechanisms, including dendrite-specific localization of MAP2 mRNA, suppression of MAP2 sorting into axons, and differential protein stability and turnover of MAP2 dendrites (Garner et al. 1988; Hirokawa et al. 1996; Kanai and Hirokawa 1995; Okabe and Hirokawa 1989).

MAP2 forms bundles and determines MT spacing (Avila et al. 1994; Chen et al. 1992; Cunningham et al. 1997; Dhamodharan and Wadsworth 1995; Felgner et al. 1997; Itoh et al. 1997; Kalcheva et al. 1998; Kowalski and Williams 1993; Kurz and Williams 1995; Vandecandelaere et al. 1996; Yamauchi et al. 1993). MAP2 can also bind to actin and to neurofilaments (Bloom and Vallee 1983; Papasozomenos et al. 1985; Pedrotti et al. 1994a; Selden and Pollard 1983). It is highly phosphorylated and this phosphorylation controls the interaction with MTs (Sanchez et al. 2000). MAP2 is thought to be a structural protein important for neurite outgrowth and maintaining the overall MT architecture in dendrites. More-over, MAP2 is likely to play a role during neuronal plasticity processes (Fanara

et al. 2010; Harada et al. 2002; Teng et al. 2001). Interesting in this respect is the observation that chemical LTD in cultured neurons induced the accumulation of EB3 along MAP2-positive MT bundles in the dendritic shaft (Kapitein et al. 2011). In addition, MAP2 is known to effect MT-based transport and has been involved in the association of rough endoplasmic reticulum membranes with MTs (Farah et al. 2005; Heins et al. 1991; Lopez and Sheetz 1993, 1995; Maas et al. 2009; von Massow et al. 1989). MAP2 also participate in the somato-dendritic localization of numerous signaling proteins, such as cAMP-dependent protein kinase (PKA) and its regulatory subunit (Davare et al. 1999; Obar et al. 1989; Rubino et al. 1989; Theurkauf and Vallee 1982), kinase-associated phosphatase (KAP) (Iriuchijima et al. 2005), phosphatase PP2A/Bα (Sontag et al. 2012), calmodulin (Kotani et al. 1985), and tyrosine-protein kinases Src and Fyn (Lim and Halpain 2000; Zamora-Leon et al. 2001). MAP2 can also bind other neuronal proteins, including calcium channels (Davare et al. 1999), MAP2 RNA transacting proteins (MARTA) (Rehbein et al. 2000), CRMP5 (Brot et al. 2010), neural cell adhesion molecule L1 (L1CAM) (Poplawski et al. 2012), and the KIND domain containing RasGEF, very-KIND (Huang et al. 2007). Changes in MAP2 expression levels have been linked to numerous neurological and neurodegenerative diseases such as schizophrenia (Rosoklija et al. 2005) and epilepsy (Jalava et al. 2007; Yan et al. 2012), Alzheimer's disease (Canas et al. 2009; Capetillo-Zarate et al. 2006; Dziewczapolski et al. 2009; Moolman et al. 2004; Takahashi et al. 2013; Wu et al. 2004), spinal cord injury (Abdanipour et al. 2014; Gonzalez et al. 2009), stress (Yan et al. 2010), myotonic dystrophy (Velazquez-Bernardino et al. 2012), and prion diseases (Zhang and Dong 2012).

3.4.3 MAP3/MAP4 Family of Microtubule-Associated Proteins

MAP3 was originally described as a heat-stable protein in a variety of tissues, including the brain, and was later found to be identical to MAP4 (Bulinski and Borisy 1980; Kobayashi et al. 2000; Parysek et al. 1984). MAP4 is encoded by a single gene from which multiple mRNAs are transcribed (Code and Olmsted 1992; West et al. 1991). During development, MAP4 appears transiently in some neurons, while persisting in others, suggesting that MAP4 could be involved in early development. In the adult brain, MAP4 is present in both neurons and glia, but in neurons it is restricted to neurofilament-rich axons (Bernhardt et al. 1985; Huber et al. 1985; Matsushima et al. 2005; Matus et al. 1983; Tokuraku et al. 2010; Voss et al. 1998). Therefore, MAP4 has been considered as a candidate to cross-link MTs and neurofilaments (Huber et al. 1985). In cultures, MAP4 shows patchy staining patterns and localizes at branching points (Tokuraku et al. 2010). In addition, a shorter and neuron-specific isoform has been described, which is restricted to neural ectoderm-derived tissues such as the brain and the adrenal medulla, and its

expression is augmented by the addition of nerve growth factor (Matsushima et al. 2005). The short MAP4 isoform still induces MT assembly, but is unable to form bundles (Matsushima et al. 2005). MAP4 promotes tubulin polymerization in vitro and co-localizes with MTs in vivo, binding both glutamylated and tyrosinated MTs (Chapin and Bulinski 1994; Huber et al. 1986; West et al. 1991). The binding of MAP4 to MTs induces conformational changes that promote the overall MT stability (Xiao et al. 2012). MAP4 has also been reported to alter the MT surface properties and affect kinesin-driven movement in vitro (Tokuraku et al. 2007). In nonneuronal cells, overexpression of MAP4 inhibits organelle motility and trafficking, and it inhibits kinesin-driven MT gliding (Bulinski et al. 1997; Tokuraku et al. 2007). In addition, it has been described to interact with p150Glued, part of the dynein-dynactin complex, and to inhibit dynein-mediated MT sliding (Samora et al. 2011). In *Xenopus* melanophores, the binding of XMAP4 to MTs negatively regulates dynein-dependent motility and positively regulates kinesin-2-based cargo movements (Semenova et al. 2014). MAP4 can also regulate the activity of MT-destabilizing factors, such as kinesin-related protein MCAK/XKCM1 and the MAP stathmin (Holmfeldt et al. 2002). Moreover, MAP4 has been suggested to inhibit katanin, by preventing its binding to MTs (McNally et al. 2002). Little is known about the precise role of MAP4 and its interaction partners in neuronal cells. MAP4 has been found upregulated by anti-depressants in rat hippocampus and is linked to chronic stress (Yang et al. 2003). It has also been shown that MAP4 can inhibit muscarinic receptor recovery after agonist exposure in neuroblastoma cells (Cheng et al. 2002). MAP4 is regulated by different kinases, such as protein kinase C (PKC) (Mori et al. 1991), mitogen-activated protein kinase (MAPK) (Hoshi et al. 1992), and protein kinases MARK (Ebneth et al. 1999; Illenberger et al. 1996). Alteration in MAP4 has been linked to cardiac hypertrophy (Cheng et al. 2005; Kumarapeli and Wang 2004), different types of cancer (Bash-Babula et al. 2002; Hait and Yang 2006; Holmfeldt et al. 2003), and Alzheimer's disease (Ray et al. 2008).

3.4.4 MAP6 Family of Microtubule-Associated Proteins

MAP6, also named STOP (stable tubule-only peptides), was discovered as the major factor able to confer cold and nocodazole resistance to neuronal MTs (Andrieux et al. 2002; Bosc et al. 1996; Guillaud et al. 1998). MAP6 is a calmodulin-regulated protein (Job et al. 1981, 1983). Calmodulin-binding sites partially overlap with the MT-binding domain, impairing the binding of MAP6 to MTs. MAP6 also includes four consensus sites for phosphorylation by CaM kinase II that regulates its binding to MTs (Bosc et al. 2003). MAP6 can also bind actin (Baratier et al. 2006). Phosphorylated forms of MAP6 cannot bind MTs and co-localize with actin along the neurites and at branching points. MAP6 is only found in vertebrates and is expressed in several tissues like the brain, heart, muscle, kidney, lung, and testis (Aguezzoul et al. 2003). In the brain, MAP6 is expressed in

neurons, astrocytes, and oligodendrocytes (Denarier et al. 1998b; Galiano et al. 2004; Guillaud et al. 1998; Ochoa et al. 2011). Two main splice isoforms are described in neurons; MAP6-E and MAP6-N (Aguezzoul et al. 2003; Denarier et al. 1998a). MAP6-E is the most abundant isoform in embryonic rodent brain and persists in adult brain. MAP6-N appears at birth and its expression is maintained in the adult brain (Bosc et al. 1996; Guillaud et al. 1998).

MAP6 has a strong preference for stable MTs (Bonnet et al. 2002; Slaughter and Black 2003). In neurons from dorsal root ganglia, MAP6 is present in the cell body and throughout the axon, but its expression is reduced in the distal portion of the axon (Fig. 3.1) (Guillaud et al. 1998). MAP6 is also present in dendrites and there are some evidences that localize MAP6 to synapses in mature hippocampal neurons (Andrieux et al. 2002; Baratier et al. 2006; Peng et al. 2004). CaMKII phosphorylation may promote MAP6 translocation from MTs to synaptic compartments where it interacts with actin. This translocation could be important during synaptic plasticity (Baratier et al. 2006). MAP6 is also important for neurite formation and dendritic arborization, where it has been suggested to act as a molecular brake for lysosomal trafficking in dendrites (Guillaud et al. 1998; Schwenk et al. 2014). Initial studies showed that MAP6 knockout mice have reduced number of synaptic vesicles and impaired synaptic plasticity (Andrieux et al. 2002). Later, it was shown that, in addition to changes in glutamatergic synaptic transmission, these mice also present alterations in dopaminergic, acetylcholinergic, nicotinic, serotonergic, and noradrenergic neurotransmission (Bouvrais-Veret et al. 2007, 2008; Brun et al. 2005; Delotterie et al. 2010; Fournet et al. 2010, 2012b; Fradley et al. 2005; Kajitani et al. 2010; Powell et al. 2007). These alterations recapitulate some clinical features observed in schizophrenia disorders (Andrieux et al. 2002; Fournet et al. 2012b). Interestingly, chronic treatments with both typical and atypical antipsychotics improve some defects in MAP6 knockout mice (Andrieux et al. 2002; Begou et al. 2008; Brun et al. 2005; Delotterie et al. 2010; Fradley et al. 2005; Merenlender-Wagner et al. 2010). In addition, treatments with MT-stabilizing compounds like epothilone D and NAP (davunetide) also improved some of the deficits (Andrieux et al. 2006; Fournet et al. 2012a; Merenlender-Wagner et al. 2010). Neuronal transport alterations have also been described in MAP6 knockout neurons, and epothilone D treatments can overcome these defects (Daoust et al. 2014). These results suggest that MT-stabilizing drugs may restore MT stability and subsequent transport functions in neurons.

3.4.5 MAP7 Family of Microtubule-Associated Proteins

MAP7, also called ensconsin and E-MAP-115 (epithelial MAP of 115 kD), was first identified in HeLa cells and purified by its ability to tightly associate with MTs (Bulinski and Bossler 1994; Masson and Kreis 1993). MAP7 is predominantly expressed in epithelial cells where its expression correlates with the presence of stable MTs (Masson and Kreis 1993). Subsequent experiments showed that its

association with MTs is very dynamic, and modest expression does not directly affect MT stability (Bulinski et al. 2001; Faire et al. 1999). The MT-binding domain of MAP7 fused to GFP (GFP-EMTB) is used in many labs to label MTs in living cells because it provides a non-perturbing label of the MT network (Bulinski et al. 1999).

MAP7 is widely expressed in the adult mouse; it is predominantly expressed in epithelial cells and in certain neuronal cell types, such as neurons of the trigeminal and dorsal root ganglia (Fabre-Jonca et al. 1998). MAP7 has been suggested to modulate MT functions and control the MT anchoring of other cellular factors (Faire et al. 1999). It has also been demonstrated to be a regulator of kinesin motors. MAP7 is a cofactor of kinesin-1 and required for organelle transport in *Drosophila* neurons (Barlan et al. 2013). MAP7 mutants display defects in motor localization without altering MT cytoskeleton (Sung et al. 2008). In addition, MAP7 has been shown to recruit kinesin-1 to the MT and regulate nuclear positioning, which is essential for skeletal muscle function in myoblasts (Metzger et al. 2012).

3.4.6   MAP9 Family of Microtubule-Associated Proteins

MAP9, also named ASAP (ASter-associated protein), has been characterized as a novel human spindle protein with a role in the correct bipolar spindle assembly and centrosome maintenance (Saffin et al. 2005). MAP9 is phosphorylated and regulated by the mitotic kinases Aurora A and PLK1 (Eot-Houllier et al. 2010; Venoux et al. 2008). It has also been demonstrated that, in response to DNA damage, MAP9 can interact and stabilize p53 (Basbous et al. 2012). In zebra fish, MAP9 is expressed during early embryo development and localizes to the mitotic spindle and centrosomes. MAP9 is expressed in the mammalian nervous system in various brain regions and associates with the mitotic spindle. In addition, both MAP9 knockdown and overexpression produce several developmental defects, leading to early embryonic lethality (Fontenille et al. 2014). However, the precise function of MAP9 remains largely unknown.

3.4.7   Tau/MAPT Family of Microtubule-Associated Proteins

Tau was originally discovered as a MAP that decreases the concentration at which tubulin polymerizes into MTs (Cleveland et al. 1977a, b; Fellous et al. 1977; Weingarten et al. 1975). Tau has many functions; it stabilizes MTs (Bre and Karsenti 1990; Drechsel et al. 1992; Drubin and Kirschner 1986), regulates MT modifications (Perez et al. 2009), alters the mechanical properties of MTs by enhancing their stiffness (Choi et al. 2009; Peck et al. 2011; Samsonov et al. 2004), and functions as a spacer between adjacent MTs (Chen et al. 1992). In neurons, the physiological function of tau is to support assembly and

stabilization of axonal MTs to promote neuritogenesis (Caceres and Kosik 1990; Cleveland et al. 1977a; Drubin and Kirschner 1986; Goode et al. 1997). Tau also interacts with the neuronal plasma membrane and anchors enzymes to MTs (Brandt et al. 1995; Lee et al. 1998; Liao et al. 1998; Sontag et al. 1999). Tau can also associate with spectrin (Carlier et al. 1984), actin (Griffith and Pollard 1982), PP1 and PP2A (Liao et al. 1998; Sontag et al. 1999), kinases like CDK5 (Sobue et al. 2000), presenilin 1 (Takashima et al. 1998), α-synuclein (Jensen et al. 1999), phospholipase C (Hwang et al. 1996), the Fyn tyrosine kinase (Klein et al. 2002; Lee et al. 1998), apolipoprotein E (Strittmatter et al. 1994), and calmodulin (Baudier et al. 1987). It can also bind to chaperones such as Hsp70, Hsp90, and Pin-1 (Dou et al. 2003; Lu et al. 1999). A recent study reveals how Hsp90 binds to tau's aggregation-prone MT-binding repeat region (Karagoz et al. 2014). Another possible role for tau is the regulation of kinesin-based transport (Ebneth et al. 1998; Sparacino et al. 2014; Terwel et al. 2002). Tau reduces the attachment of kinesins to MTs and interferes with their transport when is overexpressed, in both in vivo and in vitro experiments (Dixit et al. 2008; Ebneth et al. 1998; Seitz et al. 2002; Stamer et al. 2002; Trinczek et al. 1999; Vershinin et al. 2007).

Tau has several isoforms that are differentially expressed during development. In addition, tau contains many different posttranslational modifications; it can be modified by phosphorylation, glycosylation, ubiquitinylation, glycation, deamidation, oxidation, and truncation (Avila et al. 2004). Tau is mainly present in neurons (Arrasate et al. 1999; Chin and Goldman 1996) and specifically localizes to axons (Binder et al. 1985; Drubin and Kirschner 1986; Kosik and Finch 1987; Mandell and Banker 1996; Migheli et al. 1988), with a strong proximal to distal gradient (Black et al. 1996; Kempf et al. 1996; Mandell and Banker 1996) (Fig. 3.1). It is however unclear how the specific axonal localization of tau is controlled (Scholz and Mandelkow 2014). Under pathological conditions, tau is also present in dendrites, including dendritic spines (Ittner et al. 2010; Kremer et al. 2011). Synaptic activation in cultured cortical neurons and induction of long-term potentiation (LTP) in acute hippocampal slices trigger the translocation of endogenous tau to the postsynaptic compartment. Exposure to amyloid-β oligomers also induces mislocalization of tau to spines (Frandemiche et al. 2014). The synaptic damage induced by amyloid-β oligomers is most likely triggered by the missorting of newly synthesized tau into dendrites. In mouse models for Alzheimer's disease, mutant tau accumulates in dendritic spines, where it suppresses synaptic responses (Hoover et al. 2010). In addition, the expression of mutant tau results in a significant loss of dendritic spines and synapses (Bittner et al. 2010; Mocanu et al. 2008; Rocher et al. 2010). Indeed, in the human brain, tau aggregation also affects dendritic spines (Merino-Serrais et al. 2013). Current models suggest that tau mislocalization recruits the MT polyglutamylation enzyme TTLL6 (tubulin-tyrosine ligase-like-6) into dendrites. Enhanced polyglutamylation of dendritic MTs may subsequently recruit spastin and induces MT breakdown in dendrites (Lacroix et al. 2010; Zempel et al. 2013).

Several tau knockout lines have been generated; all of them are viable and do not display strong phenotype (Dawson et al. 2001; Fujio et al. 2007; Harada et al. 1994; Tucker et al. 2001). However, some muscle weakness and motor and cognitive deficits have been described (Ikegami et al. 2000; Lei et al. 2012; Ma et al. 2014). In addition, age-dependent brain atrophy and neuronal and synapse loss can be found in tau knockout mice (Lei et al. 2012). At cellular level, tau knockout neurons present a decrease in the axon caliber, together with a change in MT stability and organization (Harada et al. 1994). Whereas some models show normal axonal development in culture, a significant delay of the maturation of cultured neurons has been described in others (Dawson et al. 2001; Harada et al. 1994). An increased in MAP1A in tau knockout mice suggests a possible compensation effect in these animal models (Dawson et al. 2001; Fujio et al. 2007; Harada et al. 1994; Ma et al. 2014).

3.5 Discussion and Outlook

For a long time, MTs were considered as static structures distributed along the axon and dendrites. However, many fundamental neurodevelopmental processes such as differentiation, dendritic branching, and synapse formation require a continuous reorganization of the MT cytoskeleton. Moreover, the organization of the MT cytoskeleton largely depends on a tight regulation by many different extracellular and intracellular signaling pathways. Axons and dendrites present different patterns of MT organization that may underlie the different functions of these compartments. The two compartments not only differ in MT orientation but also in stability and posttranslational modifications. These biochemical variations generate distinct MT patterns in neurons and may be directly responsible for sorting cargo transport into axons or dendrites. It will be important to understand how variations in MT patterns can generate MT diversity and drive polarized cargo transport. Future research should help to resolve the basic mechanisms of MT assembly and remodeling. This knowledge will aid us to better understand dendritic development and the alterations that occur in neurological and neurodegenerative diseases.

In this chapter, we have discussed how classical MAPs regulate various MT roles during neuronal development and function. Apart from their traditional role in stabilizing and bundling MTs, MAPs have many additional functions in neurons. Many of the classical MAPs have been described to interact with numerous cellular components and participate in many different signaling pathways. Despite the structural and functional complexity of the MAP family members, the rules governing specific MT organization in axons and dendrites are slowly being revealed. The difficult task ahead will be to sort out how these different MAPs cooperate with each other in time and space to build specific MT arrays. In addition, some very basic questions still remain unknown, such as how do MAPs bind to a subset of dendritic MTs and how MAPs are specifically localized in different compartments. Moreover, what is the spatiotemporal dynamics of MAPs in

relationship to MTs dynamics itself and what is the percentage of MTs that is occupied by MAPs. In addition, many different functions of MAPs remain still unexplored. For example, their role in MT nucleation and organization is still largely unknown. In this respect, recent developments in super-resolution imaging are promising techniques to visualize the detailed subcellular localization patterns in developing and mature neurons. The strong implications for MTs and MAPs in many different neurological diseases will stimulate many new research efforts in the near future.

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